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THE JCURNAL OF Organic Chemistry®

VOLUME 42, NUMBER 9 APRIL 29, 1977

ORGANIC CHEMISTRY SYMPOSIUM

June 19-23, 1977 Morgantown, WV

The 25th ACS National Organic Chemistry Symposium will be held at West Virginia University, Morgantown, WV, on June 19-23. Sponsors are the ACS Division of Organic Chemistry and West Virginia University. Dr. J. C. Martin of the University of Illinois is the executive officer for the event.

The program features eleven outstanding organic chemists, including Dr. William S. Johnson who will receive the Roger Adams Medal in Organic Chemistry during the symposium. The Roger Adams Award of the American Chemical Society is sponsored by Organic Reactions, Inc. and Organic Syntheses, Inc.

Housing accommodations will be available at the air-conditioned University residence halls of the Towers Conference Center, as well as at local motels. Those desiring accommodations at the university should make their applications on the housing request form. Those desiring motel accommodations should make their own reservations. A listing of motels and rates is available by checking the appropriate box in the advance registration form. Meals will be available in the Towers complex. A children's program (ages 5-14) of varied activities supervised by WVU personnel will be offered in the mornings and evenings while the meetings are in progress for approximately $5 per child for the entire program.

The registration fee, which provides a copy of the printed abstracts of the symposium and admission to the meetings, is $30 for members of the Organic Division, $40 for nonmembers, and $10 for students. ACS members may join the Organic Division by paying the 1977 dues of $4 and thus qualify for the member rate. Abstracts will be available after the meeting from the division secretary, Dr. E. M. Burgess, Department of Chemistry, Georgia Institute of Technology, Atlanta, GA 30332. Send $1.00 plus a stamped, self-addressed 5 x 9 envelope.

For further information concerning the symposium contact Dr. J. C. Martin, Department of Chemistry, University of Illinois at Urbana-Champaign, Urbana, IL 61801 (217-333-0374), or the chairman of the local arrangements committee, Dr. W. R. Moore, Department of Chemistry, West Virginia University, Morgantown, WV 26506 (304-293-4742).

PROGRAM

MONDAY

9:00 A.M. Welcome and Response

9:30 A.M. ALBERT I. MEYERS. Asymmetric Syntheses via Chiral Lithium Reagents.

11:00 A.M. MARTIN F. SEMMELHACK. Arene-Metal Complexes in Organic Synthesis.

8:00 P.M. DONALD J. CRAM. Complexation of Ground and Transition States.

TUESDAY

9:00 A.M. YOSHITO KISHI. Synthetic Studies in the Field of Natural Products' Chemistry.

10:30 A.M. SAMUEL DANISHEFSKY. New Strategies for Stereospecific Synthesis

8:00 P.M. WILLIAM S. JOHNSON. The Evolution of Synthetic Strategy and the Cortisone Problem (Roger Adams Award Address).

WEDNESDAY

9:00 A.M. MAITLAND JONES, JR. Gas-Phase Reactions of Carbenes.

10:30 A.M. JOHN I. BRAUMAN. Nucleophilicities and Kinetic Basicities in the Gas Phase.

8:00 P.M. R. B. WOODWARD. Recent Advances in the Chemistry of Natural Products.

THURSDAY

9:00 A.M. DAVID A. EVANS. New Concepts in the Catalysis of Sigmatropic Rearrangements.

10:30 A.M. K. BARRY SHARPLESS. Atom Transfer Oxidations of Olefins.

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Deadline for receipt of application: June 3, 1977.

25th NATIONAL ORGANIC CHEMISTRY SYMPOSIUM
June 19-23, 1977 Morgantown, WV

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Children (No.) _____ at $1.75----------$_____

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* In papers with more than one author, the asterisk indicates the name of the author to whom inquiries about the paper should be addressed.

AUTHOR INDEX

THE JOURNAL OF Organic Chemistry®

VOLUME 42, NUMBER 9

APRIL 29, 1977

Synthesis of 4a-Aryldecahydroisoquinolines. Functionality in the Carbocyclic Ring

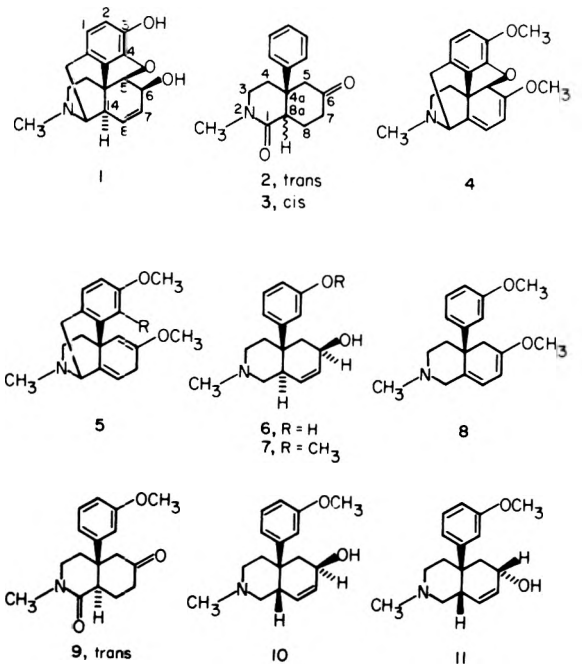
Dwight D. Weller, Richard D. Gless, and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

Received November 1, 1976

Syntheses are presented of 4a-(3'-methoxyphenyl)decahydroisoquinolines with the carbocyclic ring functionalized so as to resemble the substitution pattern in ring C of the morphine alkaloids. A versatile synthesis was developed for the starting 4-arylnipecotic acid which was then, via the methylene lactam rearrangement and intramolecular Michael reaction, stereospecifically converted to the 1,6-dioxodecahydroisoquinoline, keto amide *trans*-**9**. Reduction gave ketone *trans*-**36**, and selective functionalization at C-7 led to the key unsaturated ketal **39**. Hydrolysis yielded codeinone analogue, α,β-unsaturated ketone **40**, reduction gave codeine analogue Δ^7-allylic alcohol **7**, and ether cleavage produced the morphine analogue **6**. Cis-fused analogues were obtained through **9** and ketal amide **34** or **40** via isomerization at C-8a and were the predominant isomers at equilibrium. Alkali- or acid-catalyzed elimination of methanol from Δ^7-dimethyl ketal **39** produced mainly the thebaine analogue, $\Delta^{6(8a)}$-dienol ether **8**, which could be hydroxylated at C-8a with peracid to 14-hydroxycodeinone analogues **57** and **58**, but would not participate in Diels–Alder cycloaddition with a variety of dienophiles.

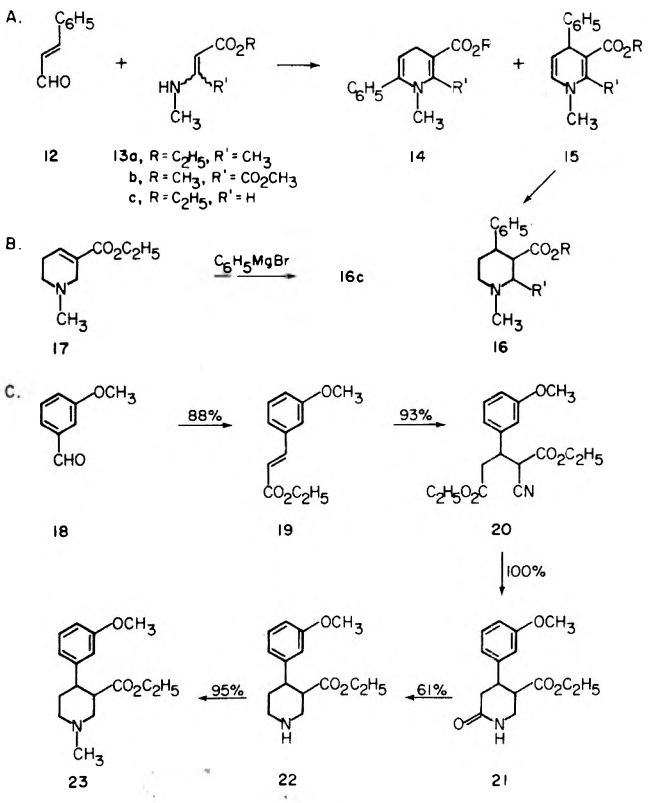
The 4a-aryldecahydroisoquinolines represent a new portion of the morphine molecule **1** which has appeared with increasing frequency in the recent literature.[1] A useful synthesis of these compounds requires both steric control of the ring juncture and functionality in the carbocyclic (C) ring. In our initial publication on this subject we demonstrated the availability of the *trans*- and *cis*-4a-phenyldecahydroisoquinolines, **2** and **3**.[1h] The C-1 and C-6 oxo functions provided control of the C-8a geometry as well as the potential for further C-ring elaboration. The logical utilization of **2** and **3** required the preparation of decahydroisoquinolines whose C rings were, with the exception of the C-5 oxygen bridge linkage, mimics of the C rings of the hydrophenanthrene opium alkaloids. An entirely analogous set of compounds with highly functionalized C rings has been prepared in the morphinan series from natural compounds, that is, directly from thebaine (**4**) or sinomenine or via prior conversion of **4** to **5**.[2,3] Parallel with these series, and to prepare the pharmacologically most interesting candidate compounds, the 4a-aryl moiety was chosen to be 3-methoxyphenyl.



We now report the synthesis of the decahydroisoquinolines **6**, **7**, and **8** (analogues of morphine, codeine, and thebaine) from the keto amide *trans*-**9**. In addition, although **9** possesses the trans ring fusion, the synthetic plan allowed for the production of both trans and cis materials, including the epimeric *cis*-codeine analogues **10** and **11**.

Formation of Decahydroisoquinolines. The synthesis of keto amide **9** required the nipecotic ester **23**. Previously we reported a general synthesis of 4-aryl 2-substituted nipecotates, but this was unsuccessful for the very important 2-substituted derivatives.[1h,4] In this process (Scheme IA) cinnamaldehyde (**12**) and readily available β-aminoacrylates **13a–c** were condensed to form the stable 1,4-dihydropyridines **15** which were easily reduced to the nipecotates **16**. The reactions with ethyl crotonate (**13a**) and the fumarate **13b** gave **15a** and **15b** in 77 and 55% yields, uncontaminated with the 6-phenyl isomers **14**. Unfortunately, the acrylate **13c** gave poor yields of mixtures of dihydropyridines **14** and **15**, forcing us to turn to a more tedious method (Scheme IB) for the preparation of 2-unsubstituted nipecotate **16c**, namely the conjugate addition of phenylmagnesium bromide to ethyl arecaidinate (**17**).[5]

Scheme I. Synthesis of 4-Arylnipecotic Acids: A, via β-Aminoacrylates; B, via Conjugate Addition of Grignard Reagents; C, via Michael Addition to Cinnamates



For the preparation of **23** a versatile synthesis of 4-aryl 2-unsubstituted nipecotic acids was developed (Scheme IC) by modification of a known procedure.[6] 3-Methoxybenzaldehyde (**18**) was converted to the amide ester **21** via standard procedures.[7,8] Selective reduction of the amide function of **21** was achieved by reaction with trimethyloxonium fluoroborate (forming the intermediate imidate) followed immediately by treatment with $NaBH_4$ in ethanol[9] to yield amino ester **22.** Reductive methylation gave the required nipecotate **23** in 48% overall yield from 3-methoxybenzaldehyde (**18**).

The conversion of nipecotate **23** into keto amide **9** followed closely the published process,[1h] relying on the methylene lactam rearrangement, selenium dioxide oxidation and allylic rearrangement, and Claisen rearrangement (Scheme II). This

Scheme II. Conversion of Nipecotate to Substituted Methylenepiperidone and Carbocyclic Ring Formation

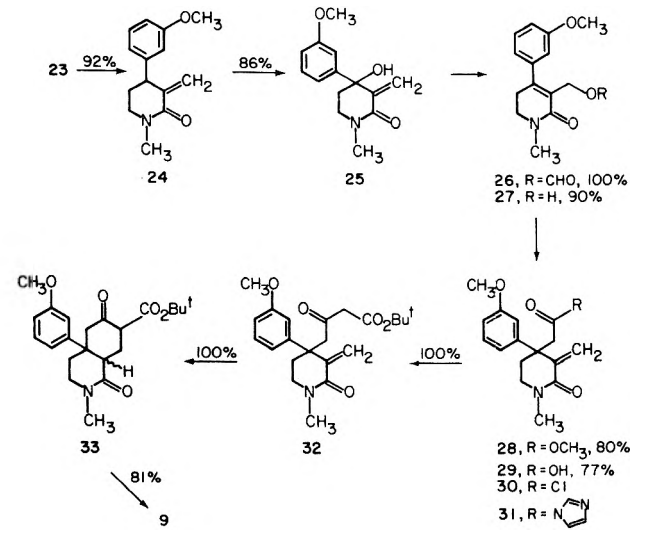


Table I. Cyclization of β-Keto Ester 32 to *cis*- and *trans*-4a-(3-Methoxyphenyl)decahydroisoquinoline (33)

Alkaline catalyst				Yield,[c] %	
Compd	Mol %	Solvent[a]	Time, h[b]	Cis	Trans
$(C_2H_5)_3N$	200	CH_3OH	48–120	12	88
CH_3ONa	10	CH_3OH	2.75	13	87
CH_3ONa	25	CH_3OH/H_2O, 2/1	2	13	87
$(CH_3)_3COK$	10	$(CH_3)_3COH$	1	45	55
$(CH_3)_3COK$	10	$(CH_3)_3COH$	12[d]	50	50
$(CH_3)_3COK$	10	$C_6H_5CH_3$	6	25	75

[a] All reactions carried out at 25 °C. [b] Reactions conducted until completion as indicated by TLC. [c] Total crude yield was a quantitative mixture of isomers. [d] Completed after 1 h; additional time for equilibration.

led to the 4-carboxymethyl-3-methylenepiperidone **29.** It was now necessary to introduce another carbon atom and close the carbocyclic ring C. To achieve this chain extension and produce a carbanionic center for conjugate addition to the methylene lactam, the carboxymethyl residue was converted to a β-keto ester.

Formation of the unstable acid chloride **30** and condensation with either *tert*-butyl lithioacetate or the magnesium enolate of *tert*-butyl hydrogen malonate accomplished this purpose and led to β-keto ester **32** but only in ~50% yield. A superior method was found in conversion of acid **29** to imidazolide **31** by the action of carbonyldiimidazole in $CHCl_3$/THF and reaction with the malonate reagent, resulting in a quantitative yield of very pure β-keto ester **32** suitable for direct use in the ring closure step.

The previous cyclization conditions (Et_3N, CH_3OH, 25 °C),[1h] when applied to the ring closure of **32** to **33,** required long times (2–5 days) and gave substantial amounts (13%) of the cis isomer. Several other alkaline catalyzed procedures were tested (Table I) and CH_3ONa/CH_3OH proved conveniently rapid although in no case could the trans/cis ratio be improved beyond 87/13. Isomeric purification may be done at this stage via recrystallization, leaving the oily *cis*-**33** in the mother liquors and returning pure *trans*-**33** in 70% (from **29**).

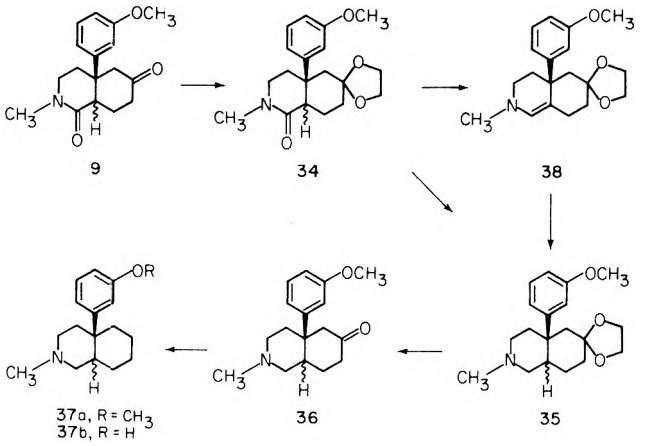
The assignment of stereochemistry and the determination of isomeric purity were performed by hydrolyzing and decarboxylating crude β-keto ester **33** to ketones **9,** followed by ketalization of the crude material to give a mixture of ethylene ketals **34.** When the crude **33** was obtained via cyclization using CH_3ONa/CH_3OH, these ketals were present in a trans/cis ratio of 87/13 by GC. This ratio was taken to be the kinetic product distribution. Compounds *trans*-**9** and *trans*-**34** are solids and were easily obtained pure by recrystallization; *cis*-**9** and *cis*-**34** are oils. That the cis isomers are the thermodynamically more stable products was shown by isomerization of *trans*-**9** and *trans*-**34** in KOH/ethanol. While the ketone was destroyed, as seen by NMR, at a rate comparable to isomerization, pure ketal *trans*-**34** was quantitatively converted to a 4/96 mix of *trans*/*cis*-**34** after 8 h at reflux.

These observations were in complete accord with the phenyl series, where the kinetic trans/cis ratio was 88/12 and the major isomer on equilibration was cis. In both series the kinetic products, which predominated in the ring closure of the β-keto esters, were solids and were assigned trans stereochemistry. The thermodynamic products, obtained under more vigorous, equilibrating conditions, were oils and were assigned as cis.[1h] The ultimate assignment in the phenyl series was based upon x-ray crystallography.[1d] The parallel results in both series (phenyl and 3-methoxyphenyl) pointed to the generality of obtaining either cis- or trans-fused materials by

these processes, independent of the angular aromatic functionality present at C-4a.

To compare our assignments with those previously reported, the amide and ketone functions at C-1 and C-6 of *trans*-**9** and *cis*-**9** were reduced (Scheme III). Not surprisingly, ether cleavage occurred under the vigorous Wolff–Kishner conditions. The methoxy amines *trans*-**37a**[1e,f] and *cis*-**37a**[1f,g] were obtained in low yields and the phenols *trans*-**37b**[c] and *cis*-**37b**[1g] were the major products. Although the cis materials were oils and formed oily picrates, the NMR of *cis*-**37a** was in accord with the reported spectrum.[1g] Amine *trans*-**37a** formed a picrate, mp 165–166 °C (lit.[1f] mp 161–162 °C), while the phenol *trans*-**37b** was a solid, mp 210–211.5 °C (lit.[1g] mp 195–205 °C).

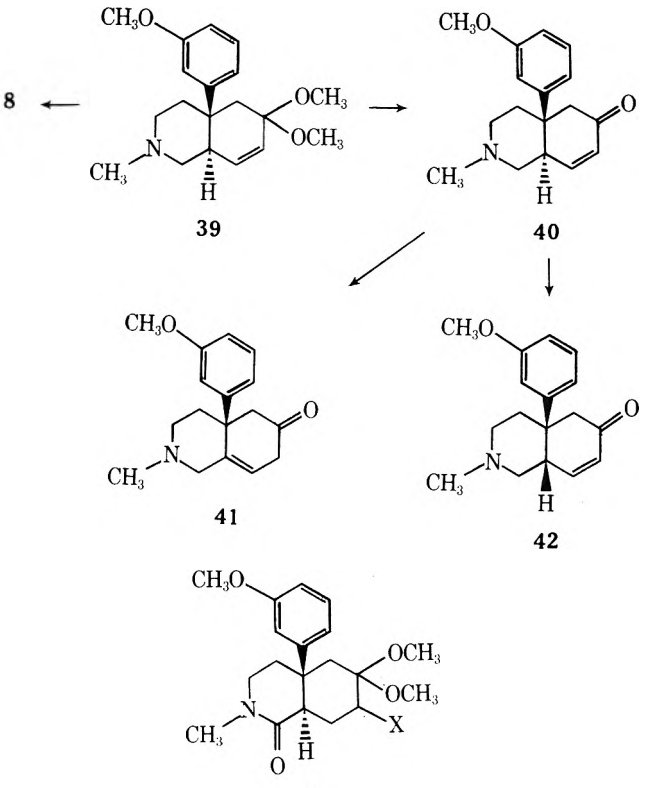
Scheme III. Reduction of Keto Amide 9



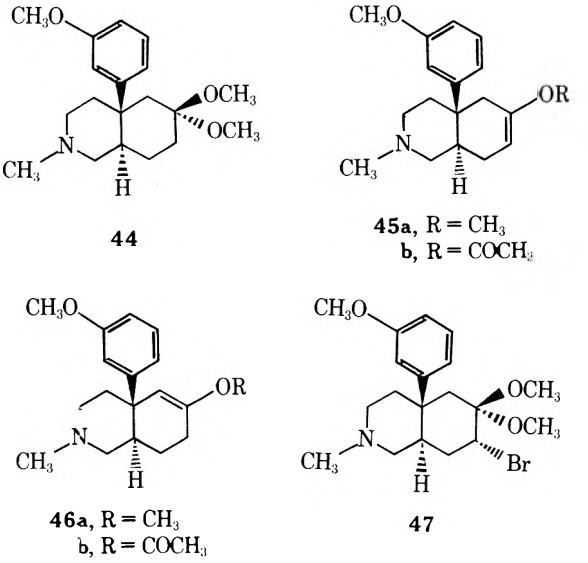
As in the phenyl series, reduction of the amide ketal *trans*-**34** with AlH_3/THF gave considerable amounts of enamine **38** which was converted to *trans*-**35** using H_2 and Rh/Al_2O_3. We investigated this sequence in the hope of finding a clean reaction which might give *trans*-**35** in a single step. Lithium aluminum hydride was without effect, as was diborane, at 25 °C; at reflux diborane gave reaction but several products resulted. Diisobutylaluminum hydride in toluene or THF gave **38** as the major product. The ratio of *trans*-**35** to **38** in the AlH_3 reduction of *trans*-**34** (57/43) could be improved by the addition of lithium aluminum hydride to a cold (−78 °C) solution of AlH_3 and *trans*-**34** in THF and warming. The ratio was now 83/17 in favor of the amine. Reverse order of hydride addition gave the same ratio of *trans*-**35** to **38** and considerable amide **34** remained.

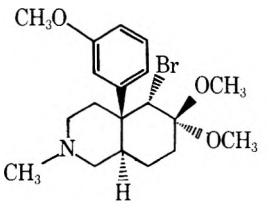
Functionalization of the Carbocyclic Ring. The prime consideration in the construction of the decahydroisoquinoline C-ring analogues of the morphine alkaloids was the incorporation of functionality sufficient to allow for formation of both the C-6 oxygen function and the Δ^7-ene and $\Delta^{6,8(8a)}$-diene. Our route to these derivatives inherently produced the C-6 ketone; thus the problem of introducing the remaining unsaturation was formally reduced to converting an one to an enone and thence to a dienol ether. Since direct action upon the ketone carried the potential of sacrificing the stereochemical integrity at C-8a, we envisioned our key intermediate to be the unsaturated ketal **39** which should yield exclusively the α,β-unsaturated ketone **40** (analogue of codeinone) via mild acid hydrolysis. The preference for the cis ring fusion in the decahydroisoquinoline series should allow production of conjugate ketone **42** and β,γ-unsaturated ketone **41** under equilibrating conditions. Additionally, **39** appeared an ideal candidate for the preparation of dienol ether **8** (thebaine analogue) via loss of methanol.

We considered two approaches to the synthesis of unsaturated ketal **39**. In the first, the doubly activated C-7 position of β-keto ester **33** should allow easy differentiation of C-5 and C-7 and introduction of a suitable substituent would be followed by hydrolysis, decarboxylation, and ketalization to give the generalized 7-substituted ketal **43**. This route would face the difficult problem of amide reduction while retaining additional functionality at C-7. In the alternative approach, amide reduction would precede ketone functionalization and the intermediate would be ketone *trans*-**36**, obtainable from **33** in 80% yield. This plan required selective reactivity at an undifferentiated C-7 position. Our recent report[10] of a high-yield conversion of dihydrocodeinone to codeinone dimethyl ketal via dihydrocodeinone enol ether had obvious applicability if selectivity at C-7 could be achieved; thus we explored the latter approach.



Ketone *trans*-**36** was easily ketalized in methanol containing trimethyl orthoformate and treatment of crude ketal **44** with phosphorus oxychloride and pyridine in toluene afforded a 91% yield of enol ethers **45a** and **46a** in an 83/17 ratio. The assignment of structure and the determination of the isomeric purity were done via NMR. The larger $W_{1/2}$ for the





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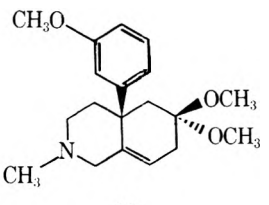

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vinyl proton of **45a** (7 Hz) compared to that of **46a** (2 Hz) was taken to reflect the larger coupling expected for the C-7 proton. A similar situation holds for enol acetates **45b** and **46b** obtained in 79/21 ratio after refluxing with tosic acid and acetic anhydride ($W_{1/2}$ for **45b**, 7 Hz; for **46b**, 4 Hz). Thus the C-7 enol predominated over the C-5 enol by a synthetically useful margin. Treatment of the enol ether mixture with *N*-bromoacetamide in methanol (methyl hypobromite) resulted in a clean conversion to the two bromo ketals **47** and **48**. Once again the predominant material (87/13 by NMR) had the larger $W_{1/2}$ ($W_{1/2}$ for **47**, 6 Hz; for **48**, 4 Hz). Neither the enol ethers nor the bromo ketals showed evidence of chromatographic separation (GC, TLC).

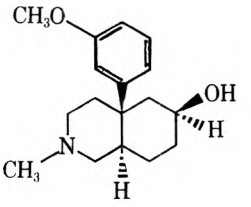
Treatment of the crude mixture of bromo ketals **47/48** with potassium *tert*-butoxide in Me_2SO at 60 °C resulted in two easily separable materials. Eluted first from silica was 7% of unreacted **48** followed by the unexpected neopinone dimethyl ketal analogue **49** in 74% yield. With the same reagents at 25 °C, a 60/40 mixture of Δ^7-ketal **39** and Δ^8-ketal **49** was obtained. Incorporation of *tert*-butyl alcohol as a cosolvent lead to prolonged reaction times but did not improve the **39/49** ratio while *tert*-butoxide in refluxing *tert*-butyl alcohol or *tert*-amyl alcohol had no effect upon the bromides. Lithium fluoride, chloride, or carbonate in Me_2SO at high temperatures lead to extensive decomposition. Fortunately, DBN in Me_2SO at 120 °C produced dehydrobromination without rearrangement and returned a 68% yield of Δ^7-ketal **39** after chromatography. The overall yields for introduction of the additional unsaturation into the C ring to produce the versatile intermediates **39** and **49** were 62 and 67%, respectively, from ketone *trans*-**36** (49 and 54% from keto amide *trans*-**9**).

When pure Δ^7-ketal **39** was treated briefly with *tert*-butoxide/Me_2SO at 60 °C a clean isomerization to Δ^8-ketal **49** was observed. At 120 °C, **49** underwent rapid loss of methanol and low yields of dienol ether **8** were isolated. The lack of some accompanying elimination to **8** during dehydrobromination of **47** at 60 °C was surprising, considering that treatment of codeinone dimethyl ketal at slightly higher temperatures gave clean elimination to thebaine with no detectable isomerization in reactions stopped prior to completion.[11] It was apparent that the replacement of a trans sp^3 center at C-8a with an sp^2 carbon was an extremely facile process in these decahydroisoquinolines and was entirely consistent with the high ratios of enamine **38** formed via AlH_3 reduction of **34**. An additional example of this process was later obtained from the acid hydrolysis of ketal **39**.

Preparation of Ring C Analogues. We planned the preparation of close relatives to the morphine alkaloids via the synthesis of unsaturated ketones **40, 41,** and **42**. With Δ^7-ketal **39** and Δ^8-ketal **49** at hand the route to **40** and **41** appeared straightforward and the only unanswered question was the formation of the cis enone **42**. Hydrolysis of **49** returned neopinone analogue **41** but **39** afforded a mixture of Δ^7- and Δ^8-enones **40** and **41** (3/1) under the standard hydrolysis conditions (3 N acetic acid, 25 °C). Both **40** and **41** proved stable to the hydrolysis conditions. As the hydrolysis of codeinone dimethyl ketal under the same nonequilibrating conditions produced no neopinone,[12] this behavior provided an additional example of the difference between the decahydroisoquinolines and the natural materials caused by the lability in the former of the trans proton at C-8a. After several trials 0.2 N $HClO_4$ was found to produce the least amount of Δ^8-enone **41** in the hydrolysis (~20%).

The synthesis of the cis Δ^7-enone **42** was performed under equilibrating conditions (CH_3ONa, CH_3OH). Beginning with either ketone **40** or **41**, a mixture of **41** and **42** was produced with no detectable trans enone **40**. The separation of conjugated and nonconjugated enones was readily accomplished via the bisulfite extraction procedure developed for ketones in the morphine series.[13] The unconjugated ketone **41** could be recovered pure after adjusting the pH of the bisulfite extract to 8.5 since only 1,2-addition to the carbonyl had occurred. The conjugated isomers **40** and **42** remained in the aqueous phase since 1,4-addition of bisulfite had occurred producing a sulfonic acid which was not regenerated via β-elimination until pH 12. Significantly no isomerization occurred in this strongly alkaline medium and both trans and cis enones, **40** and **42**, were recovered pure. From the hydrolysis of Δ^7-trans ketal **39** were obtained **41** (16%) and **40** (62%) after separation while the equilibrating conditions produced **41** (32%) and **42** (57%).

To provide a basis for the stereochemical assignment of the unsaturated alcohols to be obtained via reduction of enones **40, 41,** and **42** we first investigated the reduction products of saturated ketones *trans*- and *cis*-**36**. Treatment of ketone *trans*-**36** with H_2/Pt in acetic acid gave a single substance identified as the axial isomer **50** ($W_{1/2}$ for C-6 H, 6 Hz[14]). Reduction with either $NaBH_4$/ethanol or Na/2-propanol in toluene afforded mixtures of **50** and the equatorial isomer **51**



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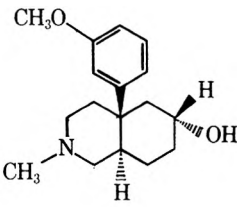

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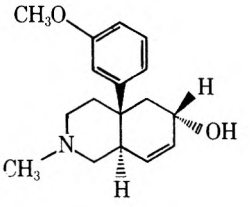

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($W_{1/2}$ for C-6 H, ~20 Hz), readily distinguished spectrally and chromatographically. Catalytic reduction of ketone *cis*-**36** under the same conditions produced two materials, A and B (1/2), while the borohydride procedure returned the same materials with an A/B ratio of 3/2. That A and B were the cis axial and equatorial alcohol isomers was shown by chromatographic separation and characterization. Although a tentative assignment for these alcohols was made in the 4a-phenyldecahydroisoquinoline series,[1d] our results were not comparable. In the previous case a single material was reported from the catalytic reduction (H_2, Pd/C, acetic acid, 1000 psi) and the *same* isomer predominated in the borohydride reduction. The assignment of stereochemistry to A and B was not possible solely from the data for the saturated alcohols but was made later using the assignments of the corresponding unsaturated alcohols.

The reduction of β,γ-enone **41** with $NaBH_4$ in ethanol produced a complex mixture from which was isolated 47% of a chromatographically homogeneous β,γ-unsaturated alcohol. Certain NMR resonances (C-6 H, NCH_3) were broadened and when the unsaturation was reduced with H_2/Pt in methanol a mixture of products was obtained. The two major products

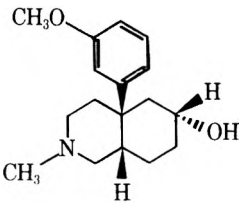
were trans axial alcohol **50** (major) and trans equatorial alcohol **51**, which presumably reflected the isomeric constitution at C-6 of the original unsaturated alcohols.

The reduction of trans α,β-enone **40** proceeded without incident using AlH_3/THF and two allylic alcohols were readily obtainable accompanied by a small amount (5%) of saturated ketone *trans*-**36**. The major material (56%) was found to be codeine analogue **7** by reduction to axial alcohol **50**, while the minor isomer (31%) was converted to equatorial alcohol **51** and thus represented the isocodeine analogue **52**. Treatment of codeine analogue **7** with potassium thioethoxide in DMF[15] yielded the morphine analogue **6** in 60% yield.

The reduction of the cis α,β-unsaturated ketone **42** was complicated by facile saturation of the C-7,8 double bond. Using AlH_3/THF as in the reduction of **40**, the major product was the saturated ketone *cis*-**36** accompanied by small amounts of unsaturated materials, and borohydride in ethanol produced a complex mixture of saturated and unsaturated alcohols. Fortunately, diisobutylaluminum hydride in toluene displayed a minimal amount of conjugate reduction, yielding only 9% of **36** along with 68% of cis Δ^7-allylic alcohols **10** and **11**.

The stereochemical assignment of the cis allylic alcohols was made possible by the striking difference in the vinyl proton absorptions of the two isomers. The major isomer possessed a doublet of doublets (J = 10 Hz) almost coalesced to a sharp singlet ($W_{1/2}$ for the central peak was 2.5 Hz), which could only be explained by very low values for $J_{8,8a}$ and $J_{6,7}$. The NMR of the minor isomer showed one vinyl proton as a doublet (J = 9 Hz) and the other downfield vinyl proton as a doublet of doublets (J = 4, 9 Hz) indicating that only one of these J values was very small. In order to apply these data we needed to identify the stable conformations of **10** and **11** and proceeded to do so by making two assumptions. Firstly, we assumed that the cyclohexene ring was represented by the half-chair conformation.[16,17] Thus **10** and **11** were restricted to the conformers **10a, 10b,** and **11a, 11b**. Secondly, we assumed that the conformer which possessed a pseudoequatorial hydroxyl function would be the *more* stable. In simple cyclohexenes (i.e., 3-chloro, 3-bromo) the pseudoequatorial stereoisomers are *less* stable owing to eclipsing of the C-3 substituent with the vinyl proton on C-1,[18] but in 4,4-dimethyl 6-substituted 1-phenylcyclohexenes the group at C-6 was largely pseudoequatorial.[19] Since the system at hand was a 4,4-disubstituted 6-hydroxycyclohexene we therefore assigned the stable conformers of **10** and **11** to be **10a** and **11b**. The stereochemical assignments were based on the expected weaker coupling of pseudoaxial allylic protons H-6 and H-8a with the neighboring vinyl protons H-7 and H-8.[19] Thus the NMR of **10a** would show $J_{7,8}$ as the only strong coupling while the spectrum of **11b** would reflect the strong couplings of $J_{7,8}$ and $J_{8,8a}$. These predictions were in complete accord with the actual data for **10** and **11**; thus the major isomer was assigned structure **10** and the minor isomer was assigned structure **11**.

When these arguments were applied to the trans unsaturated alcohols **7** and **52**, predictions were in accord with the assignments already made. In the case of **7**, our two basic assumptions were in conflict since the strain energy produced by the interaction of the 4a-α-aromatic ring and the 6-α-hydroxyl was surely comparable to $\Delta H°$ (2.7 kcal/mol)[20] for the half-chair and half-boat forms. The observed NMR was most consistent with the half-chair form, showing a sharp doublet (H-8) and a severely broadened doublet (H-7). The NMR of epimer **51** showed only a doublet of doublets. Reduction of **10** and **11** to the saturated alcohols produced B from **10** and A from **11**. Thus A was assigned to be **53** and B was the all-cis isomer **54**.



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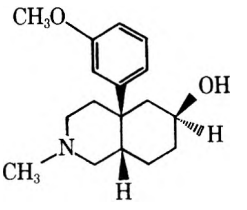

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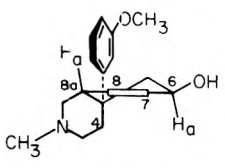
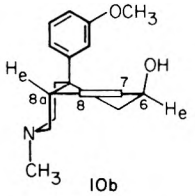
Although thebaine analogue **8** was available by the base-catalyzed elimination of CH_3OH from **49**, the low yield and the difficulty in obtaining pure material hindered its preparation in quantity. A more efficient procedure was the treatment of **39** with $POCl_3$/pyridine in hot toluene, which cleanly gave CH_3OH elimination with a 75% recovery but produced an 85/15 mixture of dienes **8** and **55**. The structure of **55** was readily assigned on the basis of the NMR of the H-5 and H-8 vinyl protons (singlet and triplet). These isomers could not be completely separated by chromatography and some of isomer **55** was present in all subsequent reactions of **8**.

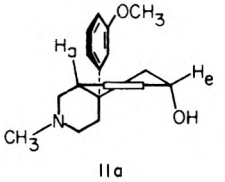
The homoannular conjugate diene common to both thebaine (**4**) and **8** is, in the case of thebaine, a highly reactive



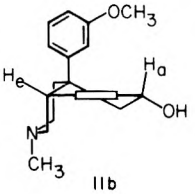
10c



10b



11a



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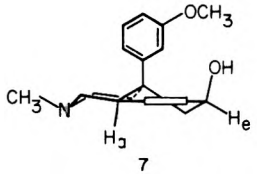

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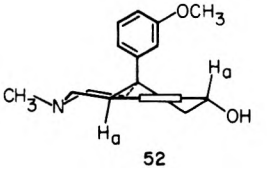

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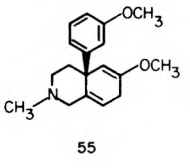

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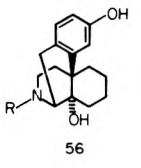

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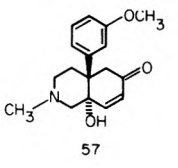

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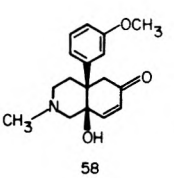

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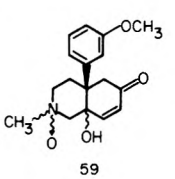

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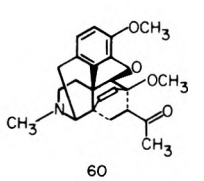

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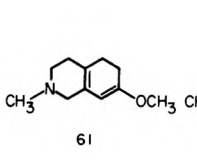

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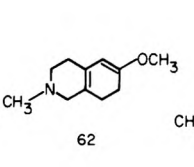

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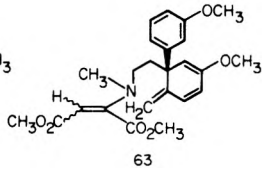
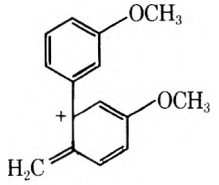


63

system capable of many transformations. Thus oxidation of **4** with peracid yields 14-hydroxycodeinone,[21] which is transformed to the important narcotic antagonist naloxone.[22] Simple 14-hydroxymorphinans such as **56** have been prepared and are both potent agonists and antagonists.[23] It was therefore of interest to prepare 14-hydroxylated derivatives in the decahydroisoquinoline series. Treatment of **8** with *m*-chloroperbenzoic acid in a mixture of acetic acid and trifluoroacetic acid at 95 °C returned two materials which were identified as **57** and **58** in 50% yield. In addition, a significant amount (14%) of the *N*-oxide **59** was isolated. Stereochemical assignments to **57** and **58** were not made, but presumably the major material (43%) was trans fused and the minor isomer (7%) was the cis material, since reactions performed under kinetically controlled conditions tend to preferentially attack the β face of the molecule at C-8a (e.g., the ring closure of **32** to **33** and the hydrogenation of **38** to *trans*-**35**). Thus the potential availability of the 14-hydroxylated compounds was clearly demonstrated.

A second important reaction of the thebaine C ring is the facile addition of dienophiles s to give 6,14-etheno bridged species such as **60** (from methyl vinyl ketone) which have been converted into highly potent analgesics.[24] When the mixture of dienes **8** and **55** was subjected to identical Diels–Alder conditions with either ethyl acrylate or methyl vinyl ketone no new products were formed and the starting dienes were recovered after chromatographic separation from polymer. These results were in direct contrast to the thebaine example and also to work done with the simpler decahydroisoquinolines **61** and **62** where fair yields of adducts were obtained under the same conditions.[25] The more reactive dimethyl acetylenedicarboxylate (DMAD) returned no cycloadduct (thebaine reacts easily)[26] but instead the unstable triene **63** was obtained in 45% yield accompanied by many other products. The structure of **63** was evident from its NMR (six distinct vinyl protons) and its mass spectral fragmentation, giving ion **64** as the base peak. This type of C–N bond cleavage with DMAD has been observed previously; e.g., the cleavage of



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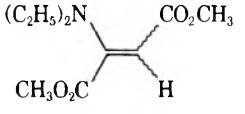

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triethylamine hydrobromide with DMAD in refluxing CH_2Cl_2 yielded enamine **65** in 85% yield[27] and similar reactions with other tertiary amines have been reported.[28] The facility with which **8** was cleaved was undoubtedly due to the allylic nature of the bond being broken.

Our last attempt to form a Diels–Alder adduct was with the extremely powerful dienophile *N*-phenylmaleimide. After 12 h in toluene at 110 °C only a negligible amount of reaction had occurred and only after 170 h were both reactants consumed. An NMR analysis of both the crude reaction mixture and of chromatographic fractions revealed no materials which possessed a 6,8a-etheno bridge. No attempt to achieve cycloaddition other than by the usual thermal conditions was made.

In summary, beginning with the easily obtainable keto amide *trans*-**9** close relatives of the morphine alkaloids possessing both cis and trans ring fusions have been prepared by a facile process and in good overall yield. The chemistry of these materials qualitatively resembled that of the natural series but quantitative differences arose owing to the additional features in the morphine skeleton. Thus enol ether **46** and diene **55** have no counterpart in the alkaloids since enolization toward C-5 is hindered by the 4,5-oxide bridge. Similarly the reduction of codeinone and neopinone and the oxidation of thebaine proceed with exclusive β-attack due to the extraordinary hindrance of the α face,[12,21] while their analogues **40**, **41**, and **8** give mixtures of epimers in these reactions. Two distinct differences did emerge, namely, the facile isomerization of the double bond from Δ^7 to $\Delta^{8(8a)}$ and the surprising nonreactivity of thebaine analogue **8** toward Diels–Alder cycloaddition, giving rise, in the case of DMAD, to the interesting triene **63**.

Experimental Section[29]

Ethyl 3-Methoxycinnamate (19). 3-Methoxycinnamic acid was prepared as described[30] except that β-picoline was used as solvent. The yield of acid was 100%, mp 118–120 °C (lit.[30] mp 117 °C). This material, diethyl sulfate (102 g, 0.66 mol), tris(2-hydroxypropyl)amine (151 g, 0.79 mol), and acetone (100 mL) were concentrated on a steam bath for 1.5 h, cooled (25 °C), poured into H_2O (1600 mL), and extracted with ether (3 × 800 mL). The combined organic phases were washed with saturated $NaHCO_3$ (800 mL) and saturated NaCl (800 mL), dried, evaporated, and distilled, affording 120 g (88%) of the cinnamate: bp 96–101 °C (0.1 mm) [lit.[31] 185–186 °C (15 mm)0; NMR δ 7.72 (d, J, 16 Hz, 1 H), 7.17 (m, 4 H), 6.46 (d, J = 16 Hz, 1 H), 4.30 (q, J = 7 Hz, 2 H), 3.83 (s, 3 H), 1.38 (t, J = 7 Hz, 3 H).

Diethyl 2-Cyano-3-(3′-methoxyphenyl)pentanedioate (20). Michael addition with ethyl cyanoacetate was carried out as directed[8] for the phenyl case, giving a 93% yield of **20**: bp 150–160 °C (0.3 mm); NMR δ 7.42–6.66 (m, 4 H), 4.25–3.79 (m, 6 H), 3.79 (s, 3 H), 2.90 (m, 2 H), 1.21 (t, J = 7 Hz, 3 H), 1.15 (t, J = 7 Hz, 3 H); IR (neat) 2235, 1725 cm^{-1}; mass spectrum *m/e* (rel intensity) 319 (30), 245 (73), 161 (100). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.9; H, 6.6; N, 4.4. Found: C, 64.1; H, 6.6; N, 4.5.

Ethyl 4-(3′-Methoxyphenyl)-2-piperidone-5-carboxylate (21). The adduct **20** (30.2 g, 92.7 mmol), PtO_2 (1.5 g), ethanolic HCl (12 N, 31.5 mL, 0.38 mol), and ethanol were shaken under H_2 (33–49 psi) for 7 h. The residue after filtration and evaporation was dissolved in $CHCl_3$ (100 mL), washed with saturated $NaHCO_3$ (200 mL), dried, and evaporated. After addition of toluene (200 mL) the solution was refluxed for 1 h and the solvent removed to give 26.7 g (100%) of crude amide **21** as a mixture of isomers. On crystallization from CH_2Cl_2/hexane a single isomer was obtained: mp 144–145.5 °C; NMR δ 7.20 (m, 2 H), 6.8 (m, 3 H), 4.14 (q, J = 7 Hz, 2 H), 3.83 (s, 3 H), 3.8–3.3 (m, 3 H), 3.17 (m, 1 H), 2.87 (d, J = 5 Hz, 2 H), 1.23 (t, J = 7 Hz, 3 H); IR (KBr) 1735, 1665 cm^{-1}; mass spectrum *m/e* (rel intensity) 277 (41), 134 (100). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.9; N, 5.0. Found: C, 65.1; H, 6.8; N, 5.02.

Ethyl 4-(3′-Methoxyphenyl)piperidine-3-carboxylate (22). To a solution of trimethyloxonium fluoroborate (14.78, 99 mmol) in CH_2Cl_2 (250 mL) was added a 24.9-g portion of the crude amide obtained above. After 43 h at 25 °C the solvent was evaporated, and the residue was dissolved in ethanol (250 mL), cooled (−10 °C, internal) and treated portionwise with $NaBH_4$ (10.2 g, 0.27 mol, 20 min) with vigorous mechanical stirring while maintaining the solution at 5–10 °C. The solution was stirred for 24 h (25 °C), H_2O (250 mL) was added, and the mixture was concentrated and acidified (pH 1) with 1.5 N HCl, neutralized with saturated $NaHCO_3$ (pH 8), and extracted with $CHCl_3$ (3 × 200 mL). The combined organic extracts were dried, evaporated, and distilled, yielding 14.47 g (61% from **20**) of amine **22**: bp 110–130 °C (0.3 mm); NMR δ 7.27 (m, 1 H), 6.80 (m, 3 H), 3.93 (q, J = 7 Hz, 2 H), 3.79 (s, 3 H), 1.99 (s, 1 H), 0.99 (t, J = 7 Hz, 3 H); IR (neat) 3350, 1725 cm^{-1}; mass spectrum *m/e* (rel intensity) 263 (35), 190 (30), 129 (37), 57 (100), 56 (72). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.4; H, 8.0; N, 5.3. Found: C, 68.4; H, 8.0; N, 5.2.

Ethyl 4-(3′-Methoxyphenyl)-1-methylpiperidine-3-carboxylate (23). A suspension of amine **22** (12.27 g, 44.7 mmol), 37% aqueous CH_2O (15 mL, 0.2 mol), 10% Pd/C (1.75 g), and ethanol (100 mL) were shaken for 12 h under H_2 (50 psi). The reaction mixture was filtered, evaporated, and distilled, giving 12.05 g of **23** (94.5%): bp 130–140 °C (0.3 mm); NMR δ 7.14 (m, 1 H), 6.75 (m, 3 H), 3.86 and 3.93 (isomeric quartets, J = 7 and 8 Hz, 2 H), 3.69 (s, 3 H), 3.28 and 3.33 (isomeric singlets, 3 H), 1.03 and 0.95 (isomeric triplets, J = 7 and 8 Hz, 3 H); IR (neat) 1725 cm^{-1}; mass spectrum *m/e* (rel intensity) 277 (31), 276 (10), 71 (37), 70 (50), 44 (100). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.3; H, 8.4; N, 5.0. Found: C, 69.2; H, 8.2; N, 5.0.

4-(3′-Methoxyphenyl)-1-methyl-3-methylene-2-piperidone (24). The ester **23** (5.0 g, 17.5 mmol), NaOH (1.49 g, 35 mmol), CH_3OH (50 mL), and H_2O (25 mL) were refluxed for 5 h. After the thorough removal of solvents, the residue was mixed with acetic anhydride (50

mL) and refluxed for 1 h, then cooled and evaporated and the crude reaction product partitioned between $CHCl_3$ (50 mL) and saturated $NaHCO_3$ (50 mL, pH 8). The aqueous layer was extracted with $CHCl_3$ (2 × 50 mL) and the combined organic phases dried and evaporated. Distillation gave 3.77 g (92%) of **24**. Recrystallization (CH_2Cl_2/hexane) gave the analytical sample: mp 67–70 °C; NMR δ 7.29 (m, 1 H), 6.82 (m, 3 H), 6.40 (t, J = 2 Hz, 1 H), 5.07 (t, J = 2 Hz, 1 H), 3.75 (s, 3 H), 3.34 (m, 2 H), 3.06 (s, 3 H), 2.17 (m, 2 H); IR (KBr) 1645, 1600 cm^{-1}; mass spectrum *m/e* (rel intensity) 231 (100), 216 (13). Anal. Calcd for $C_{14}H_{17}NO_2$ C, 72.7; H, 7.4; N, 6.1. Found: C, 72.6; H, 7.3; N, 6.0.

4-Hydroxy-4-(3′-methoxyphenyl)-1-methyl-3-methylene-2-piperidone (25). Methylene lactam **24** (633 mg, 2.68 mmol), SeO_2 (228 mg, 2.06 mmol), and chlorobenzene (8 mL) were heated at 100 °C for 50 min. Filtration, evaporation, and chromatography (SiO_2, $CHCl_3$/CH_3OH, 99/1) gave 575 mg (86%) of the tertiary alcohol **25**: mp 127–128 °C from benzene; NMR δ 7.5–6.7 (m, 4 H), 6.41 (d, J = 7 Hz, 1 H), 5.43 (d, J = 2 Hz, 1 H), 4.18 (bs, 1 H), 380 (s, 3 H), 3.8–3.0 (m, 2 H), 2.95 (s, 3 H), 2.10 (m, 2 H); IR (KBr) 3350, 1640, 1585 cm^{-1}; mass spectrum *m/e* (rel intensity) 247 (100), 230 (20), 229 (11), 228 (13), 112 (92). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.9; N, 5.7. Found: C, 68.2; H, 6.9; N, 5.6.

3-Formyloxymethyl-4-(3′-methoxyphenyl)-1-methyl-5,6-dihydro-2-pyridone (26). The tertiary alcohol **25** (254 mg, 1.04 mmol) was solvolyzed in 97% HCO_2H (10 mL) for 16 h at 25 °C and the solvent evaporated. The residue was dissolved in $CHCl_3$ (15 mL) and washed with saturated $NaHCO_3$ (15 mL), the aqueous layer was extracted with $CHCl_3$ (2 × 15 mL), and the combined organic phases were dried and evaporated to yield 288 mg (100%) of the formate. Distillation [155–165 °C (0.07 mm)] and recrystallization (benzene/hexane) gave a solid: mp 87–88 °C; NMR δ 8.08 (s, 1 H), 7.26 (m, 1 H), 6.80 (m, 3 H), 4.88 (s, 2 H), 3.80 (s, 3 H), 3.53 (t, J = 7 Hz, 2 H), 3.07 (t, J = 7 Hz, 2 H); IR 1700, 1645, 1610 cm^{-1}; mass spectrum *m/e* (rel intensity) 275 (221), 246 (75), 230 (52), 229 (100). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.4; H, 6.2; N, 5.1. Found: C, 65.5; H, 6.1; N, 5.0.

3-Hydroxymethyl-4-(3′-methoxyphenyl)-1-methyl-5,6-dihydro-2-pyridone (27). Methylene lactam **24** (4.78 g, 20.3 mmol), SeO_2 (1.69 g, 15.2 mmol), and chlorobenzene (50 mL) were heated at 100 °C for 1 h, cooled, filtered, and evaporated. The crude alcohol was dissolved in 97% HCO_2H (50 mL) and stirred at 25 °C for 27 h, and formate **26** was isolated as above. The crude formate was dissolved in CH_3OH (50 mL), K_2CO_3 (1.42 g, 10.3 mmol) was added, and after 1.5 h at 25 °C the mixture was evaporated and the residue partitioned between $CHCl_3$ (50 mL) and saturated NaCl (50 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 50 mL), and the combined organic phases dried and evaporated to give 4.50 g (90% overall) of pure allylic alcohol **27** which crystallized upon standing. This product was used directly in the following Claisen rearrangement. Recrystallization (benzene/hexane) gave material of mp 81–83 °C: NMR δ 7.18 (m, 1 H), 6.74 (m, 3 H), 4.10 (s, 2 H), 3.66 (s, 3 H), 3.35 (t, J = 7 Hz, 2 H), 3.17 (bs, 1 H), 2.90 (s, 3 H), 2.53 (t, J = 7 Hz, 2 H); IR (KBr) 3400, 1655, 1600 cm^{-1}; mass spectrum *m/e* (rel intensity) 247 (3), 230 (2), 229 (7), 44 (100). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.9; N, 5.7. Found: C, 68.0; H, 6.8; N, 5.6.

4-Methoxycarbonylmethyl-4-(3′-methoxyphenyl)-1-methyl-3-methylene-2-piperidone (28). The allylic alcohol **27** (1.22 g, 4.96 mmol), trimethyl orthoacetate (5.52 g, 46 mmol), and pivalic acid (25 mg, 0.50 mmol) were placed in diglyme (25 mL) and refluxed at 155–160 °C (internal) with fractionation to remove CH_3OH. After 18 h the solvents were evaporated and the residue distilled [bp 175–185 °C (0.15 mm)] to return 1.21 g (80%) of methyl ester **28**. Upon standing the ester crystallized: mp 85–86 °C; NMR δ 7.30 (m, 1 H), 6.86 (m, 4 H), 6.65 (s, 1 H), 5.57 (s, 1 H), 3.76 (s, 3 H), 3.47 (s, 3 H), 3.17 (m, 3 H), 2.87 (s, 4 H), 2.58 (m, 2 H); IR 1733, 1653, 1595 cm^{-1}; mass spectrum *m/e* (rel intensity) 303 (38), 230 (100). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.3; H, 7.0; N, 4.6. Found: C, 67.2; H, 7.0; N, 4.6.

4-Carboxymethyl-4-(3′-methoxyphenyl)-1-methyl-3-methylene-2-piperidone (29). To methyl ester **28** (1.20 g, 3.97 mmol) dissolved in CH_3OH (5 mL, 0 °C) was rapidly added KOH (775 mg, 11.9 mmol) in 5 mL of 1/1 CH_3OH/H_2O. After 20 h at 25 °C, $CHCl_3$ (20 mL) and H_2O (20 mL) were added, the separated aqueous layer was extracted with $CHCl_3$ (20 mL), and the combined organic phases were dried and evaporated to give 178 mg (20%) of **1,3-dimethyl-4-(3′-methoxyphenyl)-2-pyridone** (this arises from unreacted allylic alcohol under the alkaline hydrolysis conditions[1h]): NMR δ 7.20 (m, 2 H), 6.86 (m, 3 H), 6.07 (d, J = 7 Hz, 1 H), 3.81 (s, 3 H), 3.57 (s, 3 H), 2.10 (s, 3 H); IR (neat) 1640 cm^{-1} (broad); mass spectrum *m/e* (rel intensity) 229 (63), 228 (100). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.3; H, 6.6; N, 6.1. Found: C, 73.0; H, 6.6; N, 6.1.

The pH of the aqueous layer was adjusted to 1, the solution was extracted with $CHCl_3$ (3 × 15 mL), and the combined organic extracts were dried and evaporated to yield **29** (884 mg, 77%): mp 177–178 °C ($CHCl_3$/hexane); NMR δ 9.4 (bs, 1 H), 7.23 (m, 1 H), 6.86 (m, 3 H), 6.59 (s, 1 H), 5.59 (s, 1 H), 3.76 (s, 3 H), 3.18 (m, 2 H), 2.92 (s, 5 H), 2.62 (m, 2 H); IR (KBr) 1720, 1645, 1590 cm^{-1}; mass spectrum *m/e* (rel intensity) 289 (32), 230 (100). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.6; N, 4.8. Found: C, 66.2; H, 6.6; N, 5.2.

***tert*-Butyl 4-[4′-[4′-(3″-Methoxyphenyl)-1′-methyl-3′-methylene-2′-oxopiperidyl]]-3-oxobutyrate (32). A. Via *tert*-Butyl Lithioacetate and 4-Chlorocarbonylmethyl-4-(3′-methoxyphenyl)-1-methyl-3-methylene-2-piperidone (30).** Thionyl chloride (9.16 g, 77 mmol) in CH_2Cl_2 (100 mL) was cooled (−70 °C) and the acid **29** (5.78 g, 20 mmol) was added at a rate of 2 mL/min. After addition, the bath was removed, the solution allowed to warm to 25 °C (1 h), and the volatiles evaporated. Benzene (100 mL) was added and evaporated and the residual **30** used immediately: NMR δ 7.27 (m, 1 H), 6.80 (m, 4 H), 5.53 (s, 1 H), 3.78 (s, 3 H), 3.52 (s, 2 H), 3.21 (t, J = 6 Hz, 2 H), 2.87 (s, 3 H), 2.51 (bt, J = 6 Hz, 2 H); IR (neat) 1800, 1640, 1600 cm^{-1}.

To THF (33 mL) and 2,2,6,6-tetramethylpiperidine (5.78 g, 41 mmol) at −78 °C was added *n*-butyllithium (16.4 mL, 2.5 M in hexane, 41 mmol). After 5 min *tert*-butyl acetate (2.38 g, 20.5 mmol) was added dropwise followed 10 min later by the acid chloride **30** in THF (40 mL) at a rate of 2 mL/min. The solution was maintained at −78 °C for 15 min and then the reaction was quenched by addition of saturated NH_4Cl (55 mL) followed by slowly warming the slurry at 25 °C, separating the layers, and washing the aqueous phase with ether (2 × 40 mL). The combined ethereal layers were washed with 1 N HCl (20 mL) and saturated NaCl (20 mL), dried, and evaporated to give 6.92 g (90%) of crude β-keto ester **32**. Chromatography (SiO_2, $CHCl_3$/acetone, 3/1) returned 3.5 g (45%) of pure **32**.

B. Via the Acid Chloride 30 and the Magnesium Enolate of *tert*-Butyl Hydrogen Malonate. Acid chloride formation as above followed by treatment with the magnesium enolate and isolation as below yielded 59% of pure **32** after chromatography.

C. Via the Imidazolide 31 and the Magnesium Enolate of *tert*-Butyl Hydrogen Malonate. To carbonyldiimidazole (365 mg, 2.2 mmol) dissolved in 20 mL of THF was added acid **29** (578 mg, 2 mmol) in 20 mL of $CHCl_3$. After 60 min at 25 °C the clear solution was evaporated, and the residue dissolved in benzene (20 mL), reevaporated, and redissolved in THF (10 mL). Independently LiO_2C-$CH_2CO_2C_4H_9$[32] (895 mg, 5.4 mmol) in 20 mL of THF was treated dropwise with isopropylmagnesium bromide (5.2 mmol, 6.65 mL of 0.78 N in THF) giving a pale yellow solution which was heated on a steam bath until precipitation of LiBr was complete. To the heterogeneous magnesium enolate solution was added the solution of crude imidazolide and the suspension was stirred for 16 h. The mixture was poured into Et_2O (25 mL), saturated NaCl (25 mL), and 2 N HCl (10 mL). The separated aqueous layer was washed with Et_2O (2 × 10 mL), and the combined organic phases were washed with saturated NaCl (10 mL), dried, mixed with benzene (20 mL), and evaporated. The residue was taken up in benzene (50 mL), washed with saturated $NaHCO_3$ (2 × 10 mL) and saturated NaCl (10 mL), dried, and evaporated to give β-keto ester **32** (789 mg, 100%) as a colorless oil. Chromatography (SiO_2, $CHCl_3$/acetone, 3/1) returned 697 mg (90%) of pure **32**: NMR δ 7.30 (m, 1 H), 6.88 (m, 3 H), 6.60 (s, 1 H), 3.82 (s, 3 H), 2.90 (s, 3 H), 1.47 (s, 9 H); IR 1720, 1645, 1600 cm^{-1}.

***tert*-Butyl 1,6-Dioxo-4a-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline-7-carboxylate (33).** In the same manner as above acid **29** (8.67 g, 30 mmol) was converted to crude β-keto ester **32** (11.5 g, 100%) which was treated with CH_3OH (300 mL) containing CH_3ONa (3 mmol) for 7 h, then poured into saturated NaCl (400 mL) and benzene (500 mL). The aqueous phase was washed with benzene (3 × 100 mL) and the combined organic layers were dried and evaporated. The crystalline residue was dissolved in boiling benzene (20 mL), hot hexane (200 mL) was added, then the solution was concentrated to 80 mL and cooled (25 °C) to give 8.03 g (70%) of pure β-keto ester *trans*-**33**: mp 159–161 °C; NMR δ 7.22 (m, 1 H), 6.78 (m, 3 H), 3.78 (s, 3 H), 2.93 (s, 3 H), 1.49 (s, 9 H); IR 1650, 1629 cm^{-1}; mass spectrum *m/e* (rel intensity) 387 (1), 331 (5), 287 (16), 59 (100). Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.1; H, 7.5; N, 3.6. Found: C, 68.0; H, 7.5; N, 3.6.

Chromatography (SiO_2, $CHCl_3$/acetone, 9/1) of the mother liquors returned 2.73 g (24%) of a 3/1 mix of β-keto esters *cis*- and *trans*-**33**. Isomeric compositions were determined by hydrolysis, decarboxylation, and ketalization as described below (see **34**). Likewise **32** was cyclized to **33** as shown in Table I. In all cases the recovery of cyclized material was quantitative and isomer ratios were determined as below (see **34**).

***trans*-1,6-Dioxo-4a-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline (*trans*-9).** The cyclic β-keto ester *trans*-**33** (3.5 g,

9 mmol) in benzene (50 mL) was treated with TFA (50 mL) at 25 °C. After 3 h the solvents were removed, and the residue was taken up in 200 mL of toluene and refluxed for 60 min. Evaporation gave a residue which was recrystallized (benzene/hexane) to yield 2.1 g (81%) of pure *trans*-**9**: mp 156–158 °C; NMR δ 7.20 (m, 1 H), 6.75 (m, 3 H), 3.72 (s, 3 H), 2.90 (s, 3 H); IR (KBr) 1705, 1635 cm^{-1}; mass spectrum *m/e* (rel intensity) 287 (61), 57 (94), 55 (100). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.0; H, 7.4; N, 4.9. Found: C, 70.8; H, 7.4; N, 4.9.

***trans*-6,6-Ethylenedioxy-4a-(3′-methoxyphenyl)-2-methyl-1-oxodecahydroisoquinoline (*trans*-34).** To a solution of ketone *trans*-**9** (86.1 mg, 0.3 mmol) in benzene (20 mL) were added TsOH·H_2O (19.2 mg) and ethylene glycol (56 μL, 1 mmol) and the solution heated with removal of 15 mL of cloudy solvent. Cooling to 25 °C, pouring into 5% Na_2CO_3 (10 mL), washing the organic phase with saturated NaCl (5 mL), drying, and evaporating gave 105 mg (100%) of crude **34**. Recrystallization (benzene/hexane, 1:6) gave 91 mg (92%) of pure *trans*-**34**: mp 180–181 °C; NMR δ 7.1 (m, 1 H), 6.7 (m, 3 H), 3.9–3.6 (m, 7 H), 3.65 (s, 3 H); 2.67 (s, 3 H); IR 1623 (s), 1600 (sh), 1575 cm^{-1}; mass spectrum *m/e* (rel intensity) 331 (79), 232 (57), 99 (100). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.9; H, 7.6; N, 4.2. Found: C, 68.6; H, 7.5; N, 4.4.

***cis*-6,6-Ethylenedioxy-4a-(3′-methoxyphenyl)-2-methyl-1-oxodecahydroisoquinoline (*cis*-34).** Ketal *trans*-**34** (66 mg, 0.2 mmol) was dissolved in ethanol (4 mL) containing KOH (40 mg, 0.6 mmol) and refluxed (32 h). The equilibrium point (96/4, cis/trans) was reached after 8 h. The reaction was quenched by pouring into saturated NaCl (10 mL), extracted with $CHCl_3$ (2 × 5 mL), dried, and evaporated to give 65.6 mg (98%) of the mixture. Preparative GC (240 °C) gave 41 mg (63% recovery) of pure *cis*-**34** as a colorless oil: NMR δ 7.2 (m, 1 H), 6.9 (m, 3 H), 3.95 (m, 4 H), 3.50 (s, 3 H), 2.70 (s, 3 H); IR 1620, 1603, 1578 cm^{-1}; mass spectrum *m/e* (rel intensity) 331 (19), 99 (35), 55 (100). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.9; H, 7.6; N, 4.2. Found: C, 68.9; H, 7.6; N, 4.4.

trans-**34** has a GC retention time (237 °C) of 2.6 min while that for *cis*-**34** is 3.4 min. Analysis of the isomeric ratio obtained in the cyclization of **32** to **33** was by hydrolysis of the crude cyclized material (as per **33** to **9**) and ketalization (as per *trans*-**9** to **34**) without purification of intermediates. GC of the crude ketals gave the isomeric ratios in Table I.

***cis*-1,6-Dioxo-4a-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline (*cis*-9).** Ketal *cis*-**34** (20 mg, 0.06 mmol) was dissolved in 1:1 THF/1 N H_2SO_4 (2 mL) and stirred for 60 h. Ether (2 mL) and saturated NaCl (1 mL) were added, the aqueous phase washed with ether (1 mL), and the combined organic phases washed with saturated NaCl (2 mL), dried, and evaporated to yield 17 mg (99%) of pure *cis*-**9**: NMR δ 7.30 (t, *J* = 9 Hz, 1 H), 6.9 (m, 3 H), 3.78 (s, 3 H), 7.87 (s, 3 H), 2.63 (s, 2 H); IR 1712, 1634, 1603, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 287 (32), 218 (26), 55 (100). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.0; H, 7.4; N, 4.9. Found: C, 71.0, H, 7.4; N, 4.9.

Reduction of *trans*-34. The general procedure involved dissolving *trans*-**34** (0.1–0.2 mmol) in THF (2–4 mL), adding 500 mol % of either $LiAlH_4$ (1.0 M in THF), B_2H_6 (1.0 M in THF), AlH_3 (0.65 M in THF), or DIBAL (1.98 M in hexane), and stirring for 30 min at various temperatures. Reactions were monitored as described below for *trans*-**35** and by NMR.

A. AlH_3, 0 °C. Reduction and isolation gave a 57/43 ratio of amine *trans*-**35** and enamine **38**: NMR δ 5.96 (s, 1 H) and 2.60 (s, 3 H); IR 1673 cm^{-1} [compared to the known[1h] phenyl compound: NMR δ 5.97 (s, 1 H), 2.42 (s, 3 H); IR 1671 cm^{-1}]. Resubmission of the crude reduction product to the reaction conditions resulted in reisolation of the same mixture.

B. $LiAlH_4$; AlH_3, 0 °C. The THF solution of *trans*-**34** at −78 °C was treated with $LiAlH_4$, stirred for 30 s, then treated with AlH_3. After stirring for 30 min, isolation gave a mixture consisting of 61% of amine *trans*-**35**, 13% of enamine **38**, and 26% of *trans*-**34**.

C. AlH_3; $LiAlH_4$, −78 °C. The procedure was as in B, but with AlH_3 added before $LiAlH_4$. Isolation gave an 82/18 amine *trans*-**35** to enamine **38** ratio with no starting material present.

D. $LiAlH_4$. No reaction occurred at 0 °C, 25 °C, or at reflux.

E. B_2H_6. No reaction occurred at 25 °C. At reflux a complex mixture was obtained.

F. DiBAL, 0 °C. After isolation there was obtained amine *trans*-**35** and enamine **38** in a 10/90 ratio.

***trans*-6,6-Ethylenedioxy-4a-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline (*trans*-35).** Ketal amide *trans*-**34** (450 mg, 1.35 mmol) in THF (25 mL, anhydrous) in a dry ice/acetone bath was treated with AlH_3 (4.05 mmol in THF, 0.65 M) and stirred for 1 min. $LiAlH_4$ (6.75 mmol in THF, 1.01 M) was added, and the solution was warmed gradually to 0 °C and maintained at that temperature for 60 min. Excess hydride was decomposed by the addition of 1:1 THF/H_2O (125 μL) followed by 3.33 N NaOH (325 μL). The reaction solution was poured into Et_2O (50 mL) and saturated NaCl (10 mL) along with two washings of the salts with Et_2O (5 mL). Drying and evaporating yielded 426 mg (100%) of crystalline material which by NMR was 25% enamine **38** and 75% *trans*-**35**. This residue was dissolved in methanol (25 mL) and hydrogenated at 50 psi H_2 in the presence of 5% Rh/Al_2O_3 (130 mg) for 10 h. Filtration and evaporation gave 441 mg of material which was recrystallized (benzene/hexane, 1:2), returning 182 mg (42%) of pure *trans*-**35**, mp 124.5–126 °C. Chromatography (SiO_2, 1–10% NH_4OH/C_2H_5OH) of the mother liquor afforded 177 mg (41%) of pure *trans*-**35** (83% overall): NMR δ 7.3–6.9 (m, 3 H), 6.68 (dt, *J* = 2 Hz, 7, 1 H), 3.88 (s, 3 H), 4.0–3.2 (m, 7), 2.25 (s, 3 H); IR 1605, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 317 (80), 316 (45), 99 (21), 71 (100), 70 (62). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.9; H, 8.6; N, 4.4. Found: C, 71.7; H, 8.5; N, 4.5.

***cis*-6,6-Ethylenedioxy-4a-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline (*cis*-35).** Crude ketal amide *cis*-**34** (360 mg, 1.09 mmol, 96% cis, 4% trans) in THF (10 mL) at 0 °C was treated with AlH_3 (5.50 mmol in THF, 0.65 M) and the cloudy solution stirred for 60 min. Isolation as for the trans amine yielded 362 mg of crude *cis*-**35**. Chromatography (SiO_2, 1–10% NH_4OH/C_2H_5OH) returned 264 mg (73%) of pure amine ketal *cis*-**35**: NMR δ 7.2–6.9 (m, 3 H), 6.71 (bd, *J* = 8 Hz, 1 H), 4.1–3.6 (m, 7 H), 3.88 (s, 3 H), 2.12 (s, 3 H); IR 1603, 1577 cm^{-1}; mass spectrum *m/e* (rel intensity) 317 (99), 272 (82), 99 (20), 71 (100), 70 (63). Anal. Calcd for $C_{19}H_{27}N_3$: C, 71.9; H, 8.6; N, 4.4. Found: C, 71.8; H, 8.5; N, 4.3.

***cis*- and *trans*-4a-(3′-Methoxyphenyl)-2-methyl-6-oxodecahydroisoquinolines (*cis*- and *trans*-36). Trans.** The ketal amine *trans*-**35** (170 mg, 0.536 mmol) was dissolved in 1 N H_2SO_4 (15 mL) and stirred for 23 h at 25 °C. Basification (2 N NaOH) and extraction with $CHCl_3$ (3 × 10 mL), followed by washing the organic phase with saturated NaCl (10 mL), drying, and evaporating yielded 145 mg (99%) of pure amino ketone *trans*-**36** which was recrystallized from benzene/hexane, 1/1: mp 94–95 °C; NMR δ 7.4–6.9 (m, 3 H), 6.70 (dt, *J* = 2, 7 Hz, 1 H), 3.77 (s, 3 H), 2.32 (s, 3 H); IR 1706, 1603, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 273 (31), 272 (21), 71 (93), 70 (100). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.7; H, 8.5; N, 5.1. Found: C, 74.6; H, 8.3; N, 5.1.

Cis. In a manner exactly as above ketal amine *cis*-**35** (263 mg, 0.83 mmol) was converted into the ketone amine *cis*-**36** (233 mg) as an oil which was homogenous by GC: NMR δ 7.4–6.6 (m, 4 H), 3.78 (s, 3 H), 2.35 (s, 3 H); IR 1701, 1598, 1577 cm^{-1}; mass spectrum *m/e* (rel intensity) 273 (68), 71 (100), 70 (87). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.7; H, 8.5; N, 5.1. Found: C, 74.8; H, 8.5; N, 5.1.

***trans*-4a-(3′-Methoxyphenyl)-2-methyldecahydroisoquinoline (*trans*-37a).** A solution containing $H_2NNH_2·H_2O$ (900 mg, 18 mmol), KOH (105 mg, 1.6 mmol), and the ketone *trans*-**36** (136 mg, 0.5 mmol) in diethylene glycol (1.5 mL) was refluxed for 1 h and then distilled until the distillate reached 175 °C. The solution was then refluxed for an additional 1 h, cooled to 25 °C, diluted with H_2O (20 mL, pH 12), and extracted with benzene (3 × 10 mL). The organic layer was washed with 1 N NaOH (5 mL), H_2O (5 mL), and saturated NaCl (5 mL), dried, and evaporated to yield 16.9 mg (13%) of *trans*-**37a**: NMR δ 7.4–7.0 (m, 3 H), 6.72 (m, 1 H), 3.82 (s, 3 H), 2.24 (s, 3 H); IR 1600, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 259 (58), 258 (51), 151 (40), 150 (27), 71 (100), 70 (58). Anal. Calcd for $C_{17}H_{25}NO$: C, 78.7; H, 9.7; N, 5.4. Found: C, 78.7; H, 9.7; N, 5.4. A picrate was prepared, mp 165–166 °C (lit.[1f] mp 161–162 °C).

***trans*-4a-(3′-Hydroxyphenyl)-2-methyldecahydroisoquinoline (*trans*-37b).** The combined alkaline aqueous layers above were adjusted to pH 8 and extracted with benzene (3 × 15 mL). The combined organic phase was washed with NaCl (10 mL), dried, and evaporated to give 82 mg (67%) of phenol *trans*-**37b** which was recrystallized from $CHCl_3$/hexane, 8/1: mp 210–211.5 °C (lit.[1g] mp 195–205 °C); NMR δ 7.03 (m, 4 H), 6.47 (d, *J* = 7 Hz, 1 H), 2.27 (s, 3 H); IR 3670, 3590, 1592 (sh), 1582 cm^{-1}; mass spectrum *m/e* (rel intensity) 245 (68), 244 (69), 151 (39), 150 (21), 71 (100), 70 (77). Anal. Calcd for $C_{13}H_{23}NO$: C, 78.2; H, 9.4; N, 5.7. Found: C, 78.1; H, 9.4; N, 5.7.

***cis*-4a-(3′-Methoxyphenyl)-2-methyldecahydroisoquinoline (*cis*-37a).** In exactly the same manner as for the trans ketone, 199 mg (0.73 mmol) of ketone *cis*-**36** was converted to amine *cis*-**37a** (41 mg, 22%): NMR δ 7.29 (t, *J* = 8 Hz, 1 H), 7.04 (m, 2 H), 6.74 (dt, *J* = 2, 8 Hz, 1 H), 3.82 (s, 3 H), 2.24 (s, 3 H); IR 1600, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 259 (50), 258 (37), 151 (29), 150 (14), 71 (100), 70 (58). Anal. Calcd for $C_{17}H_{25}NO$: C, 78.7; H, 9.7; N, 5.4. Found: C, 78.6; H, 9.7; N, 5.4. A picrate was prepared and was an oil as reported.[1f]

***cis*-4a-(3′-Hydroxyphenyl)-2-methyldecahydroisoquinoline (*cis*-37b).** The combined alkaline aqueous layers above were adjusted to pH 8 and extracted with benzene (3 × 20 mL). The combined organic phase was washed with saturated NaCl (10 mL), dried, and

evaporated to give 87 mg (50%) of phenol *cis*-**37b**, which was distilled [bp 160 °C (0.1 mm)] [lit.[18] bp 145–155 °C (0.5 mm)]: NMR δ 7.5–6.5 (m, 5 H), 2.28 (s, 3 H); IR 3663, 1595 cm^{-1} (b); mass spectrum *m/e* (rel intensity) 245 (67) 244 (60), 151 (34), 150 (17), 71 (100), 70 (79). Anal. Calcd for $C_{16}H_{23}NO$: C, 78.2; H, 9.4; N, 5.7. Found: C, 78.0; H, 9.4; N, 5.7.

***trans*-6,6-Dimethoxy-4a-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline (44).** Ketone *trans*-**36** (3.215 g, 117 mmol), trimethyl orthoformate (5.3 g, 50 mmol), sulfuric acid (1.88 mL, 36 N, 34 mmol), and CH_3OH (350 mL) were refluxed for 20 min, an equal portion of the orthoformate was added, and reflux was continued for 20 min. The cooled solution was evaporated to 100 mL, cooled, and poured into H_2O (300 mL) containing NaOH (4 g, 100 mmol) and $CHCl_3$ (200 mL). The separated aqueous layer was washed with $CHCl_3$ (3 × 50 mL), and the combined organic phases were washed with saturated NaCl (50 mL), dried, and evaporated to give 3.80 g (100%) of ketal **44**. A small portion was distilled [135–140 °C (0.1 mm)] although the crude material was used in all subsequent reactions: NMR δ 7.16 (m, 3 H), 6.68 (dt, J = 2, 7 Hz, 1 H), 3.84 (s, 3 H), 3.14 (s, 3 H), 2.42 (s, 3 H), 2.27 (s, 3 H); IR 1601, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 319 (10), 287 (68), 272 (100), 71 (25), 70 (41). Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.4; H, 9.1; N, 4.4. Found: C, 71.6; H, 9.1; N, 4.4.

***trans*-Δ⁵- and -Δ⁶-6-Methoxy-4a-(3′-methoxyphenyl)-2-methyloctahydroisoquinolines (46a and 45a).** The crude ketal **44** (3.8 g, 11.7 mmol) was dissolved in toluene (450 mL), treated with pyridine (11.1 g, 140 mmol) and $POCl_3$ (5.73 g, 37.4 mmol), and refluxed for 2 h at which time a clear brown oil had separated. The cooled (10 °C), vigorously stirred emulsion was rapidly treated with cold (0 °C) 3 N NaOH (224 mL), then shaken until no oil remained. The separated aqueous layer was washed with benzene (2 × 50 mL), the combined organic phases were washed with saturated NaCl (50 mL), dried and evaporated, and the residue was distilled [140–150 °C (0.1 mm)] giving 3.07 g (91%) of pure enol ethers (NMR revealed a C-5/C-7 vinyl proton ratio of 13/87; the $W_{1/2}$ for C-5 H was 2 Hz and for C-7 H was 7 Hz): NMR δ 7.27 (m, 3 H), 6.68 (dt, J = 2, 7 Hz, 1 H), 3.80 (s, 3 H), 2.30 (s, 3 H); Δ⁵, 4.85 (s, 1 H), 3.47 (s, 3 H); Δ⁶, 4.70 (s, 1 H), 3.40 (s, 3 H); IR 1664, 1601, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 287 (63), 286 (23), 273 (22), 272 (100), 71 (30), 70 (45). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.2; H, 8.8; N, 4.9. Found: C, 75.0; H, 8.7; N, 4.9.

Enol Acetates 45b and 46b. Ketone *trans*-**36** (45 mg, 0.15 mmol) and acetic anhydride (2 mL) containing $TsOH \cdot H_2O$ (34 mg, 0.20 mmol) were heated at reflux for 8 h and evaporated. The residue was dissolved in $CHCl_3$ (15 mL), washed with saturated $NaHCO_3$, dried, and evaporated to give 37 mg (78%) of **45b/46b** in a 79/21 ratio: NMR δ 7.4–6.8 (m, 3 H), 6.73 (bd, J = 7 Hz, 1 H), 3.82 (s, 3 H), 2.30 (s); the Δ⁵ enol acetate **46b** had δ 5.62 (s, $W_{1/2}$ = 4 Hz, 1 H), 2.08 (s, 3 H); the Δ⁷ isomer **45b** had δ 5.37 (s, $W_{1/2}$ = 7 Hz, 1 H), 2.02 (s, 3 H).

***trans*-5- and -7-Bromo-6,6-dimethoxy-4a-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline (48 and 47).** The enol ether mixture (3.02 g, 10.5 mmol) at 0 °C in CH_3OH (65 mL) was treated with *N*-bromoacetamide (1.52 g, 11.02 mmol) in CH_3OH (65 mL) and allowed to stand for 12 h. The CH_3OH was evaporated and benzene (100 mL) and 2 N NaOH (50 mL) were added, then shaken until no oil remained. The separated organic layer was washed with benzene (2 × 50 mL), and the combined organic phases were washed with 2 N NaOH (15 mL), H_2O (15 mL), and saturated NaCl (25 mL), then dried and evaporated to yield 4.32 g (~100%) of a mixture of **47** and **48**. NMR revealed the C-5 H/C-7 H ratio to be 13/87 with $W_{1/2}$ of 4 Hz for C-5 H and 6 Hz for C-7 H. Pure 5-bromo compound **48** may be obtained via chromatograpy after HBr elimination from **48** to either **39** or **49**: NMR δ 7.0 (m, 4 H), 4.72 (s, 1 H), 3.84 (s, 3 H), 3.14 (s, 3 H), 2.55 (s, 3 H), 2.25 (s, 3 H); IR 1601, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 399 (4), 397 (4), 319 (29), 318 (100), 71 (30), 70 (55); bp 150–155 °C (0.1 mm). Anal. Calcd for $C_{19}H_{28}NO_3Br$: C, 57.3; H, 7.1; N, 3.5. Found: C, 57.5; H, 7.1; N, 3.6.

The 7-bromo isomer **47** exhibits the following NMR: δ 7.05 (m, 3 H), 6.66 (dt, J = 2, 7 Hz, 1 H), 3.84 (s, 3 H), 3.14 (s, 3 H), 2.30 (s, 3 H), 2.25 (s, 3 H).

***trans*-Δ⁷-6,6-Dimethoxy-4a-(3′-methoxyphenyl)-2-methyloctahydroisoquinoline (39).** The crude mixture of bromo ketals **47** and **48** (4.32 g, 10.5 mmol), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, 6.52 g, 52.5 mmol), and Me_2SO (36.9 g, 472 mmol) were heated at 120 °C for 15 h, cooled, and shaken thoroughly with benzene (200 mL), H_2O (500 mL), and saturated NaCl (50 mL). The separated aqueous layer was washed with benzene (2 × 100 mL), and the combined organic phases were washed with H_2O (90 mL), saturated NaCl (10 mL), H_2O (2 × 50 mL), and saturated NaCl (100 mL), dried, and evaporated to yield 3.43 g (~100%) of a mixture of bromo ketal **48** and ketal **39**. Chromatography (SiO_2, $CHCl_3/CH_3OH$, 9/1, 0.25% NH_4OH) returned 2.26 g (68%) of pure **39** and 318 mg (7.5%) of pure **48**. An intermediate fraction (454 mg, 12%) was also collected. The trans Δ⁷-ketal **39** was crystallized from benzene/hexane: mp 122–123 °C; NMR δ 7.4–6.8 (m, 4 H), 5.98 (d, J = 10 Hz, 1 H), 5.77 (bd, J = 10 Hz, 1 H), 3.84 (s, 3 H), 3.18 (s, 3 H), 2.73 (s, 3 H), 2.25 (s, 3 H); IR 1605, 1582 cm^{-1}; mass spectrum *m/e* (rel intensity) 317 (2), 286 (14), 285 (57), 270 (38), 257 (46), 254 (25), 150 (100), 71 (52), 70 (26). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.9; H, 8.6; N, 4.4. Found: C, 72.0; H, 8.6; N, 4.4.

Δ⁸(⁸ᵃ)-6,6-Dimethoxy-4a-(3′-methoxyphenyl)-2-methyloctahydroisoquinoline (49). A. The crude mixture of ketals **47** and **48** (943 mg, 2.37 mmol), potassium *tert*-butoxide (610 mg, 5.0 mmol), and Me_2SO (16 mL) was heated at 60 °C for 4 h. Isolation and chromatography as for the Δ⁷ isomer yielded 66 mg (7%) recovered **48** and 557 mg (74%) of pure **49**: NMR δ 7.27 (t, J = 7 Hz, 1 H), 7.0–6.6 (m, 3 H), 5.84 (t, J = 4 Hz, 1 H), 3.84 (s, 3 H), 3.25 (s, 3 H), 2.40 (s, 3 H), 2.22 (s, 3 H); IR 1600, 1577 cm^{-1}; mass spectrum *m/e* (rel intensity) 317 (6), 287 (7), 286 (13), 285 (38), 178 (59), 146 (100).

A methiodide was prepared in CH_3OH with excess CH_3I and recrystallized from ethyl acetate/ethanol, mp 191 °C dec. Anal. Calcd for $C_{20}H_{30}NO_3I$: C, 52.3; H, 6.6; N, 3.0. Found: C, 52.1; H, 6.7; N, 3.0.

B. The Δ⁷ ketal **39** (31.7 mg, 0.1 mmol) was converted by the procedure in part A above to **49** (25 mg, 79%).

Δ⁶,Δ⁸(⁸ᵃ)-6-Methoxy-4a-(3′-methoxyphenyl)-2-methylhexahydroisoquinoline (8). A. The Δ⁸(⁸ᵃ) ketal **49** (556 mg, 1.75 mmol), potassium *tert*-butoxide (830 mg, 7 mmol), and Me_2SO (17.5 mL) were heated at 105 °C for 90 min, followed by isolation as for the formation of **49**. The crude 363 mg after chromatography (SiO_2, $CHCl_3/CH_3OH$, 9/1, 0.25% NH_4OH) returned 102 mg (20%) of 8 as a dark oil: bp 165–170 °C (0.1 mm); NMR δ 7.4–6.6 (m, 4 H), 6.07 (dd, J = 2, 6 Hz, 1 H), 4.87 (dd, J = 2, 6 Hz, 1 H), 3.82 (s, 3 H), 3.45 (s, 3 H), 2.30 (s, 3 H); IR 1653, 1602, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 285 (100), 284 (46), 270 (27), 254 (25), 178 (60), 71 (26), 70 (11). Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.7; H, 8.1; N, 4.9. Found: C, 75.4; H, 8.2; N, 4.7.

B. The Δ⁷ ketal **39** (422 mg, 1.33 mmol) was dissolved in toluene (55 mL) and treated with pyridine (1.76 g, 16 mmol) and $POCl_3$ (650 mg, 4.25 mmol), then refluxed for 30 min, after which time a clear brown oil had separated. Isolation was as for the enol ethers **45a** and **46a** and distillation returned 279 mg (74%) of an oil, bp 125–135 °C (0.05 mm), consisting of two materials, **8** (85%) and **55** (15%), indistinguishable chromatographically. NMR of **55** had δ 5.89 (t, J = 4 Hz, 1 H), 4.17 (s, 1 H). The mixture of dienes was used in subsequent oxidation and cycloaddition reactions.

Δ⁸(⁸ᵃ)-4a-(3′-Methoxyphenyl)-2-methyl-6-oxooctahydroisoquinoline (41). Ketal **49** (50 mg, 0.158 mmol) was dissolved in 2 mL of 3 N acetic acid and stirred for 4 h. Basification (pH 8.5), extraction with $CHCl_3$ (2 × 5 mL), drying, and evaporation gave 29 mg (68%) of **41** as an oil. Attempted distillation resulted in decomposition and **41** failed to form a crystalline methiodide: NMR δ 7.27 (t, J = 7 Hz, 1 H), 6.77 (m, 3 H), 5.96 (m, 1 H), 3.78 (s, 3 H), 2.27 (s, 3 H); IR 1715, 1595, 1578 cm^{-1}; mass spectrum *m/e* (rel intensity) 271 (100), 215 (43), 164 (48), 71 (55), 70 (41). $C_{17}H_{18}NO_2$ requires 271.1572; found, 271.1563.

***trans*-Δ⁷-4a-(3′-Methoxyphenyl)-2-methyl-6-oxooctahydroisoquinoline (40).** Ketal **39** (476 mg, 1.5 mmol) in benzene (30 mL) was shaken three times with 0.2 N $HClO_4$ (30, 10, 10 mL) and the aqueous solution allowed to stand for 30 min. Basification to pH 8.5, extraction with $CHCl_3$ (3 × 10 mL), drying, and evaporation gave 410 mg (100%) of a mixture of ketones. After dissolution in benzene (25 mL) the ketones were extracted into $NaHSO_3/Na_2SO_3$, pH 7.[13] The aqueous bisulfite was cooled (0 °C), basified to pH 8.5, and extracted with benzene to give after removal of solvent 67 mg (16%) of pure **41**. The remaining bisulfite solution was further basified to pH 12 and extracted with benzene using mechanical shaking, the benzene layer being separated and replaced by a fresh layer at intervals of 2, 2, 4, and 10 h. Drying and evaporation of the combined organic extracts gave ketone **40** (285 mg, 69%): mp 78–80 °C; NMR δ 7.4–7.0 (m, 1 H), 7.00 (dd, J = 2, 10 Hz, 1 H), 6.75 (m, 3 H), 5.95 (dd, J = 3.5, 10 Hz, 1 H), 3.78 (s, 3 H), 2.30 (s, 3 H); IR 1672, 1597, 1588 cm^{-1}; mass spectrum *m/e* (rel intensity) 271 (100), 228 (28), 215 (43), 214 (31), 164 (48), 122 (35), 71 (22), 70 (14). A methiodide was prepared in CH_3OH and recrystallized from acetone, mp 201 °C dec. Anal. Calcd for $C_{18}H_{24}NO_2I$: C, 52.3; H, 5.8; N, 3.4. Found: C, 52.2; H, 5.8; N, 3.4.

***cis*-Δ⁷-4a-(3′-Methoxyphenyl)-2-methyl-6-oxooctahydroisoquinoline (42).** The trans α,β-unsaturated ketone **40** (350 mg, 1.29 mmol), CH_3ONa (2.58 mL of 0.5 M in CH_3OH, 1.29 mmol), and CH_3OH (35 mL) were stirred for 13 h at 25 °C, poured into H_2O (100 mL), and extracted with CH_2Cl_2 (4 × 25 mL), and the combined or-

ganic phases were washed with saturated NaCl (20 mL), dried, and evaporated to yield 350 mg (100%) of a 65/35 mixture of **42** and **41**. Separation was exactly as for the mixtures of **40** and **41** above giving 112 mg (32%) of **41** and 199 mg (57%) of **42**: NMR δ 7.26 (t, J = 8 Hz, 1 H), 7.1–6.6 (m, 4 H), 5.98 (dd, J = 1.5, 10 Hz, 1 H), 3.80 (s, 3 H), 2.30 (s, 3 H); IR 1672, 1595, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 271 (19), 243 (12), 200 (15), 71 (100), 70 (20). $C_{17}H_{21}NO_2$ requires 271.1572; found 271.1561.

***trans*-6α-Hydroxy-4aα-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline (50).** To ketone *trans*-**36** (25 mg, 0.090 mmol) in acetic acid (1 mL) was added PtO_2 (10 mg) and the mixture hydrogenated at 50 psi H_2 for 60 min. Filtration and evaporation gave a residue which was dissolved in H_2O (10 mL), basified (2 N NaOH), and extracted with $CHCl_3$ (3 × 10 mL), followed by washing the organic phase with saturated NaCl, drying, and evaporation to give 25 mg (100%) of a single isomer which was crystallized from hexane: mp 117–117.5 °C; TLC ($CH_3OH/CHCl_3$, 3/20, 1% NH_4OH), R_f 0.52; NMR δ 7.4–7.0 (m, 3 H), 6.70 (dt, J = 2, 8 Hz, 1 H), 3.97 (m, $W_{1/2}$ = 6 Hz, 1 H), 3.80 (s, 3 H), 2.22 (s, 3 H); IR 3571, 3413, 1605, 1577 cm^{-1}; mass spectrum *m/e* (rel intensity) 275 (100), 204 (40), 71 (84), 70 (72). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.1; H, 9.1; N, 5.1. Found: C, 73.9; H, 9.0; N, 5.1.

***trans*-6β-Hydroxy-4aα-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline (51). A.** Ketone *trans*-**36** (55 mg, 202 mmol) and 2-propanol (157 mg, 2.62 mmol, anhydrous) in toluene (2 mL, anhydrous) at reflux were treated with sodium (24.1 mg, 1.05 mmol) in five small portions, waiting for each portion to dissolve. After the last portion had reacted, TLC ($CH_3OH/CHCl_3$, 3/20, 1% NH_4OH) showed only two materials, R_f 0.52 and 0.35. The reaction mixture was cooled, mixed with benzene (10 mL), washed with H_2O (5 mL) and saturated NaCl (5 mL), dried, and evaporated to yield 55 mg of an oil. Preparative TLC (as above) returned 10 mg (18%) of **50** and 20 mg (36%) of **51** which was distilled: bp 125–130 °C (0.08 mm); NMR δ 7.4–6.9 (m, 3 H), 6.68 (dt, J = 2, 8 Hz, 1 H), 3.80 (s, 3 H), 3.5–3.7 (m, $W_{1/2}$ = 20 Hz, 1 H), 2.23 (s, 3 H); IR 3571, 3425, 1601, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 275 (100), 274 (62), 71 (72), 70 (96). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.1; H, 9.1; N, 5.1. Found: C, 74.0; H, 9.1; N, 5.1.

B. Sodium borohydride reduction of *trans*-**36** as per reduction of *cis*-**36** below gave **50/51** in a ratio of 70/30 by GC.

***cis*-6α-Hydroxy-4aα-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline (54) and *cis*-6β-Hydroxy-4aα-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline (53). A.** To ketone *cis*-**36** (27.3 mg, 0.1 mmol) in acetic acid (2 mL) was added PtO_2 (10 mg) and the mixture was hydrogenated at 60 psi H_2 for 3 h. Isolation as for **50** gave 28 mg of an oil shown by TLC (as above) to be two compounds (R_f of **53**, 0.49, and R_f of **54**, 0.42). NMR revealed that the **53/54** ratio was approximately 1/2 by inspection of the NCH_3 absorptions.

B. To ketone *cis*-**36** (100 mg, 0.364 mmol) in ethanol was added $NaBH_4$ (42 mg, 1.1 mmol) in three portions over a 1-h period. After a further 1 h at 25 °C the reaction mixture was poured into H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL), and the organic phase was washed with saturated NaCl (10 mL), dried, and evaporated to an oil. NMR showed a **53/54** ratio of 3/2. Preparative TLC returned **53** (45 mg, 45%) and **54** (35 mg, 35%) and distillation furnished analytical materials.

53: bp 130–135 °C (0.08 mm); NMR δ 7.4–6.9 (m, 3 H), 6.71 (dt, J = 2, 7 Hz, 1 H), 3.80 (s, 3 H), 4.3–3.2 (m, 1 H), 2.34 (s, 3 H); IR 3571, 3436, 1608, 1850 cm^{-1}; mass spectrum *m/e* (rel intensity) 275 (100), 274 (47), 71 (88), 70 (68). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.1; H, 9.1; N, 5.1. Found: C, 73.9; H, 9.1; N, 5.0.

54: mp 95–97 °C from benzene; bp 130–135 °C (0.08 mm); NMR δ 7.28 (t, J = 8 Hz, 1 H), 7.02 (m, 2 H), 6.75 (bd, J = 8 Hz, 1 H), 3.84 (s, 3 H), 4.3–3.2 (m, 1 H), 2.14 (s, 3 H); IR 3571, 3413, 1595, 1572 cm^{-1}; mass spectrum *m/e* (rel intensity) 275 (40), 274 (26), 71 (100), 70 (66). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.1; H, 9.1; N, 5.1. Found: C, 74.3; H, 9.1; N, 5.1.

Reduction of 41. $\Delta^{8(8a)}$-6-Hydroxy-4-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline. To ketone **41** (72 mg, 0.292 mmol) in ethanol (4 mL) at 0 °C was added $NaBH_4$ (63 mg, 1.6 mmol) in two portions at 15-min intervals. The solution was warmed to 25 °C and stirred for 60 min, poured into H_2O (30 mL), extracted with CH_2Cl_2 (3 × 20 mL), dried, and evaporated to yield an oil which was chromatographed (TLC grade SiO_2, $CHCl_3/CH_3OH$, 9/1, 0.5% NH_4OH) to give homogeneous material (TLC, GC) (34 mg, 47%): bp 130 °C (0.1 mm); NMR δ 7.28 (t, J = 7.5 Hz, 1 H), 6.82 (m, 3 H), 5.83 (m, 1 H), 4.2–3.4 (m, 1 H), 3.80 (s, 3 H), 2.13 (bs, 3 H); IR 3584, 2967, 2841, 2793, 1605, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 273 (100), 272 (25), 271 (26), 256 (22), 255 (23), 228 (29), 167 (36), 166 (84). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.7; H, 8.5; N, 5.1. Found: C, 74.6; H, 8.5; N, 5.0.

To the alcohol (27 mg, 0.1 mmol) in CH_3OH (2 mL) was added PtO_2 (10 mg) and the mixture shaken under 55 psi H_2 for 2 h. Filtration and evaporation gave 27 mg of a material which was two major components. Chromatography (as above) returned 10 mg of trans alcohol **50** and 5 mg of trans alcohol **51**.

***trans*-Δ⁷-6α- and -6β-Hydroxy-4aα-(3′-methoxyphenyl-2-methyloctahydroisoquinolines (7 and 52).** The trans ketone **40** (200 mg, 0.736 mmol) in THF (10 mL) was treated with 0.65 M AlH_3/THF (3.4 mL, 2.21 mmol) and then stirred for 30 min, all at 0 °C. THF/H_2O (1/1, 1.1 mL) was added followed by 3.3 N NaOH (3.0 mL) and ether (20 mL). The separated aqueous layer was washed with benzene (10 mL), and the combined organic phases were washed with saturated NaCl (10 mL), dried, and evaporated to give 185 mg of a colorless oil. Chromatography (TLC grade SiO_2, $CH_3OH/CHCl_3$, 9/1, 0.25–1% NH_4OH) returned first 112 mg (56%) of ***trans*-Δ⁷-6α-hydroxy-4aα-(3′-methoxyphenyl)-2-methyloctahydroisoquinoline (7)**: NMR δ 7.5–6.5 (m, 3 H), 6.72 (dt, J = 2, 7 Hz, 1 H), 5.85 (distorted dd, J = 11 Hz, 2 H), 4.2–4.0 (bs, $W_{1/2}$ = 11 Hz, 1 H), 3.78 (s, 3 H), 2.22 (s, 3 H); IR 3571, 2933, 2857, 2817, 1603, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 275 (95), 202 (98), 71 (100), 70 (60); bp 125 °C (0.1 mm). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.7; H, 8.5; N, 5.1. Found: C, 74.5; H, 8.4; N, 5.1.

Next eluted was 9 mg (4.5%) of ketone *trans*-**36** identified by spectral and chromatographic comparisons.

Lastly was obtained 62 mg (31%) of ***trans*-Δ⁷-6β-hydroxy-4aα-(3-methoxyphenyl)-2-methyloctahydroisoquinoline (52)**: NMR δ 7.4–6.6 (m, 4 H), 5.69 (dd, J = 10 Hz, 2 H), 3.9–3.4 (bs, 1 H), 3.78 (s, 3 H), 2.17 (s, 3 H); IR 3636, 1603, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 273 (55), 256 (18), 255 (21), 71 (100), 70 (37); bp 130 °C (0.1 mm). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.7; H, 8.5; N, 5.1. Found: C, 74.5; H, 8.4; N, 5.2.

Allylic alcohol **7**, when reduced as described for the α,β-unsaturated alcohol obtained from **41**, returned only **50**. Reduction of **52** in the same manner yielded **51**.

***trans*-Δ⁷-6α-Hydroxy-4aα-(3′-hydroxyphenyl)-2-methyloctahydroisoquinoline (6).** A solution of potassium thioethoxide/DMF was prepared as follows. To DMF (30 mL, degassed by freeze/thaw) was added potassium *tert*-butoxide (1.5 g, 13.4 mmol), and the suspension was degassed and flushed thoroughly with argon. Ethanethiol (1.22 mL, 1.64 mmol) was added and the butoxide dissolved leaving a clear, colorless solution. Ether **7** (40 mg, 0.15 mmol) in DMF (1 mL) was thoroughly degassed and placed under argon. The thioethoxide solution (1 mL, 0.44 mmol) was added, and the solution was heated at 150 °C for 10 h, cooled, poured into H_2O (20 mL), the pH adjusted to 14, and extracted with $CHCl_3$ (3 × 4 mL) after which the pH was lowered to 8 and the solution was extracted with 9/1 $CHCl_3$/2-propanol (4 × 4 mL). The combined organic phases were washed with saturated NaCl (10 mL), dried, and evaporated to a mixture of phenols (33 mg). Trituration of the residue with hot benzene and cooling returned 24 mg (60%) of pure **6** as an amorphous solid: NMR δ 7.3–6.5 (m, 4 H), 5.84 (distorted dd, J = 10 Hz, 2 H), 4.07 (m, 1 H), 2.29 (s, 3 H); IR 3550, 3247 (b), 1582 cm^{-1}; mass spectrum *m/e* (rel intensity) 259 (100), 258 (82), 188 (91), 71 (94), 70 (59). Sublimation gave mp 199–203 °C. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.1; H, 8.2; N, 5.4. Found: C, 73.8; H, 8.1; N, 5.4.

***cis*-Δ⁷-6α- and *cis*-Δ⁷-6β-Hydroxy-4aα-(3′-methoxyphenyl)-2-methyloctahydroisoquinolines (10 and 11).** The cis ketone **42** (171 mg, 0.63 mmol) in toluene (6.3 mL, 0 °C) was treated rapidly with diisobutylaluminum hydride (1.26 mmol, 2 M in hexane, 0 °C) and stirred for 30 min, and CH_3OH (0.25 mL) was added, followed by 2 N NaOH (10 mL) and benzene (10 mL). The separated aqueous layer was washed with benzene (10 mL), and the combined organic phases were dried and evaporated to yield 168 mg of a clear glass. Chromatography (TLC grade SiO_2, $CHCl_3/CH_3OH$, 9/1, 0.25% NH_4OH) returned in order of elution 4.2 mg (2.5%) of **42**, 17.2 mg (9%) of ketone *cis*-**36**, and 75.2 mg (44%) of ***cis*-Δ⁷-6α-hydroxy-4aα-(3′-methoxyphenyl)-2-methyloctahydroisoquinoline (10)**: NMR δ 7.30 (dd, J = 7, 9 Hz, 1 H), 6.97 (m, 2 H), 6.75 (bd, J = 8 Hz, 2 H), 5.84 (dd, J = 10 Hz, 2 H), 4.27 (t, 1 H), 3.82 (s, 3 H), 2.18 (s, 3 H); IR 3571, 2924, 2857, 2817, 1601, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 273 (39), 202 (53), 200 (21), 71 (100), 70 (40); mp 133–135 °C from benzene. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.7; H, 8.5; N, 5.1. Found: C, 74.6; H, 8.5; N, 5.1.

Eluted next was 21.6 mg (12.5%) of an intermediate fraction, then 19.3 mg (11%) of ***cis*-Δ⁷-6β-hydroxy-4aα-(3′-methoxyphenyl)-2-methyloctahydroisoquinoline (11)**: NMR δ 7.25 (t, J = 8 Hz, 1 H), 6.81 (m, 3 H), 5.85 (dd, J = 4, 9 Hz, 1 H), 5.57 (d, J = 9 Hz, 1 H), 3.82 (s, 3 H), 3.9–4.5 (m, 1 H), 2.32 (s, 3 H); IR 3570, 2933, 2849, 2807, 1601, 1582 cm^{-1}; mass spectrum *m/e* (rel intensity) 273 (27), 71 (100), 70 (45); bp 125–130 °C (0.1 mm). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.7;

H, 8.5; N, 5.1 Found: C, 74.5; H, 8.5; N, 5.0.

Reduction of **10** with $PtO_2/H_2/CH_3OH$ as for **7** gave only **54**. Reduction of **11** under these conditions afforded **53**.

Δ^7-8a-Hydroxy-4a-(3′-methoxyphenyl)-2-methyl-6-oxooctahydroisoquinolines (57 and 58). To the mixture of dienes **8** and **55** (85/15) (120 mg, 0.42 mmol) in acetic acid (3 mL) was added trifluoroacetic acid (60 mg, 0.53 mmol). *m*-Chloroperbenzoic acid (62 mg, 0.37 mmol) was added and the solution heated (95 °C) for 15 min, cooled, treated with additional peracid (41.2 mg, 0.24 mmol), and heated again (95 °C) for 20 min. The dark solution was cooled (5 °C), added to H_2O (10 mL), and basified (pH 12), then extracted with $CHCl_3$ (3 × 5 mL); the combined organic phases were dried and evaporated, affording 105 mg of an oil. Chromatography (TLC grade SiO_2, $CHCl_3/CH_3OH$, 9/1, 0.1% NH_4OH) gave three compounds. Eluted first was 52 mg (43%) of a Δ^7-8a-hydroxy ketone: NMR δ 7.20 (t, J = 8 Hz, 1 H), 6.95 (d, J = 10 Hz, 1 H), 6.9–6.8 (m, 3 H), 6.03 (d, J = 10 Hz, 1 H), 3.79 (s, 3 H), 2.29 (s, 3 H); IR 3356, 1675, 1603, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 287 (7), 259 (9), 71 (100), 70 (9). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.0; H, 7.4; N, 4.9. Found: C, 70.9; H, 7.3; N, 4.9.

Eluted next was 9 mg (7%) of the epimeric Δ^7-8a-hydroxy ketone: NMR δ 7.22 (t, J = 8 Hz, 1 H), 6.97 (d, J = 10 Hz, 1 H), 6.8–6.6 (m, 3 H), 6.15 (d, J = 10 Hz, 1 H), 3.79 (s, 3 H), 2.28 (s, 3 H); IR 3356, 1686, 1605, 1580 cm^{-1}. $C_{17}H_{21}NO_3$ requires 287.1521; found, 287.1514.

Obtained last was 19.5 mg (16%) of the *N*-oxide **59**: NMR δ 7.26 (t, J = 8 Hz, 1 H), 6.95 (d, J = 10 Hz, 1 H), 6.9–6.7 (m, 3 H), 5.82 (d, J = 10 Hz, 1 H), 3.77 (s, 3 H), 3.14 (s, 3 H); IR 3650, 3600–2300 (bs), 1678, 1605, 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 303 (0.36), 302 (0.36), 301 (0.64), 287 (17), 43 (100).

Diels–Alder Reactions of 8 with A. Ethyl Acrylate. The mixture of dienes **8** and **55** (85/15, 28.5 mg, 0.1 mmol) was dissolved in ethyl acrylate (5 mL) and heated at reflux for 15 h, cooled, evaporated, and chromatographed (SiO_2, $CHCl_3/CH_3OH$, 9/1, 0.1% NH_4OH). The recovered dienes (25 mg, 88%) were still present in a 85/15 ratio. From the reaction in a sealed tube at 170 °C, starting material was recovered in 40% yield after chromatography.

B. Methyl vinyl ketone (MVK), as in A, with MVK at reflux for 9 h returned starting material (64%).

C. Dimethyl Acetylenedicarboxylate (DMAD). The dienes (55 mg, 0.19 mmol) and DMAD (35 mg, 0.38 mmol) were dissolved in toluene (0.5 mL) and stirred for 9.5 h at 25 °C. The solution was evaporated and chromatographed twice (SiO_2, $CHCl_3/CH_3OH$, 9/1, 0.1% NH_4OH, then with $CHCl_3$) to return 33 mg (39%) of triene **63** [NMR revealed **63** to be a mixture of the fumarate (10–20%) and the maleate (80–90%) based on the multiplicity of the enamine proton, the *N*-methyl, and the *O*-methyl region]: NMR δ 7.79 (t, J = 8 Hz, 1 H), 6.85 (m, 3 H), 6.29 (d, J = 10 Hz, 1 H), 5.87 (broadened d, J = 10 Hz, 1 H), 5.64 (bs, 0.1 H), 5.31 (s, 0.9 H), 4.89 (s, 1 H), 4.70 (d, J = 8 Hz), and 4.49 (broadened d, J = 8 Hz), total of 2 H, 3.9–3.4 (complex, four large singlets at 3.92, 3.82, 3.65, 3.62 with two small singlets at 3.55 and 3.47, total 12 H), 3.4–2.9 (m, 2 H), 2.85 and 2.73 (singlets, ~4/1, total 3 H), 2.5–1.9 (m, 2 H); IR 1739, 1653, 1577 cm^{-1}; mass spectrum *m/e* (rel intensity) 427 (26), 426 (27), 368 (40), 269 (33), 254 (47), 228 (57), 227 (100), 226 (27), 225 (72). $C_{24}H_{29}NO_6$ requires 427.1995; found, 427.1991. UV (CH_3OH) λmax 274 nm (ϵ 20 800).

D. *N*-Phenylmaleimide. The dienes (37 mg, 0.135 mmol) and *N*-phenylmaleimide (25.6 mg, 0.148 mmol) in toluene were heated at 110 °C for 12 h and cooled and the solvent was evaporated. The NMR showed that little starting materials had been consumed and was nearly identical with an NMR of the starting mixture. The reaction mixture was again subjected to the same conditions and after 170 h neither starting material remained. Both NMR and TLC ($CHCl_3$ or $CHCl_3/CH_3OH$, 9/1, 0.1% NH_4OH) revealed several materials. Chromatography on SiO_2 gave no identifiable compounds.

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Registry No.—**6**, 61527-78-4; **7**, 61527-79-5; **8**, 61527-80-8; *trans*-**9**, 61527-81-9; *cis*-**9**, 61527-82-0; **10**, 61527-83-1; **11**, 61527-84-2; **19**, 33877-04-2; **20**, 61527-85-3; **21**, 61527-86-4; **22**, 61527-87-5; **23**, 61527-88-6; **24**, 61527-89-7; **25**, 61527-90-0; **26**, 61527-91-1; **27**, 61527-92-2; **28**, 61527-93-3; **29**, 61527-94-4; **30**, 61527-95-5; **31**, 61527-96-6; **32**, 61527-97-7; **33** isomer A, 61527-98-8; **33** isomer B, 61527-99-9; *trans*-**34**, 61528-00-5; *cis*-**34**, 61528-01-6; *trans*-**35**, 61528-02-7; *cis*-**35**, 61528-03-8; *trans*-**36**, 61528-04-9; *cis*-**36**, 61528-05-0; *trans*-**37a**, 51993-81-8; *cis*-**37a**, 59226-95-8; *trans*-**37b**, 51993-82-9; *cis*-**37b**, 59227-14-4; **38**, 61528-06-1; **39**, 61528-07-2; **40**, 61528-08-3; **40** methiodide, 61528-09-4; **41**, 61528-10-7; **42**, 61528-11-8; **44**, 61528-12-9; **45a**, 61528-13-0; **45b**, 61528-14-1; **46a**, 61528-15-2; **46b**, 61528-16-3; **47**, 61543-03-1; **48**, 61528-17-4; **49**, 61528-18-5; **49** methiodide, 61528-19-6; **50**, 61528-20-9; **51**, 61528-21-0; **52**, 61528-22-1; **53**, 61528-23-2; **54**, 61528-24-3; **55**, 61528-25-4; **57**, 61528-26-5; **58**, 61528-27-6; **59**, 61528-28-7; **63** isomer A, 61528-29-8; **63** isomer B, 61528-30-1; 3-methoxycinnamic acid, 6099-04-3; 1,3-dimethyl-4-(3′-methoxyphenyl)-2-pyridone, 61528-31-2; butyl hydrogen malonate, 5917-45-3; ethylene glycol, 107-21-1; $\Delta^{8(8a)}$-6-hydroxy-4-(3′-methoxyphenyl)-2-methyldecahydroisoquinoline, 61528-32-3.

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(29) All reactions were performed under a nitrogen atmosphere with magnetic stirring unless otherwise indicated and all solvents were dried over Na_2SO_4 prior to evaporation in vacuo using a Berkeley rotary evaporator. Melting points are corrected and distillation was bulb to bulb, Kugelrohr type. NMR spectra were determined in $CDCl_3$ solution with a Varian T-60 instrument using internal Me_4Si; IR spectra were recorded in $CHCl_3$ (except where noted) on a Perkin-Elmer 337 spectrophotometer; UV spectra were recorded on a Cary 14 instrument. CEC-103 and 110B mass spectrometers were used for determining mass spectra. GC refers to 5 ft, 3% OV-1 on 80/100 Chromosorb W (AW/DMCS). TLC and column chromatography were done on SiO_2 (silica gel 60, E. M. Reagents, 63–200 μ) and TLC grade SiO_2, D-5, Camag, 7–25 μ, without binder. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

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Photochemistry of Heterocyclic Compounds. 5.[1] Photochemical Reaction of 2,5-Diaryl-1,3,4-oxadiazoles with Indene

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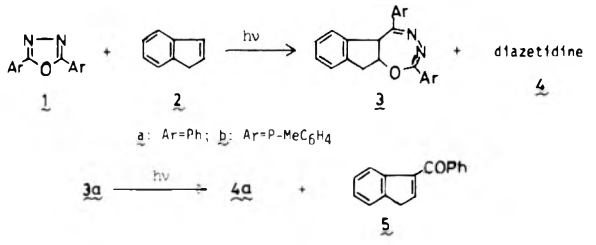
Photochemical reaction of 2,5-diaryl-1,3,4-oxadiazoles with indene has been investigated under various conditions. Irradiation of symmetrical 2,5-diaryl-1,3,4-oxadiazole with indene gives the oxadiazepine compound whose structure corresponds to a formal 1,2–1,5 cycloadduct, and/or the diazetidine compound, whose relative yields depended on the reaction conditions. In a similar photochemical reaction of 2-phenyl-5-*p*-tolyl-1,3,4-oxadiazole, a mixture of two isomeric oxadiazepines and three diazetidines is formed. Upon irradiation of 2,5-diphenyl-1,3,4-oxadiazole with indene in the presence of iodine, however, the [2 + 2] cycloadduct is obtained.

Although [2 + 2] photocycloadditions of olefins to other olefins[2] and to ketones[3] are well characterized, only a few examples of similar photocycloadditions to the carbon–nitrogen double bonds appeared in the literature.[4-7] In a preliminary communication[8] we reported some novel photoproducts from the photochemical reaction of 2,5-diphenyl-1,3,4-oxadiazole (**1a**) with indene (**2**) in the absence or presence of iodine. However, there remained some uncertainty as to the structures of products and the pathways. To resolve these problems, further investigations were undertaken. We now report here on these reactions in some detail.

Results and Discussion

In the Absence of Iodine. Irradiation of a solution of **1a** and **2** in benzene for 1 h afforded the 1:1 adduct **3a** in 31% yield, together with small quantities of the diazetidine compound **4a**, 3-benzoylindene (**5**), and benzonitrile. The yield

Scheme I



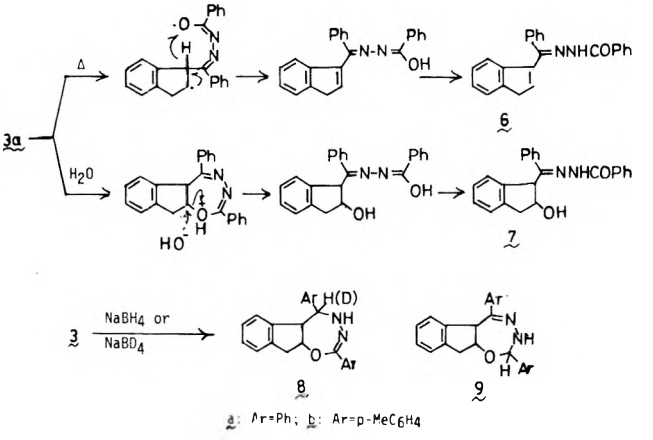
of **3a** decreased with increased irradiation time. The results under various conditions are summarized in Table I. Upon irradiation in benzene for 2 h, **3a** was converted to **4a** and **5** in 9 and 4% yields, respectively, accompanied with tarry materials. Thus, it is concluded that the primary photoproduct in this reaction is **3a**.

In the photochemical reaction of 2,5-di-*p*-tolyl-1,3,4-oxadiazole (**1b**) with **2** in diethyl ether for 1 h, the 1:1 adduct **3b** was obtained in 40% yield, along with a trace of the diazetidine compound **4b**.

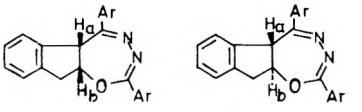
On the basis of spectral data and chemical transformations, **3a** and **3b** were assigned to be the corresponding 2,5-diaryl-5a,10a-dihydroindeno[3,2-*f*]-1,3,4-oxadiazepine whose structure corresponds to a formal 1,2–1,5 cycloadduct. The stereochemistry of **3** will be described later.

When heated in xylene under reflux, **3a** readily isomerized to 3-benzoylindene benzoylhydrazone (**6**). On treatment with water in boiling carbon tetrachloride **3a** was converted into *cis*-1-benzoyl-2-hydroxyindan benzoylhydrazone (**7**). Reduction of **3a** with sodium borohydride afforded the dihydro compound whose structure was assigned to 2,5-diphenyl-4,5,5a,10a-tetrahydroindeno[3,2-*f*]-1,3,4-oxadiazepine (**8a**), but not the 2,3,5a,10a-tetrahydro compound **9** on the basis of its spectral data. The NMR spectrum of **8a** exhibits three methine proton signals at δ 4.07 (dd), 5.23 (m), and 5.84 (d, J = 7.2 Hz), besides methylene, aromatic, and NH proton signals. When the doublet at δ 5.84 or the multiplet at δ 5.23 is irradiated, the double doublet at δ 4.07 changes to a doublet with J = 7.5 or 7.2 Hz, respectively. In addition, the doublet at δ 5.84 does not appear in the spectrum of **8a**-d_1 which was prepared by reduction of **3a** with sodium borohydride-d_4. Similarly, reduction of **3b** gave the corresponding tetrahydro compound **8b** (Scheme II).

Scheme II



Two configurations, cis-fused and trans-fused adducts, are possible for the structure of **3**. However, the spectral data do not permit a clear assignment as to which configurations would be more reasonable for **3**. Here we assumed that the



3 (cis) **3** (trans)

moiety ArC=NN=COAr in the seven-membered cyclic ring of **3** is coplanar. An inspection of the Dreiding models indicates that the dihedral angle θ between H_a and H_b is ca. 40–45° in the cis-fused adduct, whereas it is ca. 150–155° in the trans-fused adduct. The calculated J_{ab} values are 4–4.7 and 6.8–7.5 Hz when θ is 40–45 and 150–155°, respectively. The observed J_{ab} value (3.8 Hz) in **3b** is compatible with the calculated value (4 Hz) when θ is 45°.[9] Thus the cis-fused adduct appears to be a more reasonable structure than the trans-fused adduct.

Structural elucidation of the diazetidine compound **4** was accomplished on the basis of spectral data and chemical transformation. The NMR spectrum of **4a** exhibits signals at δ 3.2–4.1 (m, 5 H, 2 CH_2 and >CH), 4.57 (m, 1 H, >CH), 5.82 and 6.41 (each d, 1 H, >CH), besides aromatic protons (18 H).

Table I. Photochemical Reaction of 1a and 2 under Various Conditions[a]

Solvent	Irradn time, h	Products, % 3a	4a	5	C_6H_5CN
Benzene	1	31	1	5	3
Benzene	4	21	2	3	2
Benzene	8	Trace	4	3	2
Benzene[b]	12		5		
Et_2O	1	46	1	4	2
Et_2O	4	27	2	2	1
Et_2O	8	16	2	2	1
n-Hexane	1	31	1	5	3
Dioxane	1	30	1	2	1
Tetrahydrofuran	1	40	1	4	2
CH_3CN	1	54	1	1	2

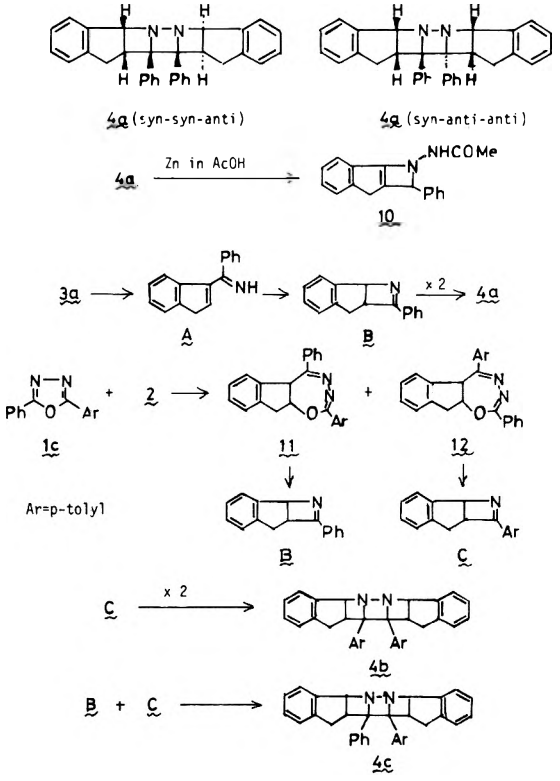
[a] A solution of **1a** and **2** (molar ratio 1:4) in the solvent was irradiated below 20 °C, in a nitrogen atmosphere. **1a** was recovered in 10–30% yield in each run. [b] Irradiated at room temperature.

The mass spectrum shows the parent ion (M^+) at *m/e* 438 and fragment ions at *m/e* 436 ($M^+ - H_2$), 408 ($436^+ - N_2$), and 219 ($M^+/2$). Reduction of **4a** with zinc dust in boiling acetic acid afforded the indenoazetine derivative **10.**

Six configurations, syn-syn-syn, anti-syn-anti, syn-anti-syn, syn-syn-anti, syn-anti-anti, and anti-anti-anti forms, are conceivable for the structure of **4a.** On the basis of NMR spectral data and of inspection of the Dreiding models, the structure of **4a** is assumed to be either syn-syn-anti or syn-anti-anti form.[10]

As mentioned above, photolysis of **3a** afforded **4a** and 3-benzoylindene (**5**). Although the exact pathway for the formation of **4a** from **3a** is not clear, it might be viewed as proceeding via initial formation of imine A from **3a** with loss of benzonitrile oxide or phenyl isocyanate.[11] This is followed by cyclization with the concurrent rearrangement to form azetine B, and subsequent dimerization of B gives **4a** (Scheme III).

Scheme III

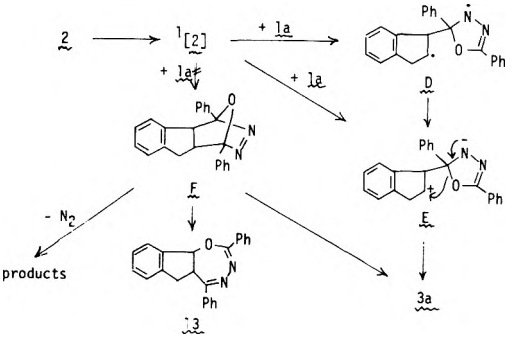


The process of the formation of B from **3a** seems to be somewhat analogous to that of photoisomerization of indoxazene to benzoxazole via a benzoisonitrile intermediate.[12] The formation of **4a** via dimerization of azetine B seems to be supported by the following result. The photochemical reaction of 2-phenyl-5-*p*-tolyl-1,3,4-oxadiazole (**1c**) with **2** afforded a mixture of two isomeric oxadiazepines, **11** and **12,** and three diazetidines, **4a, 4b,** and **4c.** As shown in Scheme III, diazetidines, **4a–c,** may be interpreted as arising via dimerization or coupling of azetines B and C which formed from **11** and **12,** respectively. Irradiation of **2** with benzonitrile did not give **4a.** In the photochemical reaction of **1a** and **2** in the presence of *p*-tolunitrile, no diazetidines, **4b** and **4c,** were formed. Thus, interaction between **2** and benzonitrile can be excluded from the pathway for the formation of **4a.**

The electronic absorption spectrum of **1a** shows strong absorption bands in the region of about 300–320 nm, while that of **2** displays no appreciable absorption above 310 nm.[13] In contrast to irradiations with light from a high-pressure mercury lamp under various conditions (Table I), irradiation of an ether solution of **1a** and **2** with monochromatic light (313 nm) for 20 h did not give **3a.** Even if irradiation of a solution of **1a** and **2** in diethyl ether with light from a high-pressure mercury lamp was performed under air for 1 h, **3a** was obtained in 27% yield; a lowering of the yield would be attributable to polymerization of **2** by oxygen.

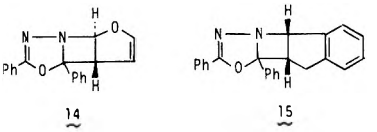
Although mechanistic considerations are still speculative, a possible pathway for the formation of **3a** is outlined in Scheme IV on the basis of above observations. The reaction

Scheme IV



starts with a singlet excited state of **2,** and the subsequent interaction with **1a** forms either diradical D or betaine E. Ring opening of E with concurrent ring closure gives **3a.** Another pathway through [2 + 4] cycloadduct F would be excluded from the possible one, since compounds such as isomeric oxadiazepine **13** and products derived from F with loss of nitrogen were not detected in the reaction mixture. In view of the exclusive cis addition, an exciplex might be involved in the reaction. However, no charge-transfer band was observed on mixing **1a** and **2.**

In the Presence of Iodine. With or without benzophenone as a sensitizer, irradiation of **1a** with furan in benzene gives the trans [2 + 2] cycloadduct **14,** whereas in the presence of



iodine 3-benzoylfuran benzoylhydrazone is formed.[4] In order to compare with the above reaction, the photochemical reaction of **1a** with **2** in the presence of iodine was investigated. The results are shown in Table II. As shown in Table II, irradiation in the presence of iodine (5 mol % to **1a**) afforded **4a** and the cis [2 + 2] cycloadduct **15,** whereas in the presence of

Table II. Photochemical Reaction of 1a with 2 in the Presence of Iodine[a]

Solvent	I_2, mol % to 1a	Irradn time, h	Product, % 4a	15
Benzene	5	12	9	4
Benzene	20	12	0	10
Et_2O	20	10	0	9

[a] A solution of **1a** and **2** (molar ratio 1:4) in the solvent was irradiated under nitrogen.

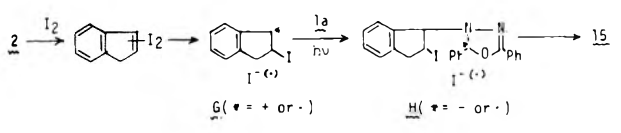
20 mol % iodine **15** was only obtained. The structure of **15** was confirmed on the basis of spectral data.

The electronic spectrum of a mixture of **1a** and iodine does not show any other absorption bands than those of **1a** and iodine. Upon irradiation of **1a** in the presence of iodine, however, a complex with iodine was obtained, which on treatment with $Na_2S_2O_3$ gave **1a** quantitatively.

Although the electronic spectrum of a mixture of **2** and iodine shows no other absorption bands than individual absorption bands of **2** and iodine, the NMR spectrum in $CDCl_3$ or C_6D_6 changes with time. After 12 h olefinic proton signals of **2** (δ 6.25 and 6.7) disappear, and new broad signals show up at δ 2–4; **2** on treatment with $Na_2S_2O_3$ afforded a white, polymeric powder of **2**. This fact indicates that iodine interacts with the olefinic bond of **2** to form a σ complex via a π complex in a similar manner as the iodine-induced isomerization of olefins.[14] After a solution of **2** and iodine (5 mol % to 2) in benzene was allowed to stand for 12 h (that is, the formation of σ complex), **1a** was added to the solution. Then the resulting solution was irradiated to give **15** in 2% yield.

The exact pathway for the formation of **15** is not clear, but we tentatively propose the pathway depicted in Scheme V.

Scheme V



Photochemical reaction of **1a** with the complex G forms the intermediate H, which undergoes ring closure with loss of iodine to yield the [2 + 2] cycloadduct **15**.

Experimental Section

Melting points are uncorrected. The IR spectra were taken with a Jasco Model IRA-1 grating infrared spectrophotometer. The NMR spectra were recorded at 60 MHz on a Hitachi R-20 spectrometer with tetramethylsilane as an internal standard and the chemical shifts are expressed in δ values. The UV spectra were taken with a Hitachi 124 spectrometer. The mass spectra were obtained on a Hitachi RMS-4 mass spectrometer with a direct inlet and an ionization energy of 70 eV. Unless otherwise stated, irradiations were performed with Pyrex-filtered light from a 300-W high-pressure mercury lamp (Taika HLV-B) below 20 °C, in a nitrogen atmosphere. Irradiation with monochromatic light (313 nm) was performed with a 100-W high-pressure mercury lamp (Riko UVL-100P) utilizing the potassium biphthalate aqueous solution[15] as a filter.

Photochemical Reaction of 2,5-Diphenyl-1,3,4-oxadiazole (1a) with Indene (2). A solution of 1.11 g (5×10^{-3} mol) of **1a** and 2.32 g (2×10^{-2} mol) of **2** in 250 mL of benzene was irradiated below 20 °C for 1 h. The solvent from the mixture was removed in vacuo to afford a residue, which was triturated with 20 mL of diethyl ether giving crystals. Filtration gave 0.53 g (31%) of oxadiazepine **3a**, which was subjected to microanalysis without further purification. The ether filtrate was evaporated in vacuo, and the residue was chromatographed on alumina using benzene and then benzene–chloroform (1:1) as eluents. From the benzene elution 1.41 g (61%) of **2**, 30 mg (3%) of benzonitrile, 9 mg (1%) of diazetidine **4a**, and 55 mg (5%) of 3-benzoylindene (**5**) were obtained, and the benzene–chloroform elution gave 0.22 g (20%) of **1a**.

3a: pale yellow needles, mp 181 °C dec; IR (KBr) 1605, 1570 cm^{-1}; mass spectrum *m/e* 338 (M^+, rel intensity 4), 233 ($M^+ - PhCO$, 41), 115 ($[2 - H]^+$, 100), 105 ($PhCO^+$, 43), 77 (31). Anal. Calcd for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.28. Found: C, 81.88; H, 5.05; N, 8.10.

4a: yellow needles, mp 284–285 °C; NMR (CF_3COOH) δ 3.2–4.1 (m, 5 H), 4.57 (m, 1 H), 5.82, 6.41 (each d, 1 H, J = 7.5 Hz), 7–8 (m, 18 H); UV max (EtOH) 246 nm (log ϵ 3.68 sh), 435 (3.73); mass spectrum *m/e* 438 (M^+, rel intensity 28), 436 ($M^+ - H_2$, 11), 408 ($436^+ - N_2$, 2), 331 ($408^+ - Ph$, 56), 230 (20), 219 ($M^+/2$, 25), 202 (19), 115 (57), 103 ($PhCN^+$, 100), 77 (56). Anal. Calcd for $C_{32}H_{26}N_2$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.62; H, 5.67; N, 6.41.

5: yellow oil; IR (neat) 1630 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.86 (d, 2 H, CH_2, J = 2.5 Hz), 6.7–8.2 (m, 10 H, =CH and aromatic protons); mass spectrum *m/e* 220 (M^+, rel intensity 12), 115 (55), 105 (89), 77 (100).

Similar photochemical reactions were carried out under various conditions, and the results are given in Table I.

Photochemical Reaction of 2,5-Di-*p*-tolyl-1,3,4-oxadiazole (1b) with 2. A solution of 1.25 g (5×10^{-3} mol) of **1b** and 2.32 g (2×10^{-2} mol) of **2** in 250 mL of diethyl ether was irradiated below 20 °C for 1 h, during which time there was precipitation of oxadiazepine **3b**. Filtration and recrystallization from benzene afforded 0.73 g (40%) of **3b**, mp 135–137 °C dec, as pale yellow needles. The ether filtrate was evaporated in vacuo, and the residue was chromatographed on alumina in a similar manner as above, giving 10 mg (1%) of diazetidine **4b**, mp 267–268 °C dec, as yellow needles, together with 0.42 g (33%) of **1b** and 1.12 g (48%) of **2**.

3b: IR (KBr) 1605, 1595, 1560 cm^{-1}; NMR (benzene-d_6) δ 2.0, 2.16 (each s, 3 H), 2.8–3.9 (pair of dd, 2 H, CH_2, J = 18, 8, and 2.5 Hz, changed to a double doublet when irradiated at δ 6.36), 4.12 (d, 1 H, >CH, J = 3.8 Hz, changed to a singlet when irradiated at δ 6.36), 6.36 (m, 1 H, >CH), 6.7–8.8 (m, 12 H, aromatic protons); mass spectrum *m/e* 366 (M^+, rel intensity 14), 247 ($M^+ - MeC_6H_4CO$, 8), 119 ($MeC_6H_4CO^+$, 100), 115 (8), 91 ($MeC_6H_4^+$, 53). Anal. Calcd for $C_{25}H_{22}N_2O$: C, 81.94; H, 6.05; N, 7.65. Found: C, 81.65; H, 6.24; N, 7.56.

4b: IR (KBr) 1570 cm^{-1}; NMR ($CDCl_3$) δ 2.49, 2.56 (each s, 3 H, CH_3), 2.85–4.0 (m, 5 H, 2 CH_2 and >CH), 5.35 (m, 2 H, 2 >CH), 6.13 (d, 1 H, >CH, J = 7 Hz), 6.7–8.1 (m, 16 H, aromatic protons); mass spectrum *m/e* 466 (M^+, rel intensity 9), 465 (38), 464 ($M^+ - H_2$, 100), 438 ($M^+ - N_2$, trace), 436 ($464^+ - N_2$, trace), 373 ($464^+ - MeC_6H_4$, 2), 233 ($M^+/2$, 10), 232 (23), 231 (23), 202 (14), 117 ($MeC_6H_4CN^+$, 3), 115 (39), 91 ($MeC_6H_4^+$, 7). Anal. Calcd for $C_{34}H_{30}N_2$: C, 87.51; H, 6.48; N, 6.00. Found: C, 87.48; H, 6.29; N, 6.16.

Photolysis of Oxadiazepine 3a. A suspension of 0.75 g of **3a** in 250 mL of benzene was irradiated below 20 °C for 2 h, during which time the reaction mixture changed to a solution. The solvent from the mixture was removed in vacuo, and the residue was chromatographed on alumina using benzene as an eluent to give 45 mg (9%) of **4a** and 20 mg (4%) of **5**, along with tarry materials.

Isomerization of Oxadiazepine 3a. A solution of 0.1 g of **3a** in 20 mL of xylene was refluxed for 30 min. The solvent from the mixture was removed in vacuo, and the residue was triturated with small amounts of diethyl ether to give pink crystals. Recrystallization from ethanol afforded 95 mg (95%) of 3-benzoylindene benzoylhydrazone (**6**), mp 184–185 °C dec, as pink needles: IR (KBr) 3360 (NH), 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.43 (d, 2 H, CH_2, J = 2.5 Hz), 6.32 (t, 1 H, =CH, J = 2.5 Hz), 7.2–8.0 (m, 14 H, aromatic protons), 8.1 (br, 1 H, NH); mass spectrum *m/e* 338 (M^+, rel intensity 28), 233 ($M^+ - PhCO$, 33), 223 ($M^+ - C_9H_7$, 9), 217 ($M^+ - PhCONH_2$, 20), 203 (13), 115 (13), 105 (100), 77 (90). Anal. Calcd for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.28. Found: C, 81.52; H, 5.34; N, 8.32.

***cis*-1-Benzoyl-2-hydroxyindan Benzoylhydrazone (7).** A solution of 0.2 g of **3a** in 20 mL of carbon tetrachloride was refluxed with 0.1 mL of water for 20 min. The reaction mixture was evaporated in vacuo to leave a residue, which was triturated with small amounts of diethyl ether to give crystals. Recrystallization from ethanol afforded 165 mg (78%) of **7**, mp 127–128 °C, as colorless prisms: IR (KBr) 3310 (NH), 3260 (OH), 1670 cm^{-1} (C=O); NMR (CCl_4) δ 2.9–3.5 (m, 2 H, CH_2), 4.25 (m, 1 H, >CH), 5.09 (d, 1 H, >CH, J = 8.4 Hz), 5.2 (br, 1 H, OH), 7.0–8.0 (m, 14 H, aromatic protons), 8.2 (br, 1 H, NH); mass spectrum *m/e* 356 (M^+, rel intensity trace), 338 ($M^+ - H_2O$, trace), 236 ($M^+ - PhCONH$, trace), 220 ($M^+ - PhCONHNH_2$, 19), 191 ($220^+ - CHO$, 3), 136 ($PhCONHNH_2^+$, 10), 115 (45), 105 (100), 77 (97). Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.50; H, 5.66; N, 7.86. Found: C, 77.66; H, 5.74; N, 7.88.

Reduction of Oxadiazepine 3a with Sodium Borohydride. A suspension of 0.2 g of **3a** in 50 mL of methanol was stirred with 0.1 g of sodium borohydride at room temperature for 2 h. The reaction

mixture was poured into 100 mL of water giving 0.2 g (ca. 100%) of crystals. Recrystallization from methanol afforded dihydro compound **8a**, mp 184–185 °C, as colorless needles: IR (KBr) 3240 (NH), 1640 cm^{-1} (C=N); NMR ($CDCl_3$) δ 2.85–3.4 (m, 2 H, CH_2), 4.07 (dd, 1 H, >CH), 5.23 (m, 1 H, >CH), 5.84 (d, 1 H, >CH, J = 7.2 Hz), 6.5–7.7 (m, 14 H, aromatic protons), 7.95 (br, 1 H, NH); mass spectrum m/e 340 (M^+, rel intensity 5), 249 ($M^+ - PhCH_2$, 10), 235 ($M^+ - PhCO$, 4), 225 ($M^+ - C_9H_7$, 36), 220 ($M^+ - PhCON$, 6), 205 ($220^+ - NH$), 147 ($PhCONHN^+{\equiv}CH$, 36), 128 ($205^+ - Ph$, 6), 121 ($PhCONH_2^+$, 44), 116 ($C_9H_8^+$, 81), 115 (27), 105 (100), 91 (32), 77 (52). Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 81.00; H, 5.86; N, 8.17.

Similarly, reduction of **3a** with sodium borohydride-d_4 in methanol-d_1 and recrystallization of the product from methanol afforded dihydro compound **8a**-d_1, mp 186–187 °C, as colorless needles in quantitative yield. Anal. Calcd for $C_{23}H_{19}DN_2O$: C, 80.91; H, 6.20; N, 8.21. Found C, 80.79; H, 5.85; N, 8.22.

In a similar reduction of oxadiazepine **3b** with sodium borohydride as above, dihydro compound **8b**, mp 203–204 °C, as colorless needles was obtained quantitatively: IR (KBr) 3250 (NH), 1640 cm^{-1} (C=N); NMR ($CDCl_3$) δ 2.25, 2.35 (each s, 3 H, CH_3), 2.7–3.4 (m, 2 H, CH_2), 4.10 (dd, 1 H, >CH, J = 6.8 and 7.5 Hz), 5.30 (m, 1 H, >CH), 5.87 (d, 1 H, >CH, J = 7.5 Hz), 6.3–7.7 (m, 13 H, NH and aromatic protons). Anal. Calcd for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57; N, 7.60. Found: C, 81.44; H, 6.54; N, 7.61.

2*H*-1-Acetamido-2-phenylazeto[3,4-*b*]indene (10). A solution of 0.2 g of diazetidine **4a** in 15 mL of acetic acid was refluxed with 2.0 g of zinc dust for 10 h. The reaction mixture was filtered, and the filtrate was poured into 200 mL of water, which was extracted with 250 mL of diethyl ether. The ether extract was evaporated in vacuo to leave crystals which on recrystallization from methanol afforded the azetine **10**, mp 216–217 °C, as colorless needles: IR (KBr) 3280 (NH), 1655 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.35 (s, 3 H, $COCH_3$), 4.57 (m, 2 H, CH_2), 5.17 (m, 1 H, >CH), 7.0–8.0 (m, 10 H, NH and aromatic protons); UV max (EtOH) 260 nm (log ε 3.44), 267 (3.61), 274 (3.74), 288 (3.84); mass spectrum m/e 276 (M^+, rel intensity 99), 234 ($M^+ - CH_2{=}C{=}O$, 100) 233 ($M^+ - COMe$, 53), 219 ($M^+ - MeCON$, 31), 161 ($PhC{\equiv}N^+NHCOMe$, 5), 130 (35), 118 ($161^+ - COMe$, 22), 116 (19), 115 (20), 203 (10), 77 (23).

Photochemical Reaction of 2-Phenyl-5-*p*-tolyl-1,3,4-oxadiazole (1c) with 2. A solution of 1.18 g (5×10^{-3} mol) of **1c** and 2.32 g (2×10^{-2} mol) of **2** in 250 mL of diethyl ether was irradiated below 20 °C for 1 h. Filtration gave 0.47 g (27%) of a mixture of oxadiazepines, **11** and **12**, as pale yellow needles: IR (KBr) 1605, 1570 cm^{-1}. The ether filtrate was evaporated in vacuo, and chromatographic separation afforded 5 mg of a mixture of diazetidines, together with 0.35 g (30%) of **1c** and 1.0 g (45%) of **2**. The IR spectrum of the mixture of diazetidines was very similar to those of diazetidines **4a** and **4b**, and its mass spectrum showed parent ions at m/e 466 (**4b**$^+$), 452 (**4c**$^+$), and 448 (**4a**$^+$).

Reduction of 0.2 g of the mixture of **11** and **12** with 0.1 g of sodium borohydride in 50 mL of methanol afforded 0.2 g of colorless crystals: mp 176–183 °C; IR (KBr) 3240 (NH), 1640 cm^{-1} (C=N); NMR ($CDCl_3$) δ 2.24, 2.30 (each s, 1.5 H, CH_3), 2.7–3.4 (m, 2 H, CH_2), 4.06 (dd, 1 H, >CH), 5.25 (m, 1 H, >CH), 5.84 (d, 1 H, >CH), 6.3–8.0 (m, 14 H, NH and aromatic protons). Thus it is clear that the initial mixture consists of equimolar amounts of **11** and **12**.

Photochemical Reaction of 1a with 2 in the Presence of Iodine. A solution of 1.7 g (7.7×10^{-3} mol) of **1a**, 3.6 g (3.1×10^{-2} mol) of **2**, and 0.1 g (3.9×10^{-4} mol) of iodine in 500 mL of benzene was irradiated for 12 h. The solvent from the mixture was removed in vacuo, and chromatographic separation of the residue on alumina using benzene as an eluent afforded 180 mg (9%) of diazetidine **4a** and 90 mg (4%) of [2 + 2] cycloadduct **15**.

15: colorless prisms, mp 196.5–197 °C; IR (KBr) 1630 cm^{-1} (C=N); UV max ($CHCl_3$) 260 nm (log ε 3.36), 268 (3.45), 274 (3.53), 306 (3.83); NMR ($CDCl_3$) δ 3.45 (m, 2 H, CH_2), 4.45 (m, 1 H, >CH), 6.45 (d, 1 H, >CH, J = 10.8 Hz), 7.0–8.1 (m, 14 H, aromatic protons); mass spectrum m/e 338 (M^+, rel intensity 100), 235 ($M^+ - PhCN$, 30), 222 ($M^+ - C_9H_8$, 6), 205 ($235^+ - NO$, 8), 194 ($222^+ - N_2$, 2), 128 ($205^+ - Ph$, 13), 119 ($222^+ - PhCN$, 2), 115 (12), 105 (97), 77 (100). Anal. Calcd for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.28. Found: C, 81.81; H, 5.11; N, 8.11.

The results under other reaction conditions are given in Table II.

Registry No.—**1a**, 725-12-2; **1b**, 2491-91-0; **1c**, 1874-47-1; **2**, 95-13-6; **3a**, 61528-63-0; **3b**, 61528-64-1; **4a**, 19921-15-4; **4b**, 61528-65-2; **5**, 61528-66-3; **6**, 59106-02-4; **7**, 61528-67-4; **8a**, 61528-68-5; **8a**-d_1, 61528-69-6; **8b**, 61528-70-9; **10**, 61528-71-0; **11**, 61528-72-1; **12**, 61528-73-2; **15**, 19921-16-5; B, 61528-74-3; C, 61528-75-4.

References and Notes

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(10) The Dreiding model for syn-syn-syn form cannot be framed owing to significant steric hindrance. On the basis of inspection of the Dreiding models for anti-syn-anti, syn-anti-syn, and anti-anti-anti forms, the hydrogens at 5a and 5d positions, and the hydrogens at 11a and 13a positions might be anticipated to display the same NMR chemical shifts, respectively.
(11) Neither benzonitrile oxide nor phenyl isocyanate could be detected in the reaction mixture.
(12) J. P. Ferris, F. R. Antonucci, and R. W. Trimmer, *J. Am. Chem. Soc.*, **95**, 919 (1973).
(13) The UV spectra of **1a** and **2** are as follows. **1a:** UV max (Et_2O) 285 nm (log ε 4.41), 302 (4.32), 315 (3.99); max (C_6H_6) ca. 290 nm (4.36), 304 (4.28), 320 (3.84). **2:** UV max (Et_2O) 256 nm (log ε 3.94), 288 (2.76), 296 (2.44); max (C_6H_6) ca. 290 nm (2.84), 298 (2.34).
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Chemistry of Heterocyclic Compounds. 23. Synthesis of Multiheteromacrocycles Possessing 2,6-Pyridino Subunits Connected by Carbon–Oxygen Linkages[1]

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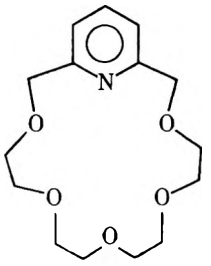
Treatment of 2-bromopyridine with diethylene glycol dianion afforded the diether **6** and triether **7** as well as traces of 2-(2-pyridyloxy)ethanol (**8**) and 2,2′-(ethylenedioxy)dipyridine (**9**). Similar products were isolated from 2-bromopyridine with ethylene glycol dianion. 2,6-Dibromopyridine (**10a**) with diethylene glycol dianion and excess sodium hydride generated the heteromacrocyclic ethers **11**, **12**, and **13** along with various expected intermediates. 2,6-Dibromopyridine (**10a**) with tri-, tetra-, penta-, and hexaethylene glycol dianions afforded the analogous 2:2 macrocyclic ethers along with the novel 1:1 macrocycles; **10b** with ethylene glycol dianion gave macrocycle **38**, which was subjected to variable temperature NMR analysis. The first (±)-oxamuscopyridine (**26**) was synthesized and characterized.

Synthetic procedures for the construction of macrocycles possessing subheterocyclic units have been known for about a century; however, it has only been within the past few years that these compounds have been shown to possess unique chemical and biochemical properties.[2] Of the 2,6-carbon–oxygen bridged pyridino macrocycles, presently the majority possess bridging oxygen atoms that are isolated from the pyridine nucleus by one[3] (e.g., **1**) or more[4] methylene groups.



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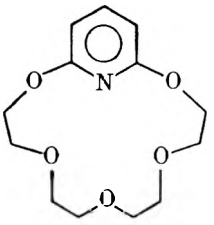
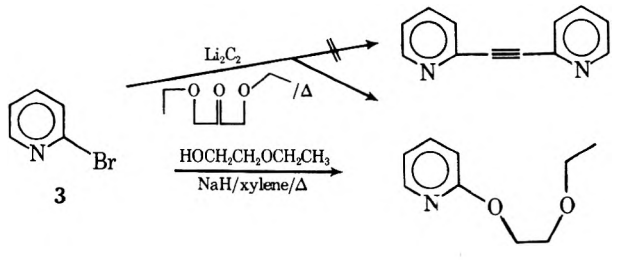


2

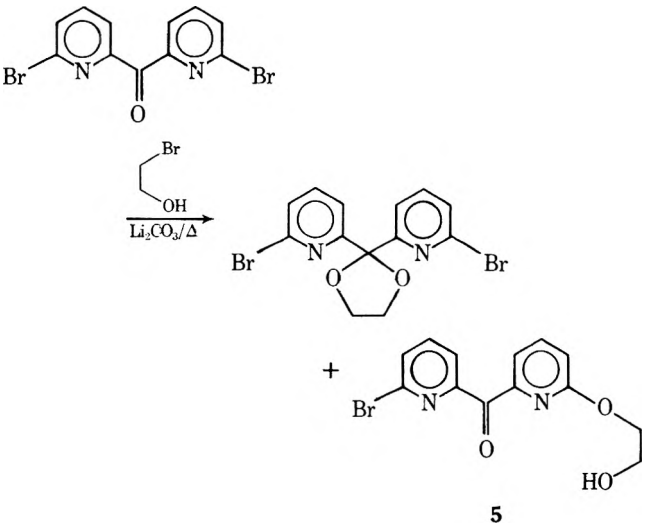
We herein describe the preparation and characterization of a second type of carbon–oxygen bridged 2,6-pyridino macrocycle in which the bridging oxygens are directly attached to the pyridine ring (e.g., **2**).

Preliminary Observations. In our quest for a simple synthesis of di(2-pyridyl)acetylene,[5] we attempted the reaction of 2-bromopyridine (**3**) with lithium carbide in bis(2-ethoxyethyl) ether at elevated temperatures; however, the major isolated product was not the desired acetylene but rather 2-pyridyl 2-ethoxyethyl ether (**4**), which resulted from direct nucleophilic substitution of halide by an alkoxide solvent fragment. In order to establish the structure of **4**, the reaction of 2-bromopyridine with sodium 2-ethoxyethoxide, generated from 2-ethoxyethanol and sodium hydride, in bis(2-ethoxyethyl) ether gave **4** in 50% yield. A similar nucleophilic



3 **4**

displacement occurred during the base-catalyzed ketalization of bis(6-bromo-2-pyridyl) ketone,[6] in which **5** was isolated as

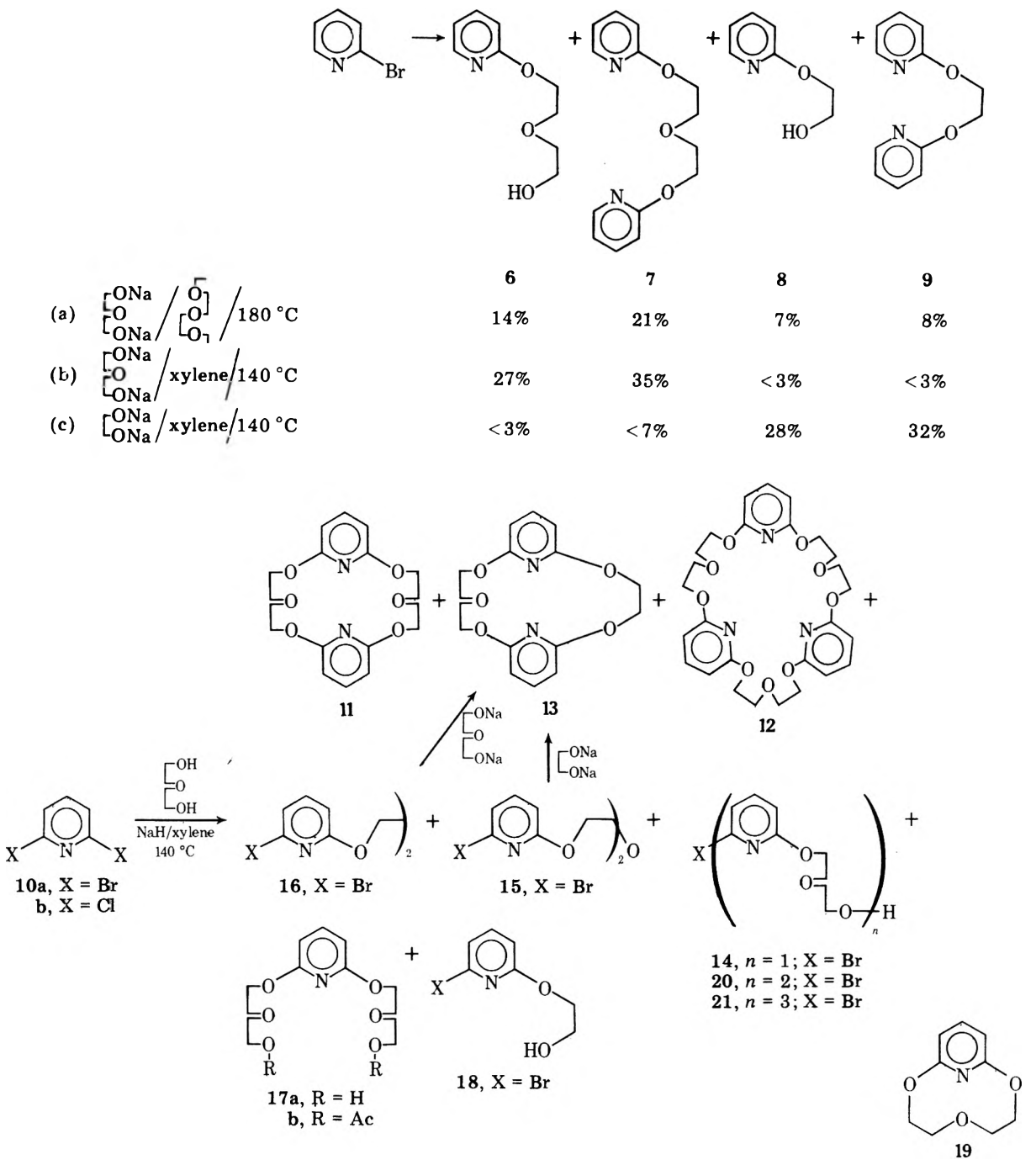


5

a trace (<5%) side product. Successful application of this substitution procedure has been demonstrated for the conversion of 2-halopyridines into 2-pyridones.[7]

In order to ascertain the generality of this reaction to the construction of macrocycles, 2-bromopyridine was treated with diethylene glycol dianion in bis(2-ethoxyethyl) ether at 160–180 °C affording the expected ethereal products **6** and **7**, along with lesser amounts of fragmentation products **8** and **9**. In order to reduce the formation of fragmentation-derived products, the reaction temperature was reduced; thus, refluxing xylene (bp 140 °C) was selected as the solvent medium to both maintain the desired temperature range and eliminate solvent-derived reactions. Reaction of 2-bromopyridine with ethylene glycol dianion at 140 °C afforded the expected products **8** and **9** as well as traces of both **6** and **7** which arose via oligomerization of ethylene glycol. Although thermal fragmentation and oligomerization of (poly)ethylene glycol(s) are well documented,[8] these side reactions are minimized when the reaction temperatures are maintained within the 135–145 °C range. Further reduction in reaction temperature caused prolonged, unreasonable reaction times.

Macrocycle Synthesis. A. Diethylene Glycol. The reaction of 2,6-dibromopyridine (**10a**) with diethylene glycol dianion afforded the 2:2 and 3:3 macrocycles (**11** and **12**, respectively) along with numerous noncyclized products. The smallest 1:1 macrocycle, **19**, which would possess a ten-membered ring, was not detected; this was probably due to the difficulty in formation of this strained carbon–oxygen bridge. Similarly, when methyl *m*-benzenedialkanoates were



subjected to the Dieckmann condensation in order to form oxometacyclophanes, the inability to generate a ten-membered ring and reluctance in the formation of the 12-membered cyclophane were indicative of the nonbonded interactions which either retard or reduce the desired nucleophilic cyclization.[9] It should be noted that 2,6-[*n*]pyridinophanes, where *n* is less than 10, can be synthesized if (a) 2,6-dihalopyridine is subjected to more reactive nucleophiles,[4] (b) different routes were used in ring formation,[10] or (c) the bridge possesses sulfur atoms.[11] A novel, unsymmetrical macrocycle **13** was isolated and then independently synthesized by treatment of **16** with diethylene glycol dianion; the attempted cyclization of **15** with ethylene glycol failed to generate **13**.

Treatment of **10b** with diethylene glycol dianion in refluxing xylene afforded a similar distribution of products. The 1:1 uncyclized intermediate **14** was cyclized under the standard reaction conditions to afford (42%) the 2:2 macrocycle **11** along with traces (<1%) of **12** and **13** as well as their immediate precursors **20** and **21**, respectively. High-dilution techniques[12] were utilized in an attempt to increase the yield of cyclized products; however, no drastic increase in macrocyclic products (**11**–**13**) was realized.

The structures of these macrocycles were easily confirmed by ^{1}H NMR spectroscopy. Since the macrocycles are generally (or nearly so) symmetrical, the 3,5-pyridyl hydrogens show up as a doublet at δ 6.2–6.3 and the 4-pyridyl hydrogen as a triplet at δ 7.4–7.5, whereas in the noncyclized products, the 3- and 5-pyridyl hydrogens appear as doublet of doublets (J = 8 and ca. 2 Hz) with different ($\Delta^{3,5}$ 0.3 ppm) chemical shifts. The type of macrocyclic bridges can also be easily ascertained by NMR in that with an even number of $-CH_2CH_2O-$ units per bridge, the methylene hydrogens appear as triplets [α: δ 4.4–4.7; β: δ 3.8–3.9; γ–δ: δ 3.6–3.7 (J = 6 Hz)], whereas with an odd number of $-CH_2CH_2O-$ units, the *middle* methylene groups appear as a singlet [α: δ 4.6–4.7; γ: δ 3.6–3.7; ϵ: δ 3.5–3.6].

B. Triethylene Glycol. When 2,6-dibromopyridine was subjected to the disodium salt of triethylene glycol in refluxing

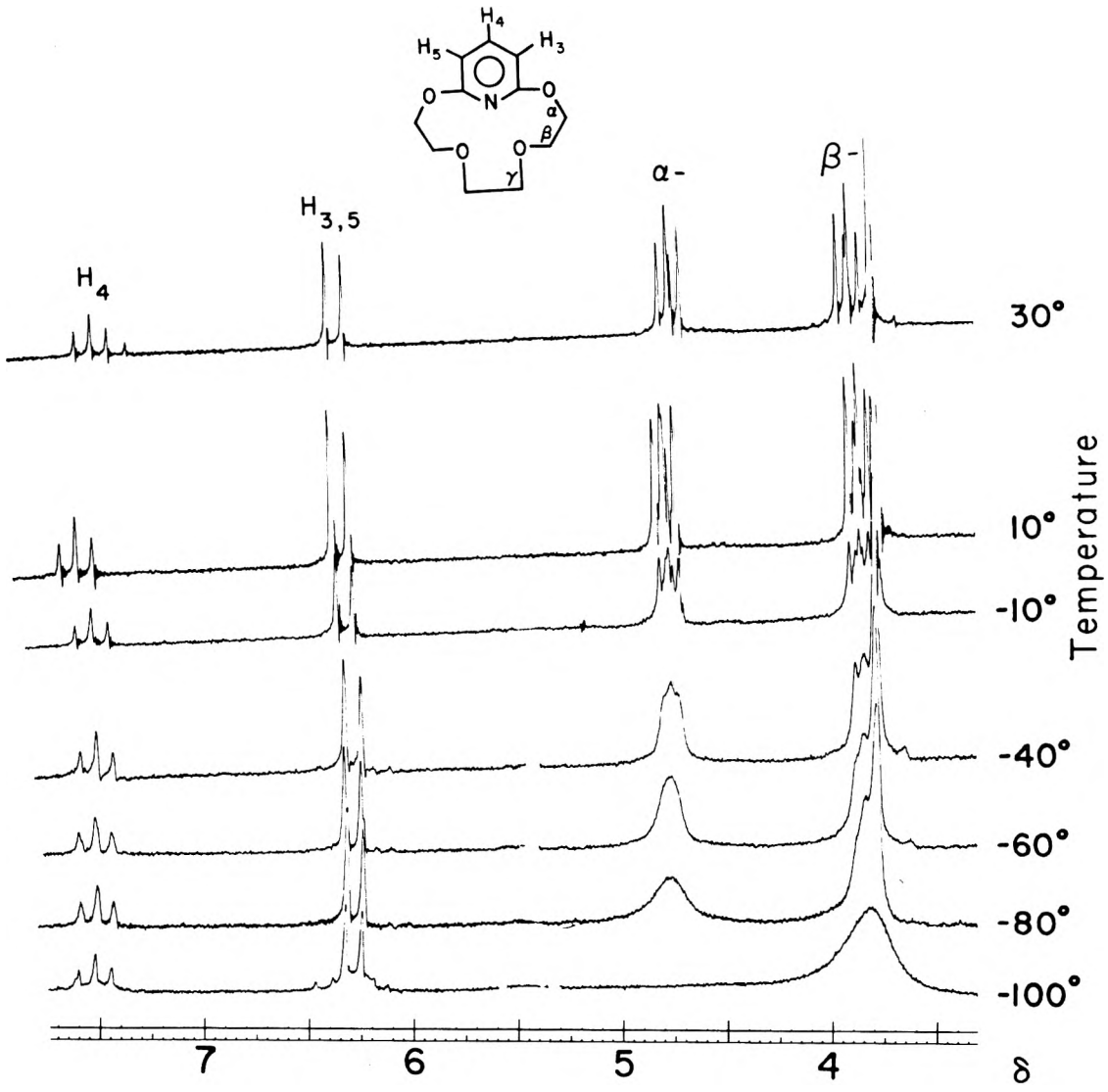
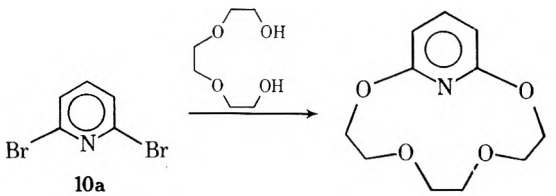


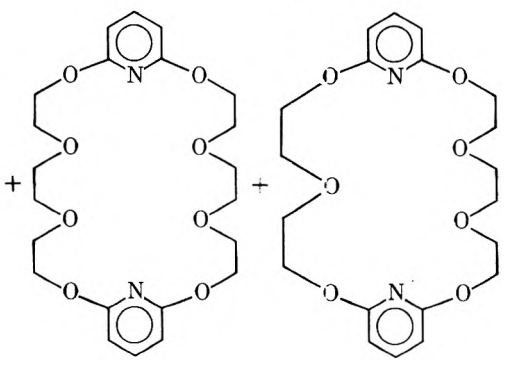
Figure 1. Variable temperature ^1H NMR spectral data for **22** in D_2CCl_2 below 10 °C and $DCCl_3$ at 30 °C.

xylene, only the two expected macrocyclic products **22** and **23** were isolated in low yields. The unsymmetrical macrocycle **24**, analogous to **13**, was not detected. The uncyclized intermediates were also not isolated, although they could be easily obtained, if desired.



10a

22



23 **24**

The NMR spectrum of **22** is shown in Figure 1. The apparent doublet of doublets at δ 4.68 and 3.84 due to the α- and β-methylenic hydrogens, respectively, remains virtually unchanged over elevated temperatures (<160 °C). These signals each become more complicated at −10 °C, then eventually disappear at ca. −100 °C (in CD_2Cl_2), whereupon the γ hydrogens simply broaden over this lower temperature range. The dynamic change is indicative of a conformational equilibrium of two enantiomeric conformers which are gradually frozen at lower temperatures. The energy barrier ($\Delta G_c^{\ddagger}$) for this conformational equilibrium was estimated to be ca. < 8 kcal/mol at an approximate coalescence temperature of −100 °C. This $\Delta G_c^{\ddagger}$ value for **22** is slightly lower than those of [7](2,6)pyridinophane ($\Delta G_c^{\ddagger}$ 9.0 kcal/mol, T_c −75.5 °C),[10] 2,6-dithia[7](2,6)pyridinophane ($\Delta G_c^{\ddagger}$ < 10.2 kcal/mol, T_c < −60 °C),[13] and [7]metacyclophane ($\Delta G^{\ddagger}$ 11.5 kcal/mol, T_c −27.6 °C).[14] The greater flexibility in **22** can be ascribed to a combination of larger carbon–oxygen bridge, and the removal of numerous methylene–methylene interactions, while these changes will be countered by the four diminished C–O–C bond angles.

Recently, the one-step construction of racemic muscopyridine (**25**) has been accomplished (20%) via cyclocoupling the di-Grignard of 2-methyl-1,10-dibromodecane with 2,6-di-

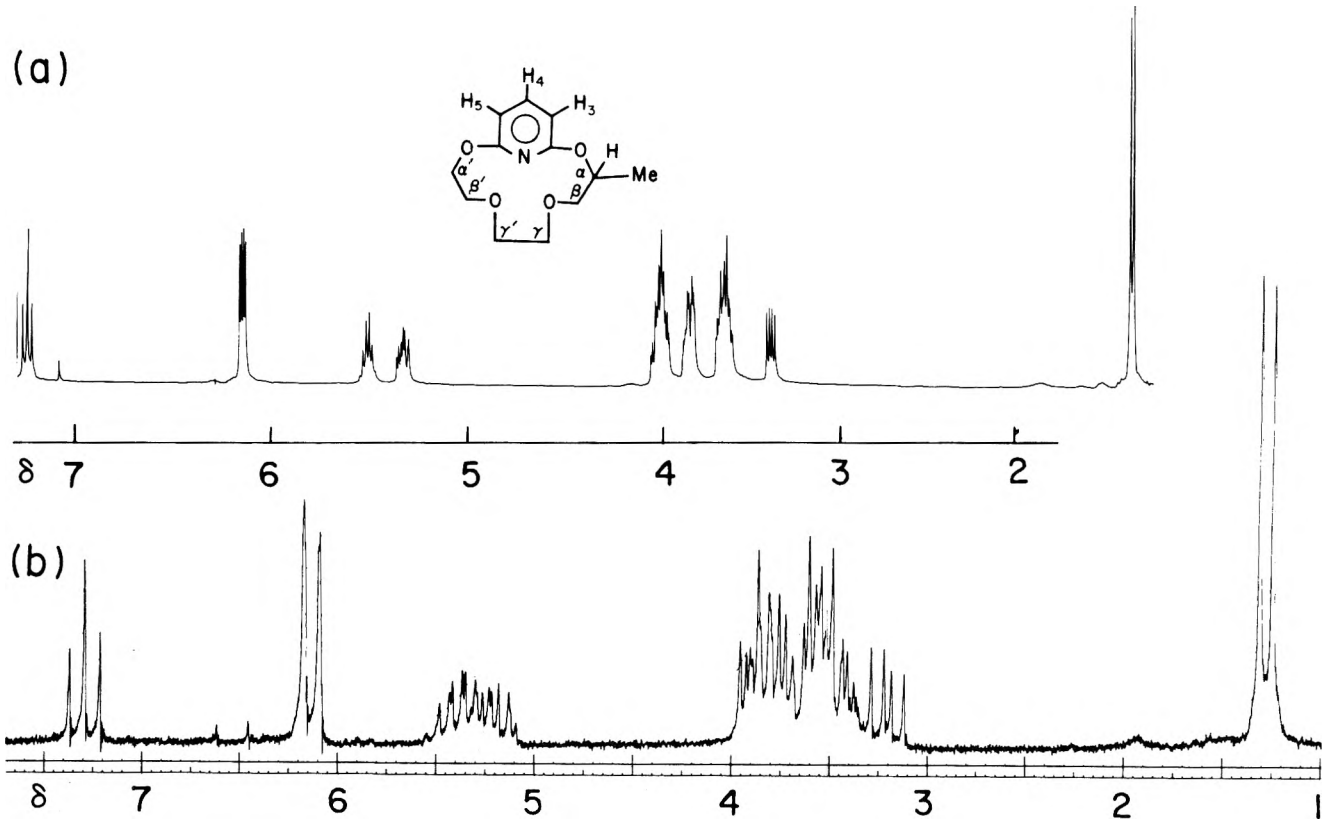
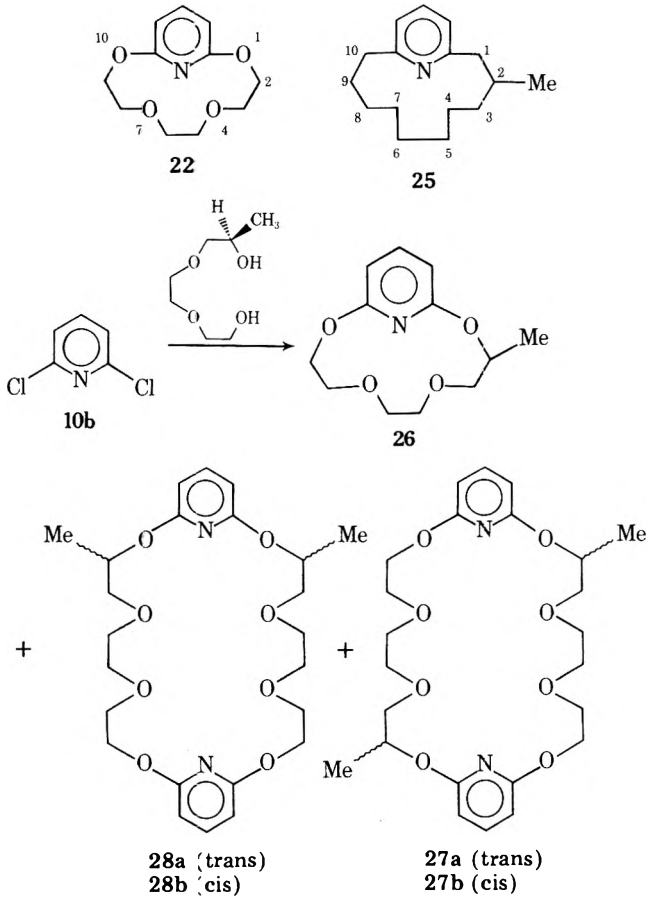


Figure 2. NMR spectra of tetraoxamuscopyridine (**26**) at 360 MHz (a) and 100 MHz (b) in $CDCl_3$.

chloropyridine in the presence of a catalytic amount of a nickel–phosphine complex.[4] Since no oxamuscopyridines have yet been reported, 2,6-dichloropyridine (**10b**) was treated with the disodium salt of 1-methyl-3,6-dioxa-1,8-octanediol, prepared from diethylene glycol and propylene oxide by standard procedures,[15] to afford the desired 1,4,7,10-tetraoxamuscopyridine (**26**) along with three isomeric 2:2 macrocycles. The major dimer has been tentatively assigned to either **27a** or **27b**, on the basis that it would be formed by dimerization of the 1:1 uncyclized intermediate leading to **26**. Other oily dimers, isolated in low yields, were not characterized further.



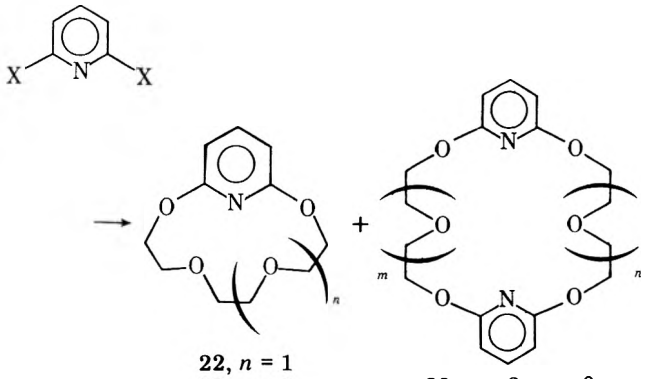
The NMR spectrum of **26** is shown in Figure 2. The increased complexity exhibited in Figure 2 is caused by (a) the diastereotopic nature of the methylene groups as a result of the α-chiral center, and (b) a possible preferred conformation as a result of a pseudoequatorial disposed methyl group. The spectral data remain virtually unchanged at elevated temperatures (~160 °C) and, as expected upon cooling to −100 °C, the attempted coalescence of the unique methylene hydrogens causes a complex broadening of the spectrum. The multiplet at δ 5.50 is assigned to the single α hydrogen and upon its irradiation the pattern at δ 3.35 collapses to a doublet and the complex pattern at δ 4.01 is simplified. The multiplet at δ 5.32 as assigned to one α' hydrogen, whereas, the second α hydrogen is located within the δ 4.01 multiplet. Inspection of molecular models of **26** indicates that one α hydrogen is forced close to the pyridine π cloud in the preferred conformation in which the α-methyl group is free of steric effects. Table I shows the hydrogen assignments for **26** as well as the average values for each methylene position based on both decoupling data and variable temperature NMR studies; the average values for **26** correspond quite well to the chemical shift data for **22**.

C. Tetra-, Penta-, and Hexaethylene Glycols. Commercially available tetraethylene glycol was treated with sodium hydride in anhydrous xylene at room temperature, followed by addition of 2,6-dibromo- (or chloro-) pyridine, and refluxed for 24 h. After standard workup, the major isolated macrocycle was **29** and **22** was realized in a lesser amount. The 2:2 symmetrical macrocycle **31** as well as unsymmetrical **30**

Table I

Bridged hydrogen chemical shifts (δ) of **26**						Av chem shifts for **26**	Chem shifts of **22**
5.50 (1 H)	5.32 (1 H)	4.01 (3 H)	3.76 (2 H)	3.58 (3 H)	3.35 (1 H)		
α-H						5.50	
	α′-Ha	α′-Hb				4.67	4.68
		β-Ha			β-Hb	3.68	
		β′-Ha	β′-Hb			3.88	3.84
			1γ-H	3γ-H		3.6 (3)	3.72

were isolated in 5 and <1% yields, respectively. High-dilution conditions increased the formation of **29** whereas the general percentages of **22**, **30**, and **31** remained approximately the same. Alternate bases (KH, CaH_2, LiH) were used in the tetraethylene glycol case but had little or no effect on the product distribution.



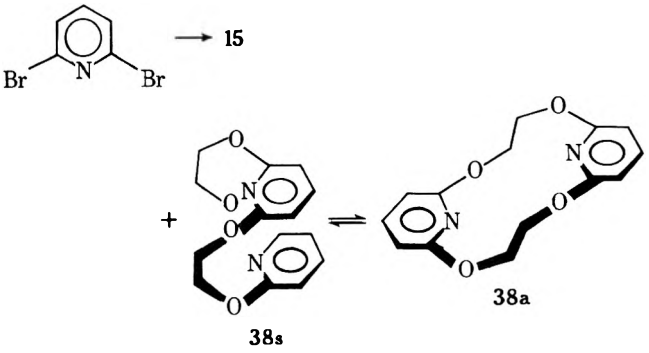
22, n = 1
29, n = 2
32, n = 3
35, n = 4

30, n = 2; m = 3
31, n = m = 3
33, n = 3; m = 4
34, n = m = 4
36, n = 4; m = 5
37, n = m = 5

Pentaethylene glycol was prepared according to the procedure of Perry and Hibbert[16] from 1,8-dichloro-3,6-dioxaoctane and ethylene glycol. 2,6-Dibromopyridine was reacted with the disodium salt of pentaethylene glycol to afford traces of the crystalline **29** and, as the major product, the viscous, colorless, oily 1:1 macrocycle **32**. Although the unsymmetrical 2:2 macrocycle **33** was not detected, the 2:2 symmetrical **34** was isolated as a crystalline solid.

Hexaethylene glycol, prepared in a similar manner,[16] was converted smoothly to the disodium salt and reacted with 2,6-dibromopyridine. Both 1:1 fragmented products **29** and **32** were isolated in ca. 3% yield. Macrocycle **35** was isolated in an astonishing 48% yield as a colorless, viscous oil. 2:2 macrocycles **34** and **36** were both isolated in 4% yield; however, the 2:2 unsymmetrical **37** was not isolated.

D. Ethylene Glycol. Reaction of 2,6-dibromopyridine with sodium glycolate in xylene or bis(2-ethoxyethyl) ether afforded (16%) macrocycle **38** along with the uncyclized intermediate **18**. A pure sample of **38** was isolated as the fastest moving component from the chromatography (ThLC) of the reaction mixture. Structure **38** was confirmed by NMR which showed a triplet at δ 7.50 for the 4-pyridyl hydrogen, a doublet at δ 6.30 for the 3,5-pyridyl hydrogens, and a broad singlet at δ 4.66 for the bridging methylenes. The variable temperature NMR spectrum (Figure 3) of **38** at 100 MHz exhibits a sharpening of the singlet at δ 4.66 at elevated temperatures, while at 15 °C coalescence of this singlet occurred and at −50 °C two complex multiplets (δ 3.57 and 4.94) were resolved. Similarly, the doublet for the 3,5-pyridyl hydrogens was transformed to two resolved doublets at −50 °C. Based on these data, the syn–anti isomer interconversion (**38s** ⇄ **38a**) was calculated to be $\Delta G_c^{\ddagger}$ = 13.5 ± 0.3 kcal/mol. This value is in accord with related flipping of syn and anti conformers.[17,19]



38s **38a**

Further work is in progress on the application of this procedure to other heterocyclic systems as well as complexation studies of these and related multiheteromacrocycles.

Experimental Section

General Comments. All melting points were taken in capillary tubes with a Thomas-Hoover Uni-Melt and are uncorrected. Infrared and ultraviolet spectra were recorded in Beckman IR-7 and Cary 14 spectrophotometers, respectively. Unless otherwise noted, ^{1}H NMR spectra were in deuteriochloroform solutions with Me_4Si as internal standard (δ 0 ppm) and recorded on either Varian A-60A or HA-100 spectrometers. Molecular weights were determined with a Hewlett-Packard 302 vapor pressure osmometer.

The recorded R_f values were determined by a standardized thin layer chromatography (TLC) procedure: 0.025 mm Brinkmann silica gel HF eluting with cyclohexane–ethyl acetate (4:1). For preparative ThLC 2-mm silica gel PF-254–366 plates were used, eluting with the stipulated solvent. Elemental analyses were performed either by Mr. R. Seab in these laboratories or by Galbraith Laboratories, Knoxville, Tenn.

All reaction solvents were distilled from lithium aluminum hydride under nitrogen. Sodium hydride (57% oil dispersion) was first washed with petroleum ether (bp 30–60 °C), then dried in vacuo prior to the reaction.

Reaction of 2-Bromopyridine with Lithium Carbide in Bis(2-ethoxyethyl) Ether. A mixture of 2-bromopyridine (10 g, 63.5 mmol) and lithium carbide (powdered, 80%, 3 g) in 50 mL of bis(2-ethoxyethyl) ether was refluxed for 24 h under nitrogen. The solvent was removed in vacuo, then the excess and unreacted lithium carbide was carefully decomposed with ice water. The suspension was extracted with ether, dried over anhydrous magnesium sulfate, and concentrated. After removal of unreacted 2-bromopyridine and solvent, the viscous residue was vacuum distilled affording a colorless oil, 4 g, bp 80–100 °C (2 mm), that was identified as 2-pyridyl 2-ethoxyethyl ether (**4**): R_f 0.36; bp 80–85 °C (2 mm); NMR δ 1.12 (t, $-CH_2CH_3$, J = 7 Hz, 3 H), 3.48 (q, CH_2CH_3, J = 7 Hz, 2 H), 3.75 (t, OCH_2CH_2OEt, J = 5 Hz, 2 H), 4.5 (t, Pyr-OCH_2, J = 5 Hz, 2 H), 6.6–6.9 (m, 3,5-Pyr-H, 2 H), 7.3–7.65 (m, 4-Pyr-H, 1 H), 8.05–8.3 (m, 6-Pyr-H, 1 H). Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84, N, 8.38. Found: C, 64.39; H, 7.92; N, 8.41.

2-Pyridyl 2-ethoxyethyl ether (**4**) was independently prepared (50%) by reaction of 2-bromopyridine (10 g, 63.5 mmol), sodium hydride (4.0 g, 30 mmol), and 2-ethoxyethanol (40 mL) utilizing the same reaction and workup procedures.

Reaction of 2-Bromopyridine with Ethylene Glycol. To a suspension of sodium hydride (4.0 g, 80 mmol) in anhydrous xylene (150 mL), ethylene glycol (2.5 g, 40 mmol) was added dropwise under

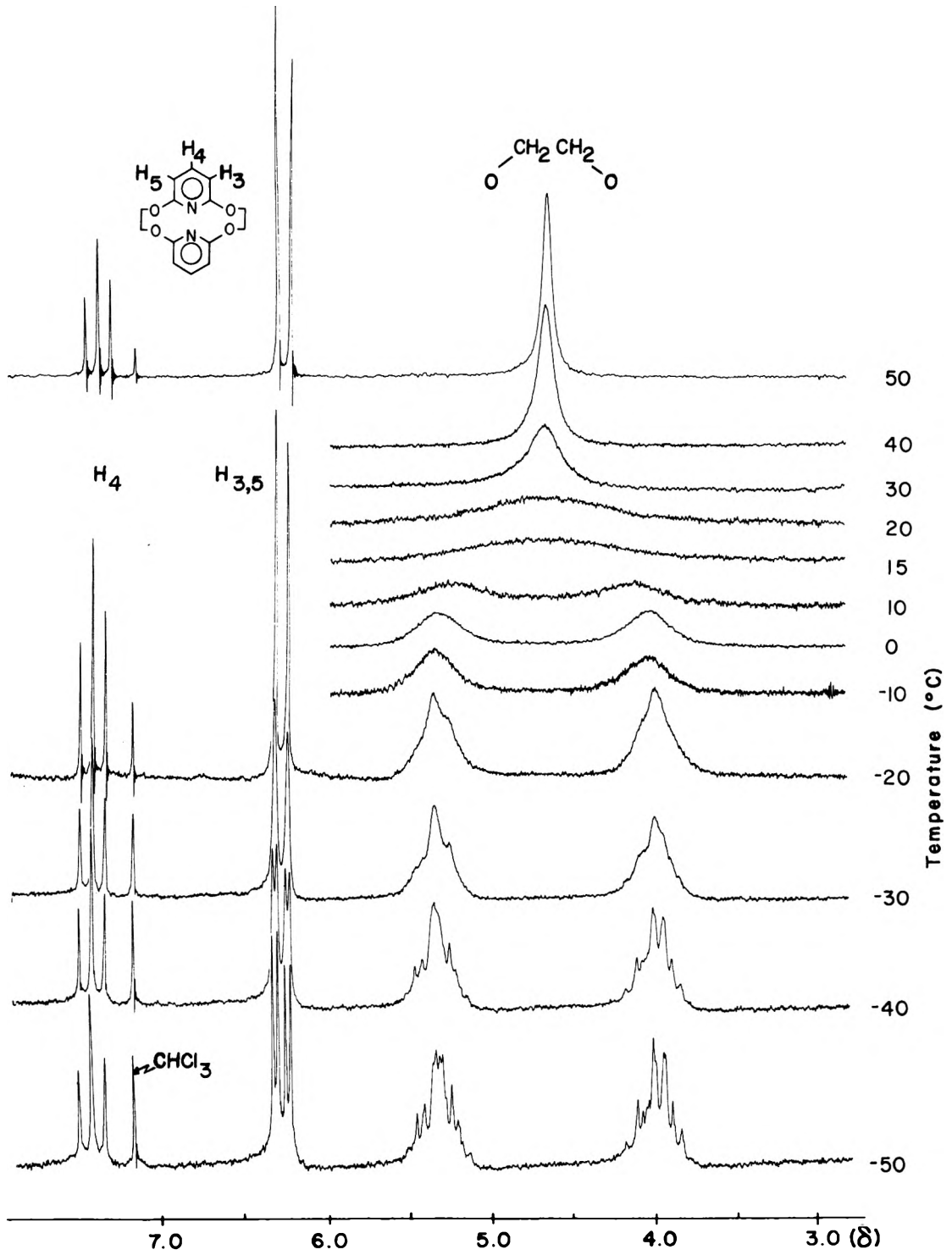


Figure 3. Variable temperature ^1H NMR spectral data for 38 in $DCCl_3$.

nitrogen. The mixture was stirred for 30 min, then 2-bromopyridine (12.6 g, 80 mmol) in 20 mL of xylene was added. After the mixture was refluxed for 24 h, the solvent and unreacted starting materials were removed in vacuo. The residue was carefully treated with crushed ice, extracted with dichloromethane, and concentrated, and an aliquot was subjected to thick layer chromatography eluting three times with cyclohexane–ethyl acetate (10:1). Four major fractions, other than unreacted 2-bromopyridine, were eluted and characterized.

2-(Pyridyloxy)ethanol (8): bp 60 °C (0.15 mm); 28%; R_f 0.06; NMR δ 3.90 (m, β-CH_2O, 2 H), 4.40 (m, α-CH_2O, 2 H), 6.79 (m, 3,5-Pyr-H, 1 H), 7.52 (dcd, 4-Pyr-H, J = 8, 8, 2 Hz), 8.07 (bd, 6-Pyr-H, 1 H); IR (neat) 3470 (broad, –OH), 1579, 1572, 1479, 1438, 1291, 1049, 781 cm^{-1}. Anal. Calcd for $C_7H_9NO_2$: C, 60.41; H, 6.52; N, 10.07. Found: C, 60.28; H, 6.42; N, 10.16.

2,2′-(Ethylenedioxy)dipyridine (9): mp 66.5–68 °C (petroleum ether, bp 60–80 °C); 32%; R_f 0.31; NMR δ 4.70 (s, $-CH_2-$, 4 H), 6.75 (m, 3,5-Pyr-H, 4 H), 7.45 (ddd, 4-Pyr-H, J = 8, 8, 2 Hz, 2 H), 8.15 (bd, 6-Pyr-H, J = 8 Hz, 2 H); IR (KBr) 1611, 1596, 1573, 1479, 1430, 1298, 1249, 1147, 1058, 990 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.43; H, 5.59; N, 13.11.

2-[2-(2-Pyridyloxy)ethoxy]ethanol (6): bp 75 °C (0.5 mm, short path); <2%; R_f 0.04; NMR δ 3.50 (bs, –OH; exchanged with D_2O, 1 H), 3.80 (m, β-CH_2O–, 6 H), 4.47 (m, α-CH_2O, 2 H), 6.77 (m, 3,5-Pyr-H, 2 H), 7.54 (ddd, 4-Pyr-H, J = 8, 8, 2 Hz, 1 H), 8.10 (bd, 6-Pyr-H, J = 8 Hz, 1 H); IR (neat) 3440 (broad, –OH), 1599, 1479, 1436, 1291, 1134, 1053, 785 cm^{-1}. Anal. Calcd for $C_9H_{13}NO_3$: C, 58.97; H, 7.15; N, 7.65. Found: C, 58.84; H, 7.20; N, 7.62.

2,2′-[Oxybis(ethyleneoxy)]dipyridine (7): mp 38–40 °C [recrystallized from petroleum ether (bp 60–80 °C), sublimed 90 °C (0.5 mm)]; <5%; R_f 0.20; NMR δ 3.90 (t, β-CH_2O, J = 6 Hz, 4 H), 4.50 (t, α-CH_2O, J = 6 Hz, 4 H), 6.80 (m, 3,5-Pyr-H, 4 H), 7.52 (m, 4-Pyr-H, J = 8, 8 Hz, 2 H), 8.13 (bd, 6-Pyr-H, J = 6 Hz, 2 H); IR (KBr) 1599,

1480, 1437, 1280, 1057, 785 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.33; H, 6.24; N, 10.84. Found: C, 64.24; H, 6.47; N, 10.75.

Reaction of 2-Bromopyridine with Diethylene Glycol. To a suspension of sodium hydride (2 g, 40 mmol) in bis(2-ethoxyethyl) ether [BEE, 150 mL, bp 84 °C (22 mm)], diethylene glycol (2.12 g, 20 mmol) was slowly added. The mixture was stirred for 30 min, then 2-bromopyridine (3.16 g, 20 mmol) was added. The reaction mixture was maintained at 140–150 °C for 24 h and worked up as previously described. The major products were 2-[2-(2-pyridyloxy)ethoxy]-ethanol [27%, bp 75–77 °C (0.5 mm, short path)], 2,2′-[oxybis(ethyleneoxy)]dipyridine [35%, mp 38–40 °C (sublimed)], and traces (<3%) of both 2-(pyridyloxy)ethanol and 2,2′-(ethylenedioxy)dipyridine.

General Macrocycle Preparation. Reaction of 2,6-Dibromopyridine with Diethylene Glycol. To a suspension of sodium hydride (1 g, 20 mmol) in 50 mL of xylene, diethylene glycol (1.16 g, 10 mmol, bp 240–250 °C) was added slowly under nitrogen. The mixture was stirred for 30 min at room temperature, then 2,6-dibromopyridine (2.37 g, 10 mmol) in 25 mL of xylene was added. After the reaction mixture was heated to 140–150 °C for 24 h, the solvent was removed in vacuo. The residue was dissolved in water, extracted with dichloromethane, and chromatographed (ThLC) on four plates eluting with cyclohexane–ethyl acetate (1:1). Owing to the numerous components, the plates were divided into the fast-moving (R_f 1–0.5) and slow-moving (R_f 0.5–0) components. The fast-moving portion of these plates was combined and rechromatographed (ThLC) developing eight times with cyclohexane–ethyl acetate (10:1) to afford five major fractions.

Fraction A yielded unreacted 2,6-dibromopyridine: 80 mg; R_f 0.50; mp 117–118 °C.

Fraction B afforded 6,6′-dibromo-2,2′-(ethylenedioxy)dipyridine (**16**): 29 mg; mp 150–152 °C (cyclohexane); R_f 0.55; NMR δ 4.62 (s, $-CH_2O-$, 4 H), 6.68 (dd, 3-Pyr-H, J = 8, 2 Hz, 2 H), 7.02 (dd, 5-Pyr-H, J = 8, 2 Hz, 2 H), 7.40 (dd, 4-Pyr-H, J = 8, 8 Hz, 2 H); IR (KBr) 1601, 1586, 1557, 1443, 1288, 1263, 1165 1032, 984, 875, 795 cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_2O_2Br_2$: C, 38.53; H, 2.69; N, 7.49 Found: C, 38.44; H, 2.66; N, 7.36.

Fraction C crystallized from petroleum ether (bp 60–80 °C) yielding macrocycle **13** as colorless needles: 90 mg; mp 94.5–95.5 °C; R_f 0.47; NMR δ 3.81 (dd, β-CH_2O, J = 6, 6 Hz, 4 H), 4.50 (dd, α-CH_2O, J = 6, 6 Hz, 4 H), 4.64 (s, $-OCH_2CH_2O-$, 4 H), 6.38 (2 d, 3- and 5-Pyr-H, J = 8 Hz each, 4 H), 7.48 (t, 4-Pyr-H, J = 8 Hz, 2 H); IR (KBr) 1605, 1590, 1471, 1447, 1302, 1253, 1033, 975 cm^{-1}; UV (EtOH) λ 225.0 nm (ε 23 100), 277.5 (14 300). Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.09; H, 5.71; N, 8.64.

Fraction D afforded 6,6′-dibromo-2,2′-[oxybis(ethyleneoxy)]dipyridine (**15**), which was recrystallized from petroleum ether (bp 60–80 °C) to give colorless needles: 820 mg; mp 91–92 °C; R_f 0.43; NMR δ 3.87 (dd, β-CH_2O, J = 6, 6 Hz, 4 H), 4.47 (dd, α-CH_2O, J = 6, 6 Hz, 4 H), 6.68 (dd, 3-Pyr-H, J = 8, 2 Hz, 2 H), 7.02 (dd, 5-Pyr-H, J = 8, 2 Hz, 2 H), 7.42 (dd, 4-Pyr-H, J = 8, 8 Hz, 2 H); IR (KBr) 1608, 1590, 1558, 1435, 1302, 1138, 1030, 983, 883, 804, 786 cm^{-1}. Anal. Calcd for $C_{14}H_{14}N_2O_3Br_2$: C, 40.30; H, 3.31; N, 6.54. Found: C, 40.22; H, 3.38; N, 6.70.

Fraction E afforded the 2:2 macrocycle **11** which was recrystallized from petroleum ether (bp 60–80 °C) to give colorless needles: 250 mg (6.5%); mp 111–112 °C; R_f 0.37; NMR δ 3.86 (t, β-CH_2O, J = 5 Hz, 8 H), 4.48 (t, α-CH_2O, J = 5 Hz, 8 H), 6.23 (d, 3,5-Pyr-H, J = 8 Hz, 4 H), 7.45 (t, 4-Pyr-H, J = 8 Hz, 2 H); IR (KBr) 1605, 1578, 1468, 1435, 1297, 1235, 1026, 1073, 1052, 1020, 789 cm^{-1}; UV (EtOH) λ 223.0 nm (ε 19 900), 2780 (14 600). Anal. Calcd for $C_{18}H_{22}N_2O_5$: C, 59.66; H, 6.12; N, 7.73; mol wt, 362. Found: C, 59.88; H, 6.27; N, 7.62; mol wt (osmometry), 364 (av).

The slower moving portions from the original plates were combined and rechromatographed (ThLC) developing eight times with cyclohexane–ethyl acetate (4:1) to afford fractions F–H.

Fraction F yielded 2-[2-[2-(6-bromopyridyloxy)]ethoxy]ethanol (**14**) as a colorless oil: 620 mg; bp 80 °C (0.3 mm, short path); R_f 0.07; NMR δ 3.20 (s, –OH, exchanged with D_2O), 3.80 (m, $-CH_2-$, 6 H), 4.45 (dd, $PyrOCH_2-$, J = 5 Hz, 2 H), 6.70 (dd, 3-Pyr-H, J = 8, 2 Hz, 1 H), 7.02 (dd, 5-Pyr-H, J = 8, 2 Hz, 1 H), 7.42 (dd, 4-Pyr-H, J = 8, 8 Hz, 1 H); IR (neat) 3500 (–OH), 1605, 1590, 1560, 1465, 1440, 1315, 1240, 1135, 1050, 790, 733 cm^{-1}. Anal. Calcd for $C_9H_{12}NO_3Br$: C, 41.24; H, 4.61; N, 5.34. Found: C, 41.27; H, 4.72; N, 5.19.

Fraction G yielded the 3:3 macrocycle **12**, which was recrystallized from petroleum ether (bp 60–80 °C) affording colorless needles: 95 mg (1.6%); mp 120.5–121.5 °C; R_f 0.20; NMR δ 3.83 (t, β-CH_2O, J = 5 Hz, 12 H), 4.42 (t, α-CH_2O, J = 5 Hz, 12 H), 6.23 (d, 3,5-Pyr-H, J = 8 Hz, 6 H), 7.45 (t, 4-Pyr-H, J = 8 Hz, 3 H); IR (KBr) 1613, 1583, 1462, 1444, 1342, 1307, 1247, 1078, 788 cm^{-1}. Anal. Calcd for $C_{27}H_{33}N_3O_9$: C, 59.66; H, 6.12; N, 7.73; mol wt. 543. Found: C, 59.59; H, 6.15; N, 7.51; mol wt (osmometry), 528 (av).

Fraction H afforded 2,2′-[2,2′-(2,6-pyridinediyldioxy)diethoxy]-diethanol (**17a**) as a high-boiling, colorless oil: 60 mg; bp 150 °C (0.3 mm, short path). R_f 0.01; NMR δ 3.80 (m, β-CH_2O, 12 H), 4.38 (t, α-CH_2O, J = 5 Hz, 4 H), 4.62 [bs, –OH (exchanged with D_2O), 2 H], 6.28 (d, 3,5-Pyr-H, J = 8 Hz, 2 H), 7.45 (t, 4-Pyr-H, J = 8 Hz, 1 H); IR (neat) 3400 (broad, –OH), 1605, 1595 1580, 1441, 1242, 1132, 1068 cm^{-1}.

Diol **17a** failed repeatedly to afford an acceptable analytical analysis. Therefore, **17a** was converted by the standard pyridine–acetic anhydride procedure to the corresponding diacetate **17b**: bp 140 °C (2 mm, short path); NMR δ 2.03 (s, $COCH_3$, 6 H), 3.75 (dd, β-CH_2O, J = 6 Hz, 8 H), 4.19 (dd, α-CH_2OAc, J = 6 Hz, 4 H), 4.38 (dd, α-CH_2O, J = 6 Hz, 4 H), 6.29 (d, 3,5-Pyr-H, J = 8 Hz, 2 H), 7.45 (t, 4-Pyr-H, J = 8 Hz, 1 H); IR (neat) 1742 (C=O), 1607, 1582, 1442, 1243, 1138, 1058, 793 cm^{-1}. Anal. Calcd for $C_{17}H_{25}NO_8$: C, 54.97; H, 6.79; N, 3.78. Found: C, 54.75: H, 6.91; N, 3.48.

Macrocycle 13. Oil-free sodium hydride (ca. 20 mg) suspended in 25 mL of anhydrous bis(2-ethoxyethyl) ether was stirred under nitrogen and diethylene glycol (30 mg, 0.28 mmol) was slowly added, followed by **16** (100 mg, 0.27 mmol). The mixture was heated at 140 °C for 24 h. After the previously described workup, preparative chromatography (ThLC) of the residue afforded, along with recovered starting material, macrocycle **13** (26 mg, 30%, mp 94–95 °C), which was recrystallized from cyclohexane and shown to be indistinguishable from the previously obtained sample.

Reaction of Excess 2,6-Dibromopyridine with Diethylene Glycol. The above general procedure was followed except that excess 2,6-dibromopyridine (23.7 g, 100 mmol) was used. Along with unreacted starting material, the major fraction isolated was alcohol **14** (25%, mp 91–92 °C). Only traces (<2%) of the desired macrocycles **11**, **12**, and **13** were isolated.

Cyclization of Alcohol 14. Alcohol **14** (3 g, 11 mmol) was dissolved in anhydrous bis(2-ethoxyethyl) ether (300 mL) and sodium hydride (600 mg, 12 mmol) was carefully added. The mixture was heated to 140–150 °C for 24 h and worked up as previously described to afford 42% of **11** (mp 110–112 °C) along with traces (<1%) of **12**, **20**, and **21**. Owing to limited amounts of pure **20** and **21**, the NMR data, which were identical with those of **14**, and osmometric analyses were used to assign their structures.

Reaction of 2,6-Dibromopyridine with Triethylene Glycol. Following the general procedure, except for the substitution of triethylene glycol (1.5 g, 10 mmol), two major macrocyclic ethers were characterized.

1:1 macrocycle **22**: mp 83–84 °C (petroleum ether, bp 60–80 °C); 6%; R_f 0.24; NMR δ 3.72 (s, γ-CH_2O, 4 H), 3.82 (t, β-CH_2O, J = 5 Hz, 4 H), 4.68 (t, α-CH_2O, J = 5 Hz, 4 H), 6.27 (d, 3,5-Pyr-H, J = 8 Hz, 2 H), 7.47 (t, 4-Pyr-H, J = 8 Hz, 1 H); IR ($CHCl_3$) 1602, 1587, 1456, 1303, 1205 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.23; mol wt, 225. Found: C, 58.73; H, 6.65; N, 6.35; mol wt (osmometry), 223 (av).

2:2 macrocycle **23**: mp 117–120 °C (petroleum ether, 60–80 °C); <2%; R_f 0.1; NMR δ 3.70 (s, γ-CH_2O, 6 H), 3.82 (t, β-CH_2O, J = 6 Hz, 8 H), 4.40 (t, α-CH_2O, J = 6 Hz, 8 H), 6.27 (d, 3,5-Pyr-H, J = 8 Hz, 4 H), 7.41 (t, 4-Pyr-H, J = 8 Hz, 2 H). Anal. Calcd for $C_{22}H_{30}N_2O_8$ (450): C, 58.66; H, 6.71; N, 6.23. Found: C, 58.53; H, 6.77; N, 6.31; mol wt (osmometry), 460. Other intermediates were easily detected but were neither isolated nor characterized.

1-Methyl-3,6-dioxa-1,8-octanediol. Diethylene glycol (35 g) was treated with sodium (0.1 g) at 50 °C under nitrogen, then warmed to 100 °C for 2 h. Propylene oxide (20 g) was added dropwise over 10 min followed by maintaining the suspension with stirring at 120 °C for 12 h. After cooling, the solution was neutralized with acetic acid (ca. 2 mL) and then vacuum distilled affording a mixture of diols, bp 160–200 °C (5 mm). Fractional distillation via a spinning band column afforded the pure (>97%) methyltriethylene glycol: bp 106 °C (2 mm); NMR δ 1.08 (d, $CHCH_3$, J = 6 Hz, 3 H), 3.2–4.0 (m, $CHCH_2$, OH, 13 H).

Reaction of 2,6-Dichloropyridine with Methyltriethylene Glycol. Sodium hydride (2.5 g, 50 mmol) suspended in xylene (300 mL) was treated with methyltriethylene glycol (4.1 g, 25 mmol) over 15 min with stirring under nitrogen, then 2,6-dichloropyridine (3.7 g, 25 mmol) in xylene (50 mL) was added. The mixture was refluxed for 30 h. After cooling, the unreacted sodium hydride was neutralized with water and the aqueous layer separated. The organic layer was dried and concentrated in vacuo affording a viscous residue, part of which was chromatographed (ThLC) eluting four times with cyclohexane–ethyl acetate (4:1). Four major macrocyclic fractions were isolated:

Fraction A gave the 1:1 macrocycle, 1,4,7,10-tetraoxamuscopyridine

(26), which crystallized from absolute ethanol as colorless plates: mp 55 °C; 210 mg (ca. 3%); R_f 0.45; NMR (300 MHz) δ 1.41 (d, $CHCH_3$, J = 6 Hz, 3 H), 3.35 (dd, β-CH_2O, J = 8, 6 Hz, 1 H), 3.58 (m, α′- and γ- or γ′-H, 3 H), 3.76 (m, γ- or γ′-H, 2 H), 4.01 (m, β- and β′-H, 3 H), 5.32 (m, α′-H, 1 H), 5.50 (m, α-H, 1 H), 6.14 (d, 3,5-Pyr-H, J = 5 Hz, 2 H), 7.25 (t, 4-Pyr-H, J = 5 Hz, 1 H) (see Figure 1); IR (Nujol) 1625, 1575, 1450, 1375, 1300, 1225, 1015, 790 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.25; H, 7.11; N, 5.85; mol wt, 239. Found: C, 60.08; H, 6.91; N, 5.84; mol wt (MS), 239 (M^+).

Fraction E furnished a 2:2 macrocycle (**27**) which was crystallized from 95% ethanol as colorless plates: mp 111 °C; 900 mg (ca. 15%); R_f 0.38; NMR δ 1.32 (d, $CHCH_3$, J = 6 Hz, 6 H), 3.72 (m, β- and γ-CH_2O, 16 H), 4.35 (t, α-CH_2O, J = ca. 5 Hz, 4 H), 5.30 (m, $CHCH_3$, J = 6, ~5 Hz, 2 H), 6.23 (d, 3,5-Pyr-H, J = 5 Hz, 4 H), 7.42 (t, 4-Pyr-H, J = 5 Hz, 2 H); IR (Nujol) 1600, 1570, 1440, 1240, 790 cm^{-1}. Anal. Calcd for $C_{24}H_{34}N_2O_8$: C, 60.25; H, 7.11; N, 5.85; mol wt, 478. Found: C, 60.02; H, 7.07; N, 5.75; mol wt (MS), 478 (M^+).

Fraction C gave an isomeric 2:2 macrocycle as a thick, viscous oil which failed to crystallize: 75 mg (<1%); R_f 0.29; NMR δ 3.32 (d, $CHCH_3$, J = 5 Hz 6 H), 3.75 (m, β- and γ-CH_2O–, 16 H), 4.4 (t, α-CH_2O–, J = 5 Hz, 4 H), 5.30 (m, $CHCH_3$, J = 6, ~5 Hz, 2 H), 6.25 (d, 3,5-Pyr-H, J = 5 Hz, 4 H), 7.35 (t, 4-Pyr-H, J = 5 Hz, 2 H); IR (neat) 2850, 1600, 1570, 1300, 1220, 1100, 950, 790, 740 cm^{-1}. Anal. Calcd for $C_{24}H_{34}N_2O_8$: C, 60.25; H, 7.11; N, 5.85; mol wt, 478. Found: C, 60.05; H, 6.84; N, 5.89; mol wt (MS), 478 (M^+).

Fraction D gave an isomeric 2:2 macrocycle as a noncrystallizable oil: 80 mg (<1%); R_f 0.22; NMR and IR are identical with those of fraction C. Anal. Calcd for $C_{24}H_{34}N_2O_8$: C, 60.25; H, 7.11; N, 5.85; mol wt, 478. Found: C, 60.34; H, 7.11; N, 5.82; mol wt (MS), 478 (M^+).

Reaction of 2,6-Dibromopyridine with Tetraethylene Glycol. The general procedure was followed except for the substitution of tetraethylene glycol. After the standard workup procedure a portion of the thick, viscous, brown oil was chromatographed (ThLC) eluting four times with cyclohexane–ethyl acetate (1:1) to afford, along with starting materials, four macrocyclic components.

Fraction A afforded the 1:1 macrocycle **22**, which crystallized from petroleum ether (bp 60–80 °C) as colorless plates (mp 84 °C) and had the same IR and NMR spectral data with the previously isolated sample.

Fraction B afforded the desired 1:1 macrocycle **29**, which crystallized from petroleum ether (bp 60–80 °C) as colorless plates: mp 76–78 °C; 100 mg (ca. 4%); R_f 0.13; NMR δ 3.62 (s, γ,δ-CH_2O, 8 H), 3.92 (t, β-CH_2O, J = 5 Hz, 4 H), 4.62 (t, α-CH_2O, J = 5 Hz, 4 H), 6.28 (d, 3,5-Pyr-H, J = 7 Hz, 2 H), 7.46 (t, 4-Pyr-H, J = 7 Hz, 1 H); IR (Nujol), 1590, 1570, 1440, 1300, 1210, 1120 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.06; N, 5.20; mol wt, 269. Found: C, 58.21; H, 7.15; N, 5.19; mol wt (MS), 269 (M^+).

Fraction C gave the unsymmetrical ether **30**, which was crystallized from alcohol as a white powder: mp 72 °C; 40 mg (ca. 1%); R_f 0.05; NMR δ 3.65 (bs, γ,δ-CH_2O, 12 H), 3.80 (t, β-CH_2O, J = 5 Hz, 8 H), 4.42 (t, α-CH_2O, J = 5 Hz, 8 H), 6.27 (d, 3,5-Pyr-H, J = 7 Hz, 4 H), 7.4 (t, 4-Pyr-H, J = 7 Hz, 2 H); IR (Nujol) 1610, 1590, 1440, 1300, 1240, 1130 cm^{-1}. Anal. Calcd for $C_{24}H_{34}N_2O_9$: C, 58.30; H, 6.88; N, 5.67; mol wt, 494. Found: C, 58.53; H, 7.08; N, 5.46; mol wt (MS), 494 (M^+).

Fraction D gave the symmetrical 2:2 macrocycle **31** as colorless needles: mp 83–84 °C; 150 mg (5%); R_f 0.03; NMR δ 3.65 (s, γ,δ-CH_2O, 16 H), 3.83 (t, β-CH_2O, J = 6 Hz, 8 H), 4.41 (t, α-CH_2O, J = 6 Hz, 8 H), 6.28 (d, 3,5-Pyr-H, J = 8 Hz, 4 H), 7.42 (t, 4-Pyr-H, J = 8 Hz, 2 H); IR (Nujol) 1600, 1575, 1450, 1325, 1300, 1250, 1100 cm^{-1}. Anal. Calcd for $C_{26}H_{38}N_2O_{10}$: C, 57.99; H, 7.06; N, 5.20; mol wt, 538. Found: C, 58.04; H, 7.12; N, 5.08; mol wt (MS), 538 (M^+).

Reaction of 2,6-Dichloropyridine with Tetraethylene Glycol. High-Dilution Conditions. Sodium hydride suspension (480 mg, 20 mmol) was washed with petroleum ether and dried with a stream of nitrogen, then anhydrous xylene (500 mL) was added. To this refluxing suspension, tetraethylene glycol (1.98 g, 10 mmol) in xylene (500 mL) and 2,6-dichloropyridine (1.5 g, 10 mmol) in xylene (500 mL) were added simultaneously over 24 h via a high-dilution apparatus,[9] then the solution was refluxed for an additional 12 h. The workup procedure mimicked the general procedure. The crude reaction products were chromatographed (ThLC) affording the same macrocyclic products except for product distribution: macrocycle **22** (mp 84 °C, ~1%); 1:1 macrocycle **29** (mp 76–78 °C, 10%); unsymmetrical macrocycle **30** (mp 72 °C, 2%); and symmetrical 2:2 macrocycle **31** (mp 83–84 °C, 3%).

3,6,9,12-Tetraoxa-1,14-tetradecanediol (pentaethylene glycol) was prepared according to the procedure of Perry and Hibbert[16] from 1,8-dichloro-3,6-dioxaoctane and ethylene glycol: bp 185–190 °C (0.15mm) [lit.[20] bp 174–176 °C (0.14 mm)].

Reaction of 2,6-Dibromopyridine with Pentaethylene Glycol. The general procedure for macrocycles was followed except for the substitution of pentaethylene glycol. The product residue was chromatographed (ThLC) eluting two times with cyclohexane–ethyl acetate (1:1); however, since separation was not complete, the faster moving components (R_f > 0.5) were combined and rechromatographed (ThLC) eluting two times with cyclohexane–ethyl acetate (1:1) to give two macrocyclic compounds.

Fraction A crystallized from petroleum ether (bp 60–80 °C) to give macrocycle **29** as colorless plates: mp 76–78 °C; 70 mg (2%); R_f 0.13; spectral data were identical with those of **29** isolated from the previous reaction.

Fraction B gave the desired 1:1 macrocycle **32** as a thick, viscous oil: bp 155–160 °C (0.15 mm); 350 mg (12%); R_f 0.06; NMR δ 3.52 (s, ε-CH_2O, 4 H), ~3.7 (m, δ,γ-CH_2O, 8 H), 3.85 (t, β-CH_2O, J = 6 Hz, 4 H), 4.55 (t, α-CH_2O, J = 6 Hz, 4 H), 6.3 (d, 3,5-Pyr-H, J = 6 Hz, 2 H), 7.45 (t, 4-Pyr-H, J = 6 Hz, 1 H); IR (Nujol) 1600, 1580, 1430, 1300, 1240, 790 cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.34; N, 4.47; mol wt, 313. Found: C, 56.96; H, 7.43; N, 4.37; mol wt (MS), 313 (M^+).

The slower moving fractions were rechromatographed (ThLC) eluting five times with cyclohexane–ethyl acetate (1:1) to give two compounds.

Fraction C gave an unknown compound as colorless needles from ethanol: mp 189 °C; 5 mg (≪1%); R_f 0.02; insufficient material was available to establish the structure.

Fraction D gave a white powder which upon recrystallization from ethanol yielded colorless needles of the 2:2 macrocycle **34**: mp 91 °C; 200 mg (~8%); R_f 0.01; NMR δ 3.65 (m, ε,δ,γ-CH_2O, 24 H), 3.85 (t, β-CH_2O, J = 5 Hz, 8 H), 4.42 (t, α-CH_2O, J = 5 Hz, 8 H), 6.3 (d, 3,5-Pyr-H, J = 5 Hz, 4 H), 7.40 (t, 4-Pyr-H, J = 5 Hz, 2 H); IR (Nujol) 1600, 1580, 1490 (b), 1250. 785 cm^{-1}. Anal. Calcd for $C_{30}H_{46}N_2O_{12}$: C, 57.50; H, 7.54; N, 4.47, mol wt, 626. Found: C, 57.46; H, 7.50; N, 4.18; mol wt (MS), 626 (M^+).

2,2′-[Oxybis(ethyleneoxyethyleneoxy)]diethanol (hexaethylene glycol) was prepared[16] from 1,5-dichloro-3-oxapentane [bp 179 °C (760 mm)] and diethylene glycol: bp 201–205 °C (0.7 mm) [lit[20] bp 203.0–205.0 (0.3 mm)].

Reaction of 2,6-Dibromopyridine with Hexaethylene Glycol. The general procedure was followed except for the substitution of hexaethylene glycol. The product residue was chromatographed (ThLC) eluting three times with cyclohexane–ethyl acetate (1:1). The following fast-moving fractions were separated.

Fraction A gave a small amount (10 mg) of unreacted dibromopyridine, mp 118 °C.

Fraction B afforded (3%) a crystalline compound which corresponded to the proven macrocycle **29**, mp 76–78 °C, 40 mg.

Fraction C afforded a thick, viscous oil which was shown spectroscopically to be identical with macrocycle **32**, 40 mg (ca. 3%).

Fraction D gave the 1:1 macrocycle **35** as a colorless oil: bp 190–193 °C (0.1 mm); 850 mg (48%); R_f 0.02; NMR δ 3.60 (m, γ,δ-CH_2O, 16 H), 3.85 (t, β-CH_2O, J = 5 Hz, 4 H), 4.55 (t, α-CH_2O, J = 5 Hz, 4 H), 5.3 (d, 3,5-Pyr-H, J = 7 Hz, 3 H), 7.45 (t, 4-Pyr-H, J = 7 Hz, 1 H); IR (neat) 2900, 1600, 1425, 1300, 1240, 950, 800 cm^{-1}. Anal. Calcd for $C_{17}H_{27}NO_7$: C, 57.14; H, 7.56; N, 3.92; mol wt, 357. Found: C, 56.77; H, 7.53; N, 3.82; mol wt (MS), 357.

The residual baseline was extracted with chloroform–ethanol (1:1). The residue was rechromatographed (ThLC) with cyclohexane and ethyl acetate (1:3) eluting two times. The following fractions were isolated.

Fraction E gave the white, crystalline 2:2 macrocycle **34**, identical in all respects with the above sample, mp 91 °C, 60 mg (4%).

Fraction F, recrystallized from ethanol, afforded a colorless powder of the 2:2 macrocycle **37**: mp 72–74 °C; 75 mg (5%); R_f 0.01; NMR δ 3.67 (m, γ,δ-CH_2O, 32 H), 3.82 (t, β-CH_2O, J = 5 Hz, 8 H), 4.4 (t, α-CH_2O, J = 5 Hz, 8 H), 6.25 (d, 3,5-Pyr-H, J = 7 Hz, 4 H), 7.41 (t, 4-Pyr-H, J = 7 Hz, 2 H); IR ($CHCl_3$) 2900, 1605, 1595, 1445, 1350, 1310, 1240, 792 cm^{-1}. Anal. Calcd for $C_{34}H_{54}N_2O_{14}$: C, 57.14; H, 7.56; N, 3.92; mol wt, 714. Found: C, 57.20; H, 7.54; N, 3.88; mol wt (MS), 714.

Reaction of 2,6-Dibromopyridine with Ethylene Glycol. To a suspension of sodium hydride (4 g, 80 mmol) in bis(2-ethoxyethyl) ether (250 mL), ethylene glycol (2.5 g, 40 mmol) was added; after 30 min, 2,6-dibromopyridine (4.74 g, 20 mmol) was added. The mixture was heated to 150 °C for 24 h, and worked up as previously described. A portion of the residue was chromatographed (ThLC) eluting six times with cyclohexane–ethyl acetate (10:1). Other than 2,6-dibromopyridine (ca. 30%), the following fractions were characterized.

Macrocycle **38**: mp 215–216 °C; 16%; R_f 0.7; NMR δ 4.66 [bs (38 °C), –CH_2O–, 8 H], 6.30 [d (38 °C), 3,5-Pyr-H, J = 8 Hz, 4 H], 7.50 (t, 4-Pyr-H, J = 8 Hz, 2 H) (see Figure 1); IR (KBr) 1605, 1590, 1470, 1450, 1300, 1250, 1080, 975 cm^{-1}. Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.29; H,

5.14; N, 10.21. Found: C, 61.32; H, 5.10; N, 10.26.

6,6′-Dibromo-2,2′-(ethylenedioxy)dipyridine (**16**): mp 150–152 °C; 4%; identical with a known sample.

2-[2-(6-Bromopyridyloxy)]ethanol (**18**): traces (<1%); NMR ($CDCl_3$) δ 3.90 (m, β-CH_2O, 2 H), 4.40 (m, α-CH_2O, 2 H), 6.68 (dd, 3-Pyr-H, J = 8,2 Hz, 1 H), 7.01 (dd, 5-Pyr-H, J = 8, 2 Hz, 1 H), 7.41 (t, 4-Pyr-H, J = 8 Hz, 1 H).

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Registry No.—**3,** 109-04-6; **4,** 61463-64-7; **6,** 56446-62-9; **7,** 56446-63-0; **8,** 56446-64-1; **9,** 56446-65-2; **10a,** 626-05-1; **10b,** 2402-78-0; **11,** 56467-84-6; **12,** 56446-66-3; **13,** 56446-67-4; **14,** 56446-68-5; **15,** 56446-69-6; **16,** 56446-70-9; **17a,** 61463-65-8; **17b,** 61463-66-9; **18,** 61463-67-0; **22,** 56446-71-0; **23,** 61463-68-1; **26,** 61463-69-2; **27,** 61463-70-5; **28,** 61463-71-6; **29,** 56446-73-2; **30,** 61463-72-7; **31,** 61463-73-8; **32,** 61463-74-9; **34,** 61463-75-0; **35,** 61463-76-1; **37,** 61463-77-2; **38,** 56446-41-4; bis(2-ethoxymethyl) ether, 112-36-7; 2-ethoxyethanol, 110-80-5; ethylene glycol, 107-21-1; diethylene glycol, 111-46-6; triethylene glycol, 112-27-6; 1-methyl-3,6-dioxa-1,8-octanediol, 61463-78-3; propylene oxide, 75-56-9; tetraethylene glycol, 112-60-7; pentaethylene glycol, 4792-15-8; hexaethylene glycol, 2615-15-8.

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Heterocyclic Amines. 7.[1] Preparation and Reactions of 2- and 3-Thienyl Isothiocyanates

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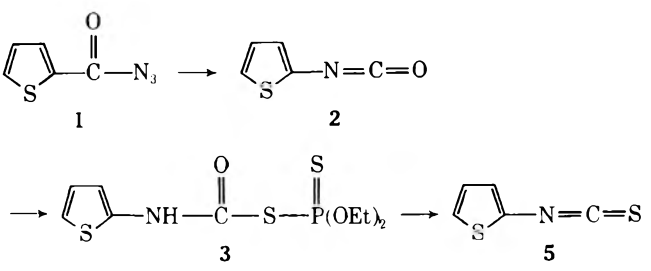
Both 2- and 3-thienyl isothiocyanates have been prepared by thermal rearrangement of the corresponding *S*-(*N*-thienylcarbamoyl)-*O,O′*-diethyl dithiophosphates. These isothiocyanates have been reacted with a variety of amines, alcohols, and mercaptans to synthesize the 2- and 3-thienyl thioureas, thioncarbamates, and dithiocarbamates.

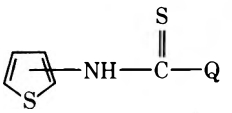
Isothiocyanates of thiophene have not been previously reported. The classical procedures for the synthesis of aromatic-type isothiocyanates[2] require the corresponding primary amines, which are difficultly accessible in the thiophene series, and require conditions which decompose the unstable aminothiophenes.[1,3,4] Thienyl isocyanates are readily available by Curtius rearrangement of thenoyl azides,[5,6] but the "thio-Curtius" rearrangement does not take place. Attempted preparation of thioacyl azides yields the cyclized thiatriazoles, which thermally decompose to nitriles[7] and sulfur, although small amounts of isothiocyanates have been detected by ultraviolet photolysis[8] of thiatriazoles. Ottmann and Hooks[9] prepared isothiocyanates by thermal decomposition of the reaction product obtained from isocyanates and *O,O′*-diethyl hydrogen dithiophosphate. We have found that by modifying their conditions, it is possible to apply this reaction in the thiophene series to prepare both 2- and 3-thienyl isothiocyanates.



Thenoyl azide (**1**) was thermally rearranged in boiling carbon tetrachloride to thienyl isocyanate (**2**). This was reacted with *O,O′*-diethyl hydrogen dithiophosphate, and upon cooling, *S*-(*N*-thienylcarbamoyl)-*O,O′*-diethyl dithiophosphate (**3**) crystallized. This was thermally rearranged to the thienyl isothiocyanate (**5**).

Because the thienyl isothiocyanates are labile in acid, it was found necessary to minimize their contact with the

Table I. Additional Derivatives of the Thienyl Isothiocyanates



Compd	Thienyl position	Q	% yield	Mp, °C	Recrystn solvent
7	2	$-NH_2$	53	186–186.5	Water
8	3	$-NH_2$	11	192–193	Water
10	3	$-NHPr(n)$	21	54–55	Toluene–ligroin
11	2	$-NHBu(t)$	47	162–162.5	None
12	3	$-NHBu(t)$	47	161–161.5	Toluene
14	3	$-OPr(n)$	57	67.5–68	Ligroin
16	3	$-OBu(t)$	21	109–110 dec	Petroleum ether
17	2	$-SPr(n)$	44	Oil	
18	3	$-SPr(n)$	13	46.5–47	Ligroin

thiophosphoric acid coproducts which codistilled from the reaction mixture. This was accomplished by chromatography after which the thienyl isothiocyanates could be successfully redistilled.

To establish the utility of the thienyl isothiocyanates as intermediates for the synthesis of 2- and 3-thienyl substituted thioureas, thiocarbamates, and dithiocarbamates, suitable conditions were worked out for the reaction of these isothiocyanates with a variety of amines, alcohols, and mercaptans. Compounds in addition to those described in the Experimental Section are listed in Table I.

Experimental Section

All melting points are uncorrected. All NMR spectra were taken on Varian A-60 or T-60 instruments with internal tetramethylsilane reference.

***S*-[*N*-(2-Thienyl)carbamoyl]-*O,O'*-diethyl Dithiophosphate (3).** A solution of 2-thenoyl azide[5] (8.0 g, 52 mmol) in 50 mL of carbon tetrachloride was heated under reflux under anhydrous conditions for 17 h. Half of the solvent was removed by distillation, the residual solution was cooled to room temperature, and while the temperature of the stirred reaction mixture was maintained below 40 °C, 9.20 g (49 mmol) of *O,O'*-diethyl hydrogen dithiophosphate was added dropwise. A few minutes after the addition was complete, stirring was discontinued and the reaction mixture was cooled in the refrigerator. The yield of crude crystalline product was 15.5 g (100%). Part of this material was recrystallized from *n*-heptane, in which the product is of low solubility (ca. 1 g per 400 mL) at the recrystallization temperature of 60 °C. No decomposition was detected when the recrystallization was carried out at 60 °C, but at 70 °C noticeable decomposition occurred. The colored impurities did not dissolve and were removed by filtration. After two recrystallizations the product melted at 103.5–104.5 °C dec, white needles: NMR ($CDCl_3$) δ 1.38 (t, 6, CH_3), 4.27 (octet, 4, CH_2), 6.73–7.00 (m, 3, thienyl H), 9.50 (br band, 1, NH); $J_{CH_2CH_3}$ = 7.5 J_{POCH_2} = 9.5 Hz.

Anal. Calcd for $C_9H_{14}NO_3PS_3$: C, 34.71; H, 4.53; N, 4.50; P, 9.95; S, 30.89. Found: C, 34.83; H, 4.58; N, 4.54; P, 10.16; S, 30.64.

***S*-[*N*-(3-Thienyl)carbamoyl]-*O,O'*-diethyl dithiophosphate** (4) was prepared similarly to the above, from 24.1 g (0.16 mol) of 3-thenoyl azide[6] and 27.6 g (0.15 mol) of *O,O'*-diethyl hydrogen dithiophosphate. The product was decolorized with acid-washed Norit A charcoal and recrystallized from *n*-heptane: yield 35.0 g (76%); mp 83.5–85.0 °C; NMR ($CDCl_3$) δ 1.39 (t, 6, CH_3), 5.97 (octet, 4, CH_2), 7.03 (q, 1, 4-H), 7.25 (q, 1, 5-H), 7.44 (q, 1, 2-H), 9.07 (br band, 1, NH); $J_{2,4}$ = 1.5, $J_{2,5}$ = 3.2, $J_{4,5}$ = 5.2, $J_{CH_2CH_3}$ = 7.2, J_{POCH_2} = 10 Hz.

Anal. Calcd for $C_9H_{14}NO_3S_3P$: C, 34.71; H, 4.53; N, 4.50; P, 9.95; S, 30.89. Found: C, 34.80; H, 4.88; N, 4.65; P, 9.93; S, 30.57.

2-Thienyl Isothiocyanate (5). Crude **3** (319 g, 1.03 mol) was pyrolyzed under reduced pressure using an oil bath heated to 150 ± 5 °C. Crude product distilled at 108–114 °C (7 mm). The NMR spectrum indicated that it was less than 50% of the desired product, much of the remainder being various thiophosphates. This material was then chromatographed, in six approximately equal batches, on dry-packed 1.5 kg silica gel 60 (EM laboratories, 70–230 mesh) columns. Elution with carbon tetrachloride brought the isothiocyanate through close behind the solvent front.

The various phosphates seem to stay near the origin under these conditions and it has been possible to reuse these columns for as many as three runs. This partially purified product (21 g) was rechromatographed on a fresh column (1.5 kg) and 15.8 g (11%) of pale yellow oil was obtained on distillation at 44 °C (0.4 mm). The sample for elemental analysis was prepared by gas chromatography on a Hewlett-Packard 5750 preparative GC, using a 12 ft × 0.5 in. 10% QF-1 column, carrier flow rate 80 mL/min, oven temperature 150 °C, retention time 10 min: NMR (CCl_4) δ 6.63–7.01 (m, 3 H, thienyl H).

Anal. Calcd for $C_5H_3NS_2$: C, 42.53; H, 2.14: N, 9.92; S, 45.41. Found: C, 42.50; H, 2.11; N, 9.75; S, 45.49.

3-Thienyl Isothiocyanate (6). **4** (15 g, 48 mmol) was heated at 18 mm pressure in an oil bath maintained at 135–140 °C until distillation stopped. The distillate was chromatographed on 50 g of silica gel 60 (EM Laboratories, 70–230 mesh) and eluted with carbon tetrachloride, then distilled on a Nester-Faust Teflon spinning band column yielding 2.28 g (34%) of a yellow oil: bp 98–99 °C; NMR (CCl_4) δ 6.87 (q, 1, 4-H), 7.02 (q, 1, 2-H), 7.20 (q, 1, 5-H); $J_{2,4}$ = 1.4, $J_{2,5}$ = 3.1, $J_{4,5}$ = 4.8 Hz; $n^{25}D$ 1.6771.

Anal. Calcd for $C_5H_3NS_2$: C, 42.53; H, 2.14; N, 9.92; S, 45.41. Found: C, 42.67; H, 2.03; N, 10.05; S, 45.27.

***N*-*n*-Propyl-*N'*-(2-thienyl)thiourea (9).** *n*-Propylamine (0.7 g, 12 mmol) was added to a solution of 0.4 g (2.8 mmol) of **5** in 10 mL of carbon tetrachloride and the mixture was stirred for 20 min. The solvent and excess amine were partially evaporated and the solid product was recrystallized from carbon tetrachloride–petroleum ether, 480 mg (85%) of white plates: mp 100.0–100.5 °C; NMR ($CDCl_3$) δ 0.88 (t, 3, CH_3), 1.59 (sextet, 2, CCH_2C), 3.58 (t, 2, NCH_2), 6.23 (br band, 1, RNH), 6.78 (m, 1, 3-H), 6.90 (m, 1, 4-H), 7.15 (q, 1, 5-H), 8.27 (br s, 1, thienyl NH); NMR (acetone-d_6) δ 0.88 (t, 3, CH_3), 1.59 (sextet, 2, CCH_2C), 3.52 (q, 2, NCH_2), 6.73 (q, 1, 3-H), 6.82 (q, 1, 4-H), 7.03 (q, 1, 5-H), ca. 7.22 (partially obscured by the 5-H) (br band, 1, RNH), 9.27 (br s, 1, thienyl NH); $J_{3,4}$ = 3.7, $J_{3,5}$ = 1.7, $J_{4,5}$ = 5.3, $J_{CH_2CH_3}$ = 7.5, $J_{CH_2CH_2}$ = 6.4 Hz.

Anal. Calcd for $C_8H_{12}N_2S_2$: C, 47.96; H, 6.04; N, 13.99; S, 32.01. Found: C, 48.16; H, 5.95; N, 13.91; S, 31.87.

***n*-Propyl *N*-(2-Thienyl)thionecarbamate (13).** A solution of 420 mg (3.0 mmol) of **5** and 1.6 g (27 mmol) of dried *n*-propyl alcohol in 15 mL of *n*-heptane was heated under reflux for 18 h. The mixture was partially evaporated to yield a white solid, 485 mg (80%), mp 46.0–48.5 °C. The analytical sample was vacuum sublimed, white needles: mp 48.0–48.5 °C; NMR ($CDCl_3$) δ 1.02 (t, 3, CH_3), 1.83 (sextet, 2, CCH_2C), 4.39 (t, 2, OCH_2), 6.70–7.03 (m, 3, thienyl H), 9.99 (br band, 1, NH); $J_{CH_2CH_3}$ = 7.5, $J_{CH_2CH_2}$ = 6.5 Hz.

Anal. Calcd for $C_8H_{11}NOS_2$: C, 47.73; H, 5.51; N, 6.96; O, 7.95; S, 31.86. Found: C, 47.66; H, 5.56; N, 7.03; O, 8.03; S, 32.00

***tert*-Butyl *N*-(2-Thienyl)thionecarbamate (15).** A stirred slurry of potassium *tert*-butoxide (895 mg, 7.1 mmol) in sodium-dried tetrahydrofuran was heated under reflux with 1.0 g (7.1 mmol) of **5** for 1 h under anhydrous conditions, 0.25 mL of water was added, and heating was continued for 15 min. The mixture was cooled to room temperature and 1 mL of 6 N hydrochloric acid was added with stirring. The precipitate of potassium chloride was filtered and the solution was evaporated to a small volume. Upon adding distilled water, an oil separated and crystallized on standing. The product was recrystallized from petroleum ether to yield 760 mg (49%) of light brown crystals, mp 95–96 °C dec. The analytical sample was vacuum sublimed to produce white crystals: mp 92.5–93.5 °C dec; NMR (acetone-d_6) δ 1.77 (s, 9, CH_3), 6.80–7.08 (m, 3, thienyl H), 10.57 (br band, 1, NH).

Anal. Calcd for $C_9H_{13}NOS_2$: C, 50.20; H, 6.08; N, 6.51; O, 7.43; S,

29.78. Found: C, 50.12; H, 6.13; N, 6.41; O, 7.58; S, 29.69.

***tert*-Butyl *N*-(2-Thienyl)dithiocarbamate (19).** A slurry of lithium *tert*-butylmercaptide (682 mg, 7.1 mmol), **5** (1.0 g, 7.1 mmol), and 10 ml of *tert*-butyl mercaptan was heated under reflux for 5 min and then stirred at room temperature in a foil-covered flask for 20 h under anhydrous conditions. The mercaptan was evaporated under a stream of nitrogen and the pasty residue was neutralized with hydrochloric acid. The resultant oil was extracted with ether and evaporation of the ether gave a crystalline product. This was chromatographed on a dry-packed 40 g silica gel 60 (EM Laboratories, 70–230 mesh) column and eluted with carbon tetrachloride. Unreacted 2-thienyl isothiocyanate comes with the solvent front and the product comes a little later. The product was recrystallized from petroleum ether with decolorization by acid-washed Norit A charcoal, yielding 1.42 g (86%) of yellow needles: mp 87.5–88.5 °C dec; NMR (CCl_4) δ 1.63 (s, 9, CH_3), 6.80–7.01 (m, 3, thienyl H), 9.17 (br band, 1, NH).

Anal. Calcd for $C_9H_{13}NS_3$: C, 46.71; H, 5.66; N, 6.05; S, 41.57. Found: C, 46.82; H, 5.56; N, 6.06; S, 41.72.

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Registry No.—**1**, 2046-39-1; **3**, 61528-47-0; **4**, 61528-48-1; **5**, 61528-49-2; **6**, 61528-50-5; **7**, 61528-51-6; **8**, 61528-52-7; **9**, 61528-53-8; **10**, 61528-54-9; **11**, 61528-55-0; **12**, 51460-50-5; **13**, 61528-56-1; **14**, 61528-57-2; **15**, 61528-58-3; **16**, 61528-59-4; **17**, 61528-60-7; **18**, 61528-61-8; **19**, 61528-62-9; *O,O'*-diethylhydrogen dithiophosphate, 298-06-6; 3-thenoyl azide, 59445-89-5; propylamine, 107-10-8; propyl alcohol, 71-23-8; potassium *tert*-butoxide, 865-47-4; *tert*-butyl mercaptan, 75-66-1.

Supplementary Material Available. Chemical analyses and NMR data for the compounds listed in Table I (3 pages). Ordering information is given on any current masthead page.

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Thiocyanations. 2. Solvent Effects on the Product Distribution of the Thiocyanogen–Olefin Reaction

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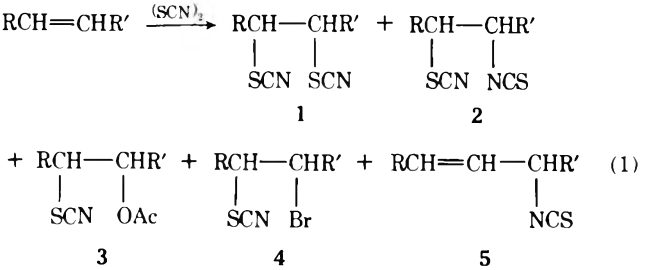
The heterolytic addition of thiocyanogen to *cis*- and *trans*-3-hexene has been carried out in a variety of solvent systems. Unlike ionic bromine addition to aliphatic olefins, this pseudohalogen reaction can yield either adduct **1** or **2** as the principal product dependent on the type of solvent employed. Dithiocyanates (**1**) are preferentially formed in polar and dipolar aprotic media, whereas isothiocyanatothiocyanates (**2**) become the principal products in nonpolar solvents. It was also observed that the product outcome was significantly altered when iron powder or ferric thiocyanate was added to the reaction medium. The effects of solvents and iron on the product composition are explicable through the Pearson HSAB concept. The free-radical thiocyanation reaction was also examined and the results are briefly discussed.

Thiocyanogen addition to alkyl olefins is a well-known procedure[3] for the preparation of α,β-dithiocyanates **1** as well as a classical analytical method for determination of the unsaturation in fats and oils. The reaction, traditionally carried out in acetic acid, had been known to yield only the adducts **1**[4] until the recent isolation of the isomeric α-isothiocyanato-β-thiocyanate **2** and ancillary coproducts **3–5** (eq 1).[5]



(1)

trans olefin → erythro (meso) (1a–4a)
cis olefin → threo (*dl*) (1b–4b)

Quantitation of product distribution has only been reported for reactions carried out in acetic acid solution.[5] Although adduct **2** has also been identified as a coproduct in benzene and carbon tetrachloride solution reactions, the extent of its formation relative to adduct **1** had not been ascertained.[6] Since adducts **1** and **2** have recently found use as synthetic intermediates,[7] a need existed for an improved method of selective conversion of olefins to either **1** or **2**.

The present investigation was initiated to determine the influence of various reaction parameters on the composition of the product mixture, since only limited information was available in the literature.[3b,6] A specific aim of this work was to determine the influence of solvent variation on the product distribution. A quantitative examination of the addition reaction was also carried out under irradiative conditions to compare the products formed by ionic and free-radical pathways. It was anticipated that an understanding of the solvents' role in determining the products formed from thiocyanogen additions would aid in clarification of the mechanism of addition of this ambident pseudohalogen to olefins.

Results

The present study was implemented with *cis*- and *trans*-3-hexene as convenient model olefins[8] for which the products were easily analyzed by GLC. Earlier studies in this laboratory[5] have indicated that the product outcome is not influenced by the chain length and hence it was anticipated that the results obtained on 3-hexene could be projected to longer

chain internal olefins. The general thiocyanation procedure[5] consisted of the generation from lead thiocyanate of thiocyanogen in a specific solvent, filtration of insoluble salts, and delivery of the reagent to volumetric flasks containing the olefin. Any changes introduced in the procedure depended on the nature of the variables under study.

The parameters considered for reactions in each solvent included lead salt effects,[3,4] free-radical inhibitors, the ratio of thiocyanogen to olefin, and the influence of iron catalysts.[6] Because of thiocyanogen's photosensitivity leading to free-radical processes, the present series of thiocyanations were maintained in the absence of light except for the specifically photoinitiated conditions. Free-radical inhibition under dark conditions was suggested from preliminary studies of the reaction. Two variations in the molar ratio of olefin to the thiocyanogen reagent were studied to determine the effect of relative concentration on product distribution and overall yield.

The data showing the effects of the parameters for each solvent are assembled in Tables I and II. With the exception of acetic acid, the solvents listed in the tables are arranged in order of decreasing dielectric constant ϵ.

The results indicate that the stability of thiocyanogen as a reagent, unlike bromine and other halogens, is solvent dependent. The reagent is sensitive to the alcohol[3b] stabilizer in commercial chloroform, and this accounts for erratic results obtained in this system. The lower conversions for the thiocyanogen additions in acetonitrile suggest that the reagent is relatively unstable in dipolar aprotic media in comparison to acetic acid and the three nonpolar solvents employed.

Product distributions generally differed between reactions in filtered and unfiltered solutions. In the presence of insoluble lead salts retained after reagent generation there was a lack of stereospecificity and formation of significant amounts of bromothiocyanate adducts 4. Experiments in which the recovered lead salts were readded to the filtered solutions prior to olefin addition yielded product mixtures analogous in composition to those obtained with filtered solutions of thiocyanogen (Experimental Section).

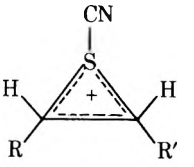
A related unexplained phenomenon concerns thiocyanogen additions in which the reagent was generated in benzene from lead thiocyanate that had been stored under refrigeration for several months (Table I). The thiocyanogen formed from the "aged" lead thiocyanate gave a product distribution in this solvent showing little variation among the complete set of parameters studied. This was in contrast to the corresponding set of experiments in which the reagent was derived from freshly prepared lead thiocyanate. The contrasting results found in this group of experiments established the necessity of using only freshly prepared lead thiocyanate in order to achieve reproducible data.

The addition of iron powder to the acetic acid experiments did not influence the product outcome, but marked changes occurred in the nonpolar media. In these solvents, the dithiocyanate adduct (1) became the principal product almost to the exclusion of adduct 2. A refinement of this procedure using $Fe(SCN)_3$ instead of powdered iron further increased the conversion to 1 as well as the overall yield of the reaction.

Only limited studies of the photoinitiated addition of thiocyanogen to olefins were carried out, principally to contrast the results obtained in polar and nonpolar media. As in the addition of iron to the acetic acid medium, photoinitiation in this solvent did not affect the final product outcome. In benzene, however, the allylic isothiocyanate 5 was the principal product. This adduct, together with the isomeric dithiocyanates 1 (erythro and threo), were the only previously reported[9] products of the free-radical addition. In addition to these two compounds, we have found that the isomeric isothiocyanato thiocyanates 2 (erythro and threo) are also formed under irradiative conditions.

Discussion

The solvents listed in Tables I and II showed marked differences in their effect on the course of thiocyanations. Acetic acid, in which the additions were stereospecific and completely insensitive to variations in the reaction parameters, was effective for the preparation of adduct 1 as the predominant isomer. In this medium the product distribution and overall yield were invariable even under protoinitiated conditions. On the basis of a two-step kinetically controlled ionic reaction mechanism previously proposed for thiocyanations in acetic acid,[4,5] adduct specificity would be expected. In the initial step of the proposed pathway addition of the ^+SCN ion leads to the formation of a *S*-cyanosulfonium cation 6 as the intermediate species. This is attacked by the ambident thiocyanate anion or the solvent itself. The stereospecific formation of products 1–4 (eq 1) suggests that the intermediate 6 is the only cationic



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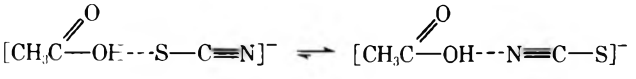
species formed in this medium. The predominance of α,β-dithiocyanates 1 and the invariance of yield and product distribution in this medium may be attributed to the ability of acetic acid to coordinate with the thiocyanate anion in a solvent cage principally through hydrogen bonding at its nitrogen terminus as in the equilibrium depicted below. Collapse



of the caged pair will occur with preferential carbon–sulfur bond formation leading to adduct 1. Formation of adduct 2 indicates some participation by the alternate hydrogen-bonded sulfur pair through reaction of the nitrogen terminus with 6. Adducts of the type 3 arise through solvation of the intermediate 6 in polar media, and subsequent formation of the acetate product, a reaction that may be anticipated on the basis of the high solvent to reagent ratio. Although consistently high conversions of olefins to α,β-dithiocyanates were obtained in acetic acid, difficulties experienced in product separations have limited the usefulness of this solvent for preparation of these compounds.

A rationale for the results of the thiocyanations carried out in CH_3CN, CH_2Cl_2, $CHCl_3$, and benzene became apparent when specific controls were placed on the parameters of this reaction. For example, the data in Tables I and II obtained for experiments using unfiltered and filtered thiocyanogen solutions containing no free-radical inhibitor display a wide distribution of nonstereoselective isomeric products arising from concurrent ionic and free-radical pathways. However, when 15 mol % inhibitor is added to the filtered thiocyanogen solution, products of inverted stereochemistry are much reduced in $CHCl_3$ and benzene and all but eliminated in CH_2Cl_2 and CH_3CN. Since no further change in product composition occurred above the addition of 15 mol % inhibitor in $CHCl_3$ and benzene, we consider that the products of inverted stereochemistry found in these experiments must arise via an *ionic* pathway. Therefore, the discussion of solvent–intermediate interactions is confined to those data obtained with filtered solutions of thiocyanogen using 15 mol % inhibitor (Tables I and II).

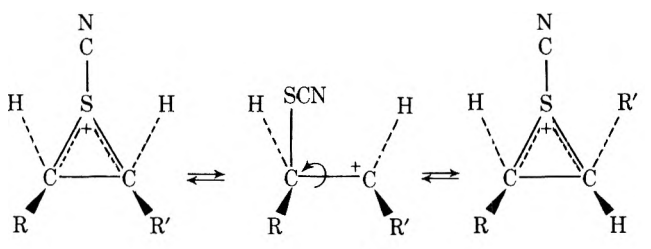
The stereoselective nature of the addition observed in

Table I. Thiocyanation of *trans*-3-Hexene. Parameter Effects on Product Composition and Yields

Solvent[a]	R in NCS–CH–CH–R[b]	Unfiltered	Filtered									
		No inhib[c]	No inhib[c]		15% inhib[c,d]		15% inhib[d] 2.4 mol $(SCN)_2$		15% inhib[c,d,e] 10% iron		No inhib[c] light	
Acetic acid	$-Br_{(e)}$	0.7	0.6		0.7		0.7		1.3			
	$-OAc_{(e)}$	4.2	3.9		3.3		3.4		4.9			
	$-NCS_{(e)}$	11.5	12.3		11.4		11.0		11.6			
	$-SCN_{(e)}$	83.4	83.2		84.6		84.9		82.2			
	Yield[h]			97.8		89.1		99.0		96.5		99.0
Acetonitrile	$-NCS_{(e)}$		30.7		31.3		31.1		9.4			
	$-NCS_{(t)}$											
	$-SCN_{(e)}$		69.3		68.7		68.9		84.2			
	$-SCN_{(t)}$								6.4			
	Yield[h]			31.4		37.0		61.7		45.0		
Methylene chloride	–Br	3.5										
	$-NCS_{(e)}$	33.3	49.8		52.2		54.0		8.3			
	$-NCS_{(t)}$	1.0	1.0		0.1							
	$-SCN_{(e)}$	58.6	47.0		46.9		44.9		89.3			
	$-SCN_{(t)}$	3.6	2.2		0.8		1.1		2.4			
	Yield[h]			89.6		73.4		67.6		82.6		86.7
Chloroform[f]	–Br	10.3										
	$-NCS_{(e)}$	39.5	56.6		59.4		61.2		0.7			
	$-NCS_{(t)}$	2.1	3.3		0.7		0.5					
	$-SCN_{(e)}$	43.1	35.6		37.3		35.5		93.6			
	$-SCN_{(t)}$	5.4	4.5		2.6		2.8		5.5			
	Yield[h]			61.1		55.3		51.2		73.5		86.6
Benzene[g]	Et–CH=CH–CHCH$_3$ (NCS)[i]	4.9	5.1		2.6		4.5				60.8	
	–Br	10.2	0.6		6.7		5.1					
	$-NCS_{(e)}$	20.2	26.7		34.4		31.7		2.5		4.4	
	$-NCS_{(t)}$	9.6	16.5		5.9		8.1				2.3	
	$-SCN_{(e)}$	36.4	30.8		40.9		37.5		92.3		19.9	
	$-SCN_{(t)}$	18.7	20.4		9.5		13.1		5.2		12.6	
	Yield[h]			31.7		58.9		57.9		75.5		75.1	68.2
Benzene	Et–CH=CH–CHCH$_3$ (NCS)											
	–Br	10.2									60.1	
	$-NCS_{(e)}$	25.8	55.0		62.0		65.8		3.4		3.8	
	$-NCS_{(t)}$	12.5	8.1		1.0		1.9				2.7	
	$-SCN_{(e)}$	32.2	30.8		35.3		30.9		92.9		19.3	
	$-SCN_{(t)}$	19.3	6.1		1.4		1.4		3.7		14.1	
	Yield[h]			55.3		50.9		48.1		58.2		82.8	68.4

[a] All solvents except acetic acid are in order of decreasing dielectric constant ϵ. [b] Structures of products are formulated in eq 1. [c] Reactions in these columns carried out in the ratio 1.2 mol $(SCN)_2$/1.0 mol olefin. [d] 2,6-Di-*tert*-butyl-4-methylphenol. [e] Reactions carried out in acetic acid and benzene used powdered iron, and those run in acetonitrile, methylene chloride, and chloroform used $Fe(SCN)_3$ as catalyst. [f] Ethanol stabilizer removed prior to use. The presence of alcohol in chloroform polymerizes $(SCN)_2$, changes product distribution, and reduces the overall conversions by half. [g] These data reflect the results obtained with "aged" $Pb(SCN)_2$. [h] Total isolated yield of thiocyanated products. [i] Product is primarily *trans*-CH_3CH_2CH=$CHCH(NCS)CH_3$ (ref 9).

benzene and chloroform solutions may be due to the exceedingly slow rate of the reaction in these solvents.[10] Slow addition rates may, to a limited extent, allow for ring opening of the intermediate cation **6** prior to collapse of the solvent–anion coordinated pair as shown in eq 2.[11] Since the extent of formation of the minor stereoisomeric products is less for *cis*-3-hexene (Table II) compared to *trans*-3-hexene (Table I) because of the faster reaction rates of cis olefins,[10] it is logical that the longer lifetime of the cyclic intermediate **6** is responsible for the formation of these compounds.



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(2)

It is evident from the data in Tables I and II that the overall ratio of the major reaction products **2**/**1** is dependent on the dielectric constant ϵ of the solvent medium employed. The results of the present study, compiled in Table III, clearly establish a trend of increasing production of adduct **2** relative to adduct **1** with decreasing ϵ. In some studies[12,13] of equilibrium interconversions of thiocyanates–isothiocyanates, a linear correlation has been determined for this relationship; however, since thiocyanogen addition is kinetically controlled[6,10] a *linear plot* of the data in the present study would not be expected. Although the results of the present experiments may be correlated with both the rate of reaction[10] and the dielectric constant of the medium, these relationships do not completely explain the product outcome. For this reason it is necessary to understand the nature of the solution effects on the intermediate ambident thiocyanate anion.

The phenomena of ambident behavior of this anion has

Table II. Thiocyanation of *cis*-3-Hexene. Parameter Effects on Product Composition and Yields

Solvent[a]	R in NCS R[b] | | -CH-CH-	Unfiltered	Filtered					
		No inhib[c]	No inhib[c]	15% inhib[c,d]	15% inhib[d] 2.4 mol $(SCN)_2$	15% inhib[c,d,e] 10% iron	No inhib[c] light	
Acetic acid	$-Br_{(t)}$	2.9	0.9	0.5	0.7		0.8	
	$-OAc_{(t)}$	10.7	9.7	10.2	9.6	11.7	9.4	
	$-NCS_{(t)}$	8.0	12.5	12.2	12.6	7.3	12.0	
	$-SCN_{(t)}$	78.4	76.9	77.1	77.1	81.0	77.8	
	Yield[g]	97.1	92.0	97.0	98.3	97.0		90.1
Acetonitrile	$-NCS_{(e)}$							
	$-NCS_{(t)}$		31.0	30.9	31.6	10.7		
	$-SCN_{(e)}$					11.6		
	$-SCN_{(t)}$		69.0	69.1	38.4	77.7		
	Yield[g]		43.1	46.0	61.7	39.8		
Methylene chloride	-Br	12.9						
	$-NCS_{(e)}$	2.4	2.6					
	$-NCS_{(t)}$	31.5	45.7	48.7	52.4	14.6		
	$-SCN_{(e)}$	3.9	2.5					
	$-SCN_{(t)}$	49.3	49.2	51.3	47.6	85.2		
	Yield[g]	90.4	73.2	84.5	86.8	85.0		
Chloroform[f]	-Br	7.3						
	$-NCS_{(e)}$	3.1		0.2	0.6			
	$-NCS_{(t)}$	39.6		54.5	56.8	1.4		
	$-SCN_{(e)}$	4.8		0.7	0.7	0.8		
	$-SCN_{(t)}$	45.2		44.6	41.9	97.8		
	Yield[g]	79.4		76.3	97.6	84.5		
Benzene	Et-CH=CH-CHCH$_3$ (NCS)[h]						44.9	
	-Br	8.6					1.9	
	$-NCS_{(e)}$	12.0	13.5	0.2	1.2		7.4	
	$-NCS_{(t)}$	26.8	46.5	56.7	60.9	1.8	7.2	
	$-SCN_{(e)}$	19.9	8.5	0.6	1.1	0.9	21.7	
	$-SCN_{(t)}$	32.7	31.5	42.5	37.0	97.3	16.9	
	Yield[g]	61.7	52.8	71.6	83.6	91.7		67.5

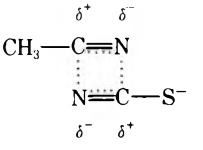
[a] All solvents except acetic acid are in order of decreasing dielectric constant ϵ. [b] Structures of products are formulated in eq 1. [c] Reactions in these columns carried out in the ratio 1.2 mol $(SCN)_2$/1.0 mol olefin. [d] 2,6-Di-*tert*-butyl-4-methylphenol. [e] Reactions carried out in acetic acid and benzene used powdered iron and those run in acetonitrile, methylene chloride, and chloroform used $Fe(SCN)_3$ as catalyst. [f] Solvent purified to remove ethanol prior to use. [g] Total isolated yield of thiocyanated products. [h] Product is primarily *trans*-CH_3CH_2CH=$CHCH(NCS)CH_3$, among allylic isothiocyanate mixture (ref 9).

Table III. Change in Product Ratio with Increasing Dielectric Constant[a]

Solvent	ϵ	2/1[b]
Benzene	2.3	2.15
$CHCl_3$	4.8	1.47
CH_2Cl_2	8.9	1.14
CH_3CN	37.5	0.46

[a] The results represent the average obtained from the thiocyanation of *cis*- and *trans*-3-hexene. [b] **2**, *erythro*- and *threo*-3-isothiocyanato-4-thiocyanatohexane; **1**, *erythro*- and *threo*-3,4-dithiocyanatohexane.

been studied in displacement reactions,[12,13] in equilibrium interconversions of thiocyanate and isothiocyanate compounds,[12,14] and in the elucidation of bonding modes in many metal–thiocyanate and metal–isothiocyanate complexes.[15] Recourse to Pearson's HSAB concept[16] has provided the best means of explaining the bonding behavior of this anion.[17] Under this classification, the large sulfur atom is a "soft base" with charge dispersal over a large volume compared to the nitrogen atom, a "hard base" bearing a greater charge to size ratio. To determine the relative influence of solvent on the reactions of hard and soft bases with hard and soft acids, Klopman[18] developed a theoretical basis of the Pearson concept that included the solvent as a parameter. Klopman's equations predict that hard base–hard acid interactions are charge controlled and depend primarily on the ionic interactions of the reagents, whereas soft base–soft acid interactions are frontier controlled in reactions of nucleophiles having low electronegativity and are enhanced by high polarizability and low solvation energies of the reactants. In solvents of low dielectric constant, ions and ion pairs are more strongly associated than in polar solvents. The ambident thiocyanate anion is thus more effectively solvated at the soft sulfur atom by nonpolar solvents, presumably by charge transfer interactions, leading principally to a charge controlled nitrogen attack on the episulfonium cation. Strong ion pair association would account for slower reaction rates (only qualitatively determined) in nonpolar solvents. With increasing dielectric constant in the order PhH < $CHCl_3$ < CH_2Cl_2 ≪ CH_3CN, the rates increased in favor of sulfur attack (Table III). Increasing ϵ, therefore, changed the direction of reaction from charge controlled (nitrogen attack) to frontier controlled (sulfur attack) with diminution in the 2/1 adduct ratio. A dipolar aprotic solvent like acetonitrile may, however, also associate with thiocyanate anion by dipole alignment, pictorially represented below in one possible arrangement, that would leave



the polarizable sulfur terminus less restricted than nitrogen,[17] effectively contributing to the bonding mode of the thiocyanate anion.

Table IV. Thiocyanation of *trans*-3-Hexene in Benzene.[a] Effect of Catalyst on Product Distribution and Yield

R in product NCS R | | –CH–CH–	Percent products: No added metal	Iron powder[c]	$Fe(SCN)_3$
$-NCS_{(e)}$	62.3	3.4	0.2
$-NCS_{(t)}$	1.0		
$-SCN_{(e)}$	35.3	92.9	98.9
$-SCN_{(t)}$	1.4	3.7	0.9
Yield[b]	48.1	82.3	92.8

[a] Reactions conditions: 1.2 mol $(SCN)_2$/1.0 mol olefin + 15 mol % inhibitor. [b] Total isolated yield of thiocyanated products. [c] Incomplete studies indicate that grade of iron powder used affects product distribution and yield.

The use of iron catalysts was an intriguing alternative to acetic acid for directing the primary, if not exclusive, formation of dithiocyanates. The hypothesis of ferric thiocyanate as the active agent arising by reaction of iron and thiocyanogen in nuclear thiocyanations of aromatic rings[3a] was also confirmed for the present series of olefin thiocyanations. Remarkably, the ferric thiocyanate catalyzed thiocyanations of internal olefins in benzene solution gave almost exclusively the dithiocyanate adduct 1 compared to 35% yield in catalyst-free reactions (Table IV).

The metal catalyst provided an example of the utility of the HSAB concept as an aid in the clarification of the mechanism. Since ferric thiocyanate in solution is a metal coordination complex,[15e,f] the metal–ligand interaction is responsible for the stereochemical specificity. The HSAB concept predicts that Fe^{3+} is a hard acid[16,18] and should be expected to form hard anion–hard metal ligand bonds. The nitrogen terminus of thiocyanate is coordinatively bound to ferric ion with the sulfur terminus in free projection. It has been observed in other cases[15c,f] that the degree of hardness or softness of a metal atom is solvent dependent. Burmeister[15c] found that Pd^{2+} (a soft acid) in complexes showed only Pd–S bonding in "class a" solvents (dipolar, aprotic; high ϵ) whereas in "class b" solvents (benzene, $CHCl_3$; low ϵ) Pd–S, Pd–N, and bridged –NCS– bonding was observed. Presumably, the Pd^{2+} ion becomes *harder* with decreasing dielectric constant. Our results with ferric thiocyanate indicate a similar trend. In benzene,[15c] metal–ligand bonding is exclusively through nitrogen, whereas both Fe–NCS and Fe–SCN evidently appear as the solvent dielectric constant is increased (Tables I and II). Using Pearson's terminology, it would seem that Fe^{3+} cation becomes softer as the solvent medium is shifted from benzene to acetonitrile. Unfortunately, the instability of thiocyanogen in solvents of higher dielectric constant than acetonitrile limits the determination of the soft–soft interactions for this system.

A further test of the HSAB concept as it relates to these studies would involve the effect of other metal salts on the course of thiocyanation addition reactions. It would seem unlikely that ferric ion among metal ions is unique in directing the course of this addition. Metal–ligand interactions in nonpolar solvents may further explain the results of thiocyanations in the presence of unfiltered lead salts by which a higher proportion of dithiocyanate adduct was obtained than in lead salt-free solutions. Like ferric thiocyanate, lead may be influencing the direction of attack through interaction with the nitrogen end of the thiocyanate anion. However, the limited solubility of lead thiocyanate in these solvent studies precludes a verifiable extension of the concept

Finally, brief mention must be made of the results obtained with thiocyanogen addition under homolytic conditions (Tables I and II). Reports in the literature are in slight disagreement with our results presented in this study. Guy and Thompson[9] had irradiated thiocyanogen in the presence of *cis*- and *trans*-3-hexene in benzene solution. They obtained two products: identical mixtures of erythro and threo dithiocyanates I (30%) and the allylic isothiocyanate (5, 70%). We, on the other hand, have additionally found that under similar conditions the erythro and threo isothiocyanatothiocyanates (2) are formed in amounts ranging from 7 to 15%. The presence of these compounds is not unexpected, since the reaction involves the thiocyanate radical, which, like the thiocyanate anion, should display ambident behavior. It can

$$\cdot S{-}C{\equiv}N \leftrightarrow S{=}C{=}N\cdot$$

be seen from the results in Tables I and II that the erythro and threo adducts 1 and 2 from both olefins are formed in nearly equal amounts. These findings would support the view[9] that the intermediate in this reaction is formed by reversible addition of the thiocyanate radical to the olefin. Since *erythro*-2 and *threo*-2 are in equal amounts in these reactions, a requirement for free-radical addition, their formation cannot be attributed to a concurrent ionic pathway.

Experimental Section

Equipment. Product mixtures were analyzed on a Model 810 F & M gas chromatograph (8 ft × 3/16 in. SS column containing 15% HI-EFF DEGS on 50/60 Mesh Anakrom[19] ABS). The IR spectra were obtained with a Perkin-Elmer Model 457 grating infrared spectrophotometer and NMR spectra were recorded on a Jeolco Model 60H spectrometer.

Solvents and Materials. Benzene and acetonitrile (both Mallinckrodt nanograde) and methylene chloride (Fisher ACS grade) were used as obtained. The acetic acid (Baker Reagent grade) contained an added 1% acetic anhydride. Commercial chloroform (Baker Reagent grade) contained 0.75% ethanol as preservative. For reactions requiring alcohol-free chloroform, the alcohol was removed by successive treatments of stirring with concentrated sulfuric acid for several hours, repetitive water washings, drying over potassium carbonate, and distillation prior to use.

cis- and *trans*-3-hexenes were obtained from Chemical Samples Co. The isomeric purity of the olefins was established by bromination of each olefin to its corresponding α,β-dibromide and GLC analysis of the crude product mixtures. Lead thiocyanate was prepared by the method of Lambou and Dollear.[20]

General Reaction Procedures. The techniques and experimental conditions used for reactions in each solvent were similar. Thiocyanogen solution for the unfiltered reactions was prepared separately in each experiment whereas this reagent was prepared in single batches for use in the series of filtered experiments. Equipment was thoroughly dried prior to use. All reactions were run at room temperature under a nitrogen atmosphere.

Reactions with Unfiltered Thiocyanogen. Thiocyanogen was prepared in the specific solvent under investigation by batchwise addition of bromine (1.92 g, 0.012 mol) to a stirred solution of lead thiocyanate (7.95 g, 0.024 mol) in 70 mL of solvent. The mixture was stirred in the dark for 1.5 h prior to addition of the olefin (0.84 g, 0.01 mol) dissolved in 10 mL of solvent. Stirring was continued for 24 h, then the mixture was quenched with sodium thiosulfate solution. The internal standard, methyl stearate (0.25 g in 10 mL of benzene), was added and the organic layer was filtered and reduced in volume. The crude reaction mixture was analyzed by glc without further workup.

Reactions with Filtered Thiocyanogen. Bromine (13.5 g, 0.084 mol) was added to a stirred solution of lead thiocyanate (54.5 g, 0.168 mol) in solvent (490 mL) in the manner described above. The thiocyanogen solution was filtered through a sintered glass funnel and the calculated volumes delivered to the series of reaction vessels with a glass syringe fitted with a Teflon needle. In the present study, the admixture of thiocyanogen (70 mL containing 0.012 mol) and olefin (0.01 mol per 10 mL of solvent) provided the 1.2 mole ratio and twice the volume of thiocyanogen solution gave the 2.4 mole ratio for reactions. Inhibition of the homolytic reaction was examined with 2,6-di-*tert*-butyl-4-methylphenol as the inhibitor at concentrations of 5 mol % (0.132 g, 0.6 mmol) and 15 mol % (0.396 g, 1.8 mmol) for the 1.2 mole ratio of thiocyanogen to olefin. Other concentrations were accordingly calculated. Metal catalysis was determined with powdered iron (0.1 g, 1.8 mmol) or ferric thiocyanate.

The homolytic reaction between thiocyanogen and olefin (1.2 mole ratio) was carried out under nitrogen for 24 h by irradiation with a 300-W incandescent bulb.

Control Experiments. The following experiments were carried out on the products **1a** and **2a** from *trans*-3-hexene to demonstrate the resistance of the products to isomerization under the experimental conditions employed. A sample of 3,4-dithiocyanatohexane **1a** was added to unfiltered thiocyanogen in benzene solution and stirred in the dark for 24 h. The crude reaction mixture showed only **1a** by GLC analysis. Repetition of the experiment with the corresponding **2a** similarly demonstrated that **2a** was not isomerized.

The effect of added salts on the product composition of the thiocyanation of *trans*-3-hexene was determined in the following manner. A benzene solution of thiocyanogen was prepared, filtered, and delivered into four flasks each containing a mixture of 0.01 mol of *trans*-3-hexene in 10 mL of benzene. Lead thiocyanate (2.0 g) was freshly prepared and added to flask a, freshly prepared lead bromide (2.0 g) was added to flask b, a mixture of 2.0 g of lead thiocyanate and 2.0 g of lead bromide was added to the contents of flask c, and 2.0 g of the crude salts obtained from the filtration of thiocyanogen solution was added to flask c. The above four mixtures were stirred in the dark under nitrogen for 24 h. Analysis of the contents of flasks a, b, c, and d by GLC showed nearly identical chromatographic traces for all four mixtures, essentially unchanged from a trace obtained from the filtered thiocyanation additions carried out in benzene.

Registry No.—*trans*-3-Hexene, 13269-52-8; *cis*-3-hexene, 7642-09-3; $(SCN)_2$, 505-14-6.

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(19) Reference to brand or firm name does not constitute endorsement by the U.S. Department of Agriculture over others of a similar nature not mentioned.
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Thiocyanations. 3.[1] Preparation of 2-Imino-1,3-dithiolane Salts by Cyclization of *vic*-Dithiocyanates

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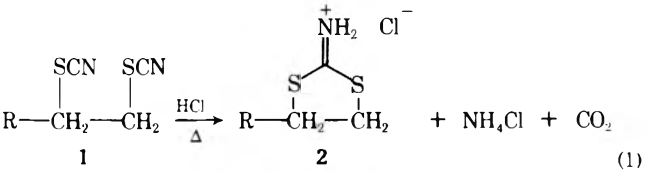
A series of 2-imino-1,3-dithiolane salts has been formed stereospecifically through the cyclization of *vic*-dithiocyanate derivatives of alkenes and unsaturated fatty acids. This cyclization has been accomplished using methanesulfonic acid as both coreactant and solvent. Methods of isolation of the product salts are briefly described.

Derivatives of 2-imino-1,3-dithiolane salts[3,4] demonstrate synthetic utility as intermediates in the preparation of pesticidally active compounds.[5–7] Although the heterocyclic structure was initially derived by cyclization of *vic*-dithiocyanates of ethane and propane by Miolati in 1891,[8] the method has received little attention since that time. Iminodithiolane derivative were subsequently prepared by reaction of *vic*-dithiols and cyanogen chloride[4–7] and by acid-catalyzed cyclization of allylic[6a,9] or β-hydroxyalkyl[10] esters of dithiocarbamic acid.

The alkyl substituted iminodithiolanes that had been prepared previously[4–10] were short-chain species of fewer than seven carbon atoms. Our efforts to obtain new long-chain aliphatic substituted compounds by incorporation of the heterocyclic structure into unsaturated fatty acids were precluded by difficulties encountered in the preparation of *vic*-dithiols[11] and by the indirect syntheses required for dithiocarbamate derivatives. As a result of our recent studies on the elucidation of olefin thiocyanations,[12] the *vic*-dithiocyanates that were readily obtainable presented the opportunity to study their chemistry as an essentially unexplored route to the titled compounds.

The 2-imino-1,3-dithiolane hydrochlorides (**2**) were first prepared by Miolati[8] from *vic*-dithiocyanates (**1**) in refluxing hydrochloric acid (eq 1). This technique required prolonged

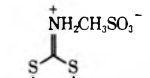
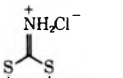
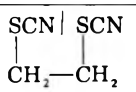
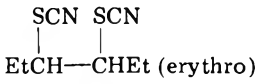
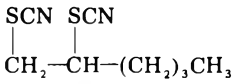
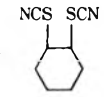


1 2 (1)

R = H; CH_3

heating and resulted in diminished yields. Miolati[8] improved the yield of **2** by a method using the tin and hydrochloric acid

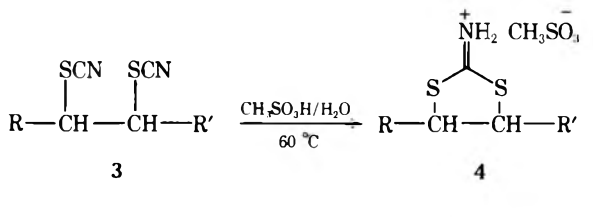
Table I. Methanesulfonates and Hydrochlorides from the Cyclization of Some 1,2-Dithiocyanates

	Starting dithiocyanate	Yield, %	Reaction time, h	Mp,[a] °C: 	Mp,[a] °C: 
6		70	4	155–157[c]	
7		85	2	132–134 (cis)[d]	
8		80	4	122–124 (trans)[e]	
9		70	8		159–161[f]
10		90	12	90–95[g]	
11		90	6.5		238–240[b,h]

[a] Melting points were usually accompanied by decomposition. [b] Addor reported mp 243–246 °C (ref 4). [c] Registry no., 61522-05-2. [d] Registry no., 61521-98-0. [e] Registry no., 61522-00-7. [f] Registry no., 49549-01-1. [g] Registry no., 61522-07-4. [h] Registry no., 61522-08-5.

reduction of 1 followed by treatment of the resultant tin–hydrochloride double salt with hydrogen sulfide. Both methods, however, resulted in the formation of a nearly inseparable mixture of 2 and the coproduct ammonium chloride. We have reexamined these procedures with the model compounds (1, eq 1) and longer chain dithiocyanates. It was found that solubilities of the longer chain compounds in this medium in comparison to ethylene dithiocyanate are greatly diminished and conversions to adduct 2 are negligible. We therefore attempted to modify the Miolati method with cosolvents such as tetrahydrofuran, dioxane, and dimethyl sulfoxide to solubilize the dithiocyanate adducts in concentrated hydrochloric acid. None of these attempts lead to cyclization to the desired products. These failures led to the conclusion that cyclization would occur effectively only in the presence of a concentrated strong acid medium. Among the acids examined, namely phosphoric, trifluoroacetic, and methanesulfonic acids, cyclization was accomplished only with the latter, which served in the dual role of catalyst and solvent.

The dithiocyanates dissolved in methanesulfonic acid containing a small amount of water and cyclized smoothly at 60 °C within 1–8 h (eq 2). This cyclization does not involve the



3 4

+ $CH_3SO_3NH_4$ + CO_2 (2)

5

asymmetric vicinal carbon atoms so that the method is advantageous for the stereospecific formation of the adducts 4.[14] The rate of disappearance of dithiocyanate was easily monitored by infrared spectroscopy using the following technique. Samples of the reaction mixture were neutralized with aliquots of 1,2-epoxybutane. This mild reaction converted the methanesulfonic acid to neutral hydroxybutylmethanesulfonate esters with no effect on unreacted dithiocyanate. Completion of the cyclization reaction was indicated by the absence of the strong infrared band for –SCN at 2150 cm^{-1}.

The difficulties encountered by Miolati in separating 2 from ammonium chloride were not experienced in the methanesulfonic acid experiments. Dilution of the product mixture with chloroform resulted in the precipitation of the comparable ammonium methanesulfonate (5). Removal of excess methanesulfonic acid from the product 4 was first attempted by neutralization with mild base. This method failed owing to the instability of the free iminodithiolanes formed in this process. Less drastic techniques used to isolate 4 achieved the desired results. In one method the aqueous methanesulfonic acid was removed from the product 4 using ethyl ether in a continuous extraction apparatus. Although this method required several days for completion, satisfactory yields of the product salts 4 were obtained. A second, more rapid method of product recovery involved the use of ion exchange chromatography. After removal of ammonium methanesulfonate the crude product mixture was passed through a chloride anion exchange column resulting in the recovery of the product as the hydrochloride salt 2. The yields and melting points for both classes of iminodithiolane salts prepared in this study are listed in Table I. The desired products were obtained for all of the dithiocyanates cyclized except for those adducts derived from oleic and elaidic acids. Both of these dithiocyanates were consumed in the reaction forming a water-soluble mixture, but attempts to isolate the products were unsuccessful. Identical spectral and NMR data for both products suggest that a possible zwitterionic structure is formed between the polar groups in these compounds enhancing their solubility in the aqueous reaction medium.

Addor[4] has observed that two characteristic infrared frequencies are assignable to the 2-imino-1,3-dithiolane hydrochlorides, which exhibit an absorption for the >C=N group at 1560 cm^{-1} and a band for the $-NH_2$ bending vibra-

tions at 1488 cm^{-1}. Replacement of chloride ion for the methanesulfonate group did not result in any significant shifts in the positions of these two bands. Infrared spectra of the hydromethanesulfonate salts[3] as KBr pellets showed an absorption band at 1570 cm^{-1} for the >C=N group and at 1480 cm^{-1} for the $-NH_2$ group. A detailed analysis of the ^1H NMR spectra of the 2-imino-1,3-dithiolane hydromethanesulfonates is described in part 5 of this series.[14]

Experimental Section

Reagents. The *vic*-dithiocyanate adducts were prepared by thiocyanogen addition to the olefinic compounds as described in previous reports.[1,12] Ethylene dithiocyanate was a commercial sample supplied by Eastman Kodak.[15] Anion ion exchange resin AG 1-X4 (Bio-Rad Laboratories) was obtainable in analytical grade for the interchange of methanesulfonate and chloride anions.

Procedure. Examples of the Preparation of 2-Imino-1,3-dithiolane hydrogen Methanesulfonates and Chlorides. *cis*-4,5-Diethyl-1,3-ditholane-2-iminium Methanesulfonate from *erythro*-3,4-Dithiocyanatohexane 7. Compound **7** (1.0 g, 5.0 mmol) was added to a solution of 100 mg of water in 5 g of freshly distilled methanesulfonic acid. Upon heating the mixture to 60 °C the solid dithiocyanate dissolved and a vigorous evolution of carbon dioxide occurred. Aliquots were removed at frequent intervals as described in the text to test for completion of reaction. Upon completion of the reaction, coproduct **6** was removed as described below. The reaction mixture was then diluted with water and placed in a continuous extraction apparatus using ethyl ether as the extracting solvent. The product was extracted into ether which upon evaporation left a solid residue. The recovered salt was purified by recrystallization from methanol/ether and gave 1.15 g (85%): mp 132–134 °C dec; IR (KBr pellet) 2850, 1540, 1460, 1200, and 1050 cm^{-1}. Anal. Calcd for $C_8H_{17}NO_3S_3$: C, 35.4; H, 6.35; N, 5.15; S, 35.4. Found: C, 35.23; H, 6.34; N, 5.14; S, 35.7.

On the basis of this procedure, the hydromethanesulfonate salts of compounds **6**, **8**, **9**, and **11** were isolated and satisfactory spectral data and elemental analyses were obtained.

***trans*-4,5-Hexahydrobenzo-1,3-dithiolane-2-iminium Methanesulfonate from *trans*-1,2-Dithiocyanatocyclohexane 11.** Using the same procedure as described above, **11** was cyclized in 6.5 h to the title compound. However, the product could not be removed from the excess methanesulfonic acid by continuous extraction with ether. Exchange of methanesulfonic acid for volatile hydrochloric acid was simply attained by aqueous dilution of the crude methanesulfonic acid mixture after cyclization and elution through a column of AG 1-X4 resin (chloride form) and evaporation of the eluates. Comparison of the melting point and published spectral data[4] established the structure of this compound. By a similar technique the dithiocyanate **9** was also converted to the hydrochloride salt.

Ammonium methanesulfonate (5) precipitated upon addition of chloroform to the crude reaction mixture. The compound was isolated as a white, crystalline solid, purified by repeated washings with chloroform (mp 198–201 °C dec), and identified by IR (KBr pellet): 3100, 1920, 1200, 1050, 780, and 560 cm^{-1}. Anal. Calcd for CH_7NO_3S: C, 10.62; H, 6.19; N, 12.4; S, 28.5. Found: C, 11.04; H, 6.26; N, 12.38; S, 28.9.

Registry No.—**5**, 22515-76-0; **6**, 629-17-4; **7**, 30647-63-3; **8**, 61521-96-8; **9**, 61522-04-1; **10**, 55602-15-8; **11**, 30647-66-6.

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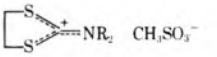
(2) Agricultural Research Service, U.S. Department of Agriculture.
(3) The *Chemical Abstracts* systematic name for structure **2** (R = H) is "cyclic ethylene dithioimidocarbamate hydrochloride". A convenient, acceptable name for 2,2-imino-1,3-dithiolane (ref 4) was adapted to the compounds reported in this paper. The methanesulfonate salts are accordingly termed hydromethanesulfonates. The alternative name applicable to the methanesulfonate of **4**, 2-imino-1,3-dithiolinium methanesulfonate, is descriptive of the carbonium ion (structure below) and reflects the reactivity toward



nucleophiles [see T-L. Ho, *Chem. Rev.*, **75**, 1 (1975); T. Nakai and M. Okawara, *Bull. Chem. Soc. Jpn.*, **43**, 1864 (1970); J. L. Richards, D. S. Tarbell, and E. H. Hoffmeister, *Tetrahedron*, **24**, 6485 (1968)].
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(11) Preparations of *vic*-dithiols to be reported in a subsequent publication.
(12) L. S. Silbert, J. R. Russell, and J. S. Showell, *J. Am. Oil. Chem. Soc.*, **50**, 415 (1973).
(13) Dry hydrochloric acid dissolved in nonpolar solvents also failed to effect cyclization of adduct **1**. Under these conditions hydrochloric acid may be too weak an acid to function effectively as a catalyst or requires the presence of water to bring about cyclization.
(14) Part 5: R. J. Maxwell, P. Pfeffer, and L. S. Silbert, *J. Org. Chem.*, accompanying paper in this issue.
(15) Reference to brand or firm name does not constitute endorsement by the U.S. Department of Agriculture over others of a similar nature not mentioned.
(16) Infrared spectra were recorded on a Perkin-Elmer Model 457 spectrophotometer.

Thiocyanations. 4. Cyclization of 1-Isothiocyanato-2-thiocyanates. A Stereospecific Route to the Preparation of 4,5-Thiazolidine-2-thiones[1,2]

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When 1-isothiocyanato-2-thiocyanates **2** are heated in ethanolic potassium hydroxide, they cyclize to 4,5-thiazolidine-2-thiones. It was found that 4,5-thiazolidine-2-thiones prepared in this manner are formed stereospecifically. The representative examples of adducts **2** cyclized to the heterocyclic derivatives are discussed and a mechanism based on the experimental observations is proposed.

vic-Dithiocyanates **1**, which are obtained by the trans addition[4,5] of thiocyanogen to olefins (eq 1), have long been useful intermediates for the preparation of thiiranes[6] **3** (eq 2) and, more recently, were effectively cyclized to 2-imino-1,3-dithiolane salts **4** (eq 3).[2] The isomeric adduct, 1-isothiocyanato-2-thiocyanate **2**, has been identified and isolated as a minor product of the thiocyanation reaction.[4,7] However, studies in this laboratory[8] have shown that the relative amounts of the two isomers **1** and **2** formed are solvent dependent so that either isomer may be prepared as the primary product (eq 1). The versatility of this reaction provides isomer **2** as a potential intermediate which could extend the utility of the thiocyanation reaction to other heterocyclic preparations.

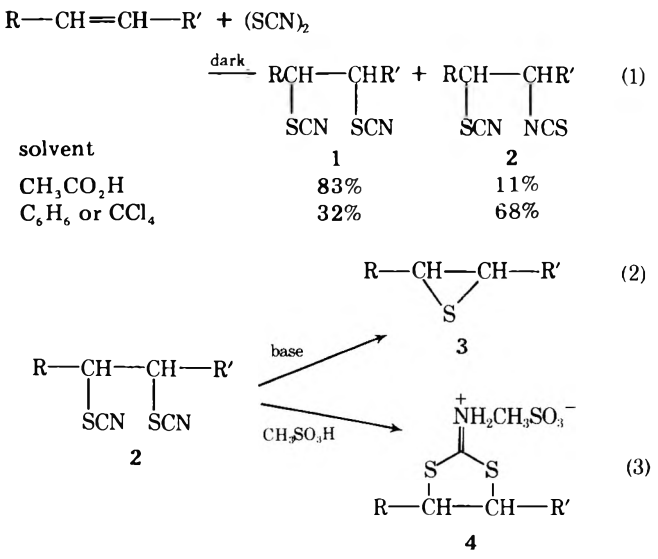
In contrast to the known base-induced cyclization of *vic*-dithiocyanates to form the three-membered thiirane ring[6] (eq

Table I. Yields and Stereochemistry of Thiazolidine-2-thiones from 1-Isothiocyanato-2-thiocyanates

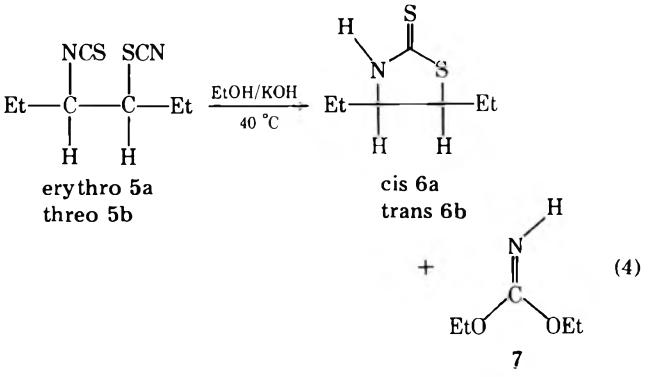
R—CH(SCN)—CHR′	R	R′	R—CH(S)—CH—R′	Yield, %
5a erythro	CH_3CH_2–	CH_3CH_2–	6a cis	70
5b threo	CH_3CH_2–	CH_3CH_2–	6b trans	60
8[a]	C_4H_9–	H–	9a	85 {85
	H–	C_4H_9–	9b	85 {15
10 trans	–C_4H_8–		11 trans	60
12 erythro	C_8H_{17}–	C_8H_{17}–	13 cis	90
14 erythro	Ph	CH_3	15 cis	30
16	–$(CH_2)_8CO_2H$	H	17	50
18 erythro	$CH_3(CH_2)_7$–	–$(CH_2)_7CO_2H$	19 cis	60
20 threo	$CH_3(CH_2)_7$–	–$(CH_2)_7CO_2H$	21 trans	45

[a] 8 was an unseparable mixture of two positional isomers; however, the products of cyclization were separated to pure 9a and 9b.

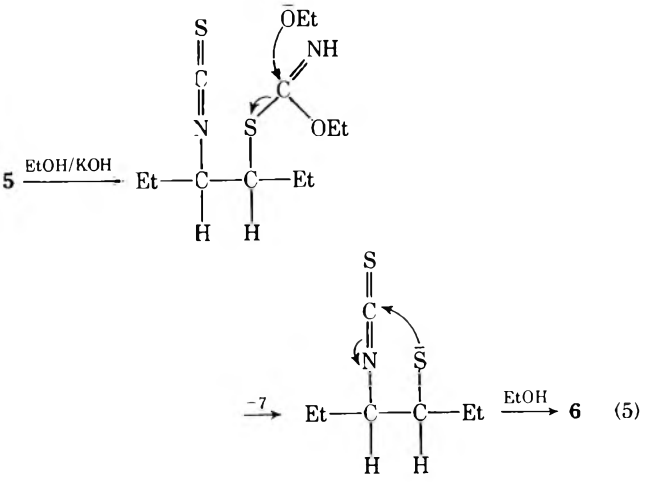
2), we have found that 1-isothiocyanato-2-thiocyanate adducts **2** cyclize in base to form the five-membered heterocycle 4,5-



thiazolidine-2-thione **6** as formulated in eq 4 for the erythro adduct **5a** and threo adduct **5b**. Diethyl imidocarbonate **7** was

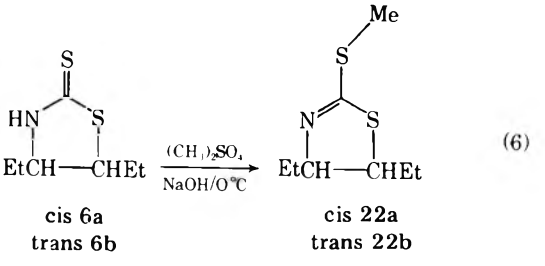


also isolated as the coproduct of this reaction and was identified by IR and NMR spectra and by comparison of its GLC retention time with that of an authentic sample prepared by an independent method.[9a,b] The isolation of coproduct **7** aided in establishing a mechanism for the cyclization of **5a** and **5b**. In the proposed mechanism shown in eq 5 initial attack by base on **5** occurs at the thiocyanate group and does not involve the asymmetric methine carbon atoms whose stereochemical identity is maintained in the product **6**. A series of aliphatic 4,5-thiazolidine-2-thiones listed in Table I was obtained in yields ranging from 45 to 90%, whereas the aromatic adduct



14 provided the corresponding **15** less efficiently.

Proof of structure of the geometric isomers **6a** and **6b** was aided by the earlier study of Foglia et al.,[10] who synthesized the two compounds by an alternate procedure. They demonstrated with ^1H NMR spectroscopy that **6a**, the isomer with the larger methine coupling constant (J_{ab} = 6.8 Hz), was the cis isomer and that **6b** (J_{ab} = 4.2 Hz) was the trans isomer. Our IR and NMR spectra for these isomers agreed with those of Foglia; hence, the geometry of **6a** and **6b** was established. However, spectral comparison does not rule out the possibility of contamination of each isomer by small amounts of its geometric isomer. To establish the stereospecificity of the cyclization reaction, the crude reaction products **6a** and **6b**, from the cyclization of **5a** and **5b**, were each converted to the 2-methylthio-Δ^2-thiazoline derivative (eq 6). This sequence does



not alter the stereochemistry at the asymmetric carbon atoms of **6a** and **6b** so that no change in geometric configuration should occur in this reaction. The thiazoline derivatives **22a** and **22b** were obtained as volatile liquids. Each product was examined without further purification to prevent changes in composition during workup. It has been reported[11] that the IR spectra of thiazolines display an intense absorption at 1575

cm^{-1} which is ascribed to the C=N linkage of the thiazoline ring. The IR spectra of **22a** and **22b** showed this absorption. Foglia et al.[10] have reported that the GLC characteristics of isomeric thiazolines are analogous to those of the corresponding isomeric oxazolines[12] wherein the cis isomers for both series have longer relative retention times than the trans isomers. The crude products **22a** and **22b** were analyzed by GLC and each was found entirely free of the opposite geometric isomer. This indicates complete stereospecific cyclization of the precursors **5a** and **5b** to the thiazolidine-2-thiones **6a** and **6b**, respectively. From these results it may be inferred that the proposed trans addition of thiocyanogen to olefins in formation of 1-isothiocyanato-2-thiocyanates[4,5] is verified.

The cyclization of **5a** and **5b** to form **6a** and **6b** appears to be the only reported method for the stereospecific synthesis of both *cis*- and *trans*-thiazolidine-2-thiones. Other reports[10,13] indicate that while the *trans*-thiazolidine-2-thione may be obtained free of the cis isomer, the formation of the cis compound is accompanied by no less than 8% of the trans isomer.

Experimental Section

Melting points (uncorrected) were determined on a Kofler hot stage.[14] Infrared spectra were measured with a Perkin-Elmer Model 457 grating spectrophotometer. NMR spectra were recorded on a Jeolco C-60H spectrometer. Mass spectra were obtained with a Du Pont Model 21492 mass spectrometer. GLC analyses were carried out with an F&M Model 810 gas chromatograph.

Materials. *cis*- and *trans*-3-hexene and 1-phenylpropene were obtained from Chemical Samples Co., and their purity was established by GLC. 1-Hexene and cyclohexene were Phillips Petroleum products and were found to be 99+% pure. 10-Hendecenoic acid and *trans*-9,10-octadecenoic acid were prepared in this laboratory. Methyl *cis*-9,10-octadecenoate (99% purity) was purchased from Applied Science Labs. All solvents used in this study were reagent grade.

Preparation and Purity of 1-Isothiocyanato-2-thiocyanates. The procedures used to prepare these adducts have been reported elsewhere.[4,8] All of the 1-isothiocyanato-2-thiocyanates prepared were isolated from the product mixtures by silica gel chromatography as amber-colored, viscous oils. Analysis of these compounds by GLC confirmed their stereochemical purity. The IR spectra of these compounds are characterized by the intense absorption at 2150 cm^{-1} (s) for -SCN and at 2060 cm^{-1} (broad) for -NCS. A detailed analysis of the ^1H NMR spectra of **5a** and **5b** will be published elsewhere.[5]

Cyclization of 1-Isothiocyanato-2-thiocyanates. The 1-isothiocyanato-2-thiocyanate adduct (15 mmol) and KOH (2.0 g) in absolute ethanol (35 mL) were heated at 45 °C for 45 min. The reaction mixture was acidified with dilute HCl, extracted with $CHCl_3$, and dried over Na_2SO_4. After removal of solvent, the residue was purified by silica gel chromatography. The purity of samples, excluding **17**, **19**, and **21**, was determined by GLC.

***cis*-4,5-Diethylthiazolidine-2-thione (6a)** from *erythro*-3-isothiocyanato-4-thiocyanatohexane (**5a**) was isolated as a viscous oil. The product was identified by comparison of the IR and NMR spectra of the authentic compound prepared by an alternate procedure,[10] and by the preparation of the 3-*p*-nitrobenzoyl-*cis*-4,5-diethylthiazolidine-2-thione derivative, mp 93–94 °C (lit.[10] 93–94 °C).

***trans*-4,5-Diethylthiazolidine-2-thione (6b)** was obtained from *threo*-3-isothiocyanato-4-thiocyanatohexane (**5b**), and identified by comparison of its melting point, 58.5–59.5 °C (lit.[10] 59–60 °C), NMR, IR, and mass spectra with those of the authentic compound prepared by an alternate procedure.[10]

4-Butylthiazolidine-2-thione (9a) and 5-butylthiazolidine-2-thione (9b) were obtained from 1(2)-isothiocyanato-2(1)-thiocyanate (**8**). The adduct **8** was a mixture of two isomeric isothiocyanatothiocyanates. GLC of the product **9** showed two overlapping peaks in the ratio 85/15. Chromatography on a silica gel column completely separated the two components **9a** and **9b**, although an insufficient amount of **9b** was obtained for a satisfactory elemental analysis: **9a** mp 55–56 °C; **9b** mp 89–90 °C; **9a** NMR ($CDCl_3$) 9.3 (very broad, 2), 4.3 (broad, apparent pentuplet, 1), 3.6 and 3.2 (8 lines, 2), 2.4 (t, 2), and 1.3 ppm (s, 14); **9b** NMR ($CDCl_3$) gave spectrum similar to that of **9a** except that the methine protons superimposed upon the methylene protons (3.5–4.2 ppm, 3). **9a** Anal. Calcd for $C_7H_{13}NS_2$: C, 47.96; H, 7.48; N, 7.48; S, 36.58. Found: C, 47.92; H, 7.93; N, 7.65; S, 36.94.

***trans*-Hexahydrobenzothiazolidine-2-thione (11)** was obtained from *trans*-1-isothiocyanato-2-thiocyanatocyclohexane (**10**), and isolated as a solid which on recrystallization from benzene gave platelets, mp 174–175 °C (lit.[15] 173–174 °C).

cis-**4,5-Dioctylthiazolidine-2-thione (13)** from *erythro*-9-isothiocyanato-10-thiocyanatooctadecane (**12**) was recovered as a viscous oil. The IR and NMR spectra were identical with those obtained from the authentic compound.[10]

***cis*-5-Methyl-4-phenylthiazolidine-2-thione (15)** from *erythro*-1-isothiocyanato-2-thiocyanato-1-phenylpropane (**14**) was isolated as a solid and recrystallized from methylene chloride/benzene: mp 159.8–160.0 °C; IR (KBr) 3100 (NH), 1490 (CSNH), 1250, 1030 (C=S), 810, 690 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NS_2$: C, 57.38; H, 5.30; N, 6.69; S, 30.63. Found: C, 57.60; H, 5.46; N, 6.52; S, 29.97.

4-(8-Carboxyoctyl)-thiazolidine-2-thione (17) from 10-isothiocyanato-11-thiocyanatohendecanoic acid (**16**) (isomeric purity not established) was recovered as a solid and recrystallized from hexane/ether: mp 100–102 °C; IR (KBr) 3230 (NH), 1695 (C=O), 1505 (CSNH), 1180, 1045 (C=S), 950, 840 cm^{-1}; NMR ($CDCl_3$) methine resonance (4.3 ppm), methylene (3.6 and 3.2). Anal. Calcd for $C_{12}H_{21}NO_2S_2$: C, 52.33; H, 7.68; N, 5.09; S, 23.28. Found: C, 52.53; H, 7.93; N, 4.94; S, 23.06.

***cis*-4(5)-Octyl-5(4)-(7-carboxy)heptylthiazolidine-2-thione (19)** was obtained from *erythro*-9(10)-isothiocyanato-10(9)-thiocyanatooctadecanoic acid (**18**). The adduct **18** was a mixture of two positional isomers whose composition remained unchanged in the product **19**. The product was a solid which was recrystallized from acetone/hexane: mp 109–111 °C; neut equiv, calcd, 373.6, found, 370; IR (KBr) 3100 (NH), 1700 (C=O), 1495 (CSNH), 1175, 1010 (C=S), 810 cm^{-1}. Anal. Calcd for $C_{19}H_{35}NO_2S_2$: C, 61.08; H, 9.44; N, 3.74; S, 17.16. Found: C, 61.05; H, 9.73; N, 3.72; S, 17.20.

***trans*-4(5)-Octyl-5(4)-(7-carboxy)heptylthiazolidine-2-thione (21)** was obtained from *threo*-9(10)-isothiocyanato-10(9)-thiocyanatooctadecanoic acid (**20**). The adduct **20** was a mixture of two positional isomers whose composition remained unchanged in the product **21**. The product was a solid recrystallizable from acetone/hexane: mp 79–80 °C; neut equiv, calcd 373.6, found 370; IR (KBr) 3100 (NH), 1700 (C=O). 1495 (CSNH), 1160, 1000 (C=S), 875, 715 cm^{-1}. Anal. Calcd for $C_{19}H_{35}NO_2S_2$: C, 61.08; H, 9.44; N, 3.74; S, 17.16. Found: C, 61.00; H, 9.50; N, 3.74; S, 17.44.

Diethyl imidocarbonate was prepared by the procedure described by Nef[9a] using bromocyanogen and potassium hydroxide in ethanol at 0 °C: IR (CH_2Cl_2) 3340, 3365 (NH), 1650 (C=N), 1080, and 1025 cm^{-1}. The IR spectrum agreed with that obtained for **7**. Identical results were also obtained by comparison of the NMR spectra[9b] and GLC retention times of both samples.

2-Methylthio-*cis*-4,5-diethyl-2-thiazoline (22a) was prepared from *cis*-thiazolidine **6a** in accordance with the published procedure.[10] The IR spectrum of the crude reaction product was in complete agreement with the published values.[10] GLC analysis of this sample showed only one component.

2-Methylthio-*trans*-4,5-diethyl-2-thiazoline (22b) was prepared from *trans*-thiazolidine **6b** and dimethyl sulfate as described above. The IR spectrum agreed with the published values. GLC analysis of this sample showed one component having a shorter retention time than that of cis **22a**.

Registry No.—**5a**, 61522-02-9; **5b**, 61522-01-8; **6a**, 27787-21-9; **6b**, 27932-05-4; **8** isomer 1, 61522-04-1; **8** isomer 2, 61522-37-0; **9a**, 61522-38-1; **9b**, 61522-39-2; **10**, 61522-40-5; **11**, 61522-41-6; **12**, 50843-80-6; **13**, 27787-27-5; **14**, 60211-99-6; **15**, 61522-42-7; **16**, 61522-43-8; **17**, 61522-44-9; **18** isomer 1, 61522-45-0; **18** isomer 2, 61522-46-1; **19** isomer 1, 61522-47-2; **19** isomer 2, 61522-48-3; **20** isomer 1, 61522-49-4; **20** isomer 2, 61522-50-7; **21** isomer 1, 61522-51-8; **21** isomer 2, 61522-52-9; **22a**, 27787-25-3; **22b**, 27787-22-0; diethyl imidocarbonate, 2812-77-3.

References and Notes

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Thiocyanations. 5. Nuclear Magnetic Resonance Analysis of the Stereochemistry of α,β-Dithiocyanates and α-Isothiocyanato-β-thiocyanates[1,2]

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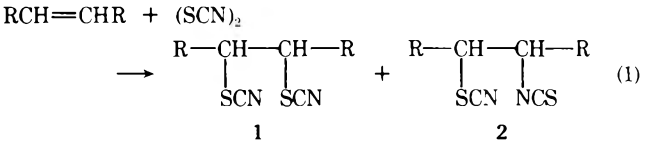
The stereochemical structures of 3,4-dithiocyanatohexanes as representative examples of aliphatic α,β-dithiocyanates could not be determined by direct conformational NMR analysis because of symmetry but were resolved by cyclization to and configurational analysis of their 2-imino-1,3-dithiolane salt derivatives. The aromatic 1,2-dithiocyanatophenylpropanes which have C–H asymmetry are subject to conformational analysis. Conformational analysis is also applicable to resolution of structures of the isomeric 3-isothiocyanato-4-thiocyanatohexanes.

Although the stereochemical structures of *vic*-dithiocyanate adducts were initially investigated by McGhie and coworkers,[4] our recent study of olefin thiocyanations emphasized the need for a reexamination of their structural assignments.[2]

On the basis of chemical evidence, McGhie and co-workers[4] proposed a trans addition of thiocyanogen to olefins to explain the reaction's stereochemistry; i.e., formation of erythro adducts from trans olefins and threo adducts from cis olefins. Their structural assignments for these adducts were based on the known pseudohalogen nature of thiocyanogen and on a comparison of a series of melting points of related isomeric dibromides, epoxides, and thiiranes. Such criteria are often inconsistent[4] and can be misleading; therefore, this approach to a determination of stereochemical assignments is provisional and not definitive for it is now recognized that the stereochemistry of electrophilic addition depends upon the structure of the olefin, the nature of the reagent, and the reaction conditions.[5]

McGhie[4] and earlier investigators[6] had examined only *vic*-dithiocyanate adducts as these were the sole products isolated from the addition of thiocyanogen to cis and trans olefinic compounds. However, more recently two independent investigations of the product distribution obtained by thiocyanations in acetic acid solution showed that formation of the *vic*-dithiocyanate adduct is accompanied by formation of several ancillary coproducts,[2,7] principally adduct **2**,



suggesting a further need for clarification of the reaction's stereochemistry.

A more direct and definitive method than chemical analysis of acquiring stereochemical determinations may be provided using NMR spectroscopy. However, a direct determination of the vicinal coupling constants is difficult for dithiocyanate adducts of aliphatic olefins because of their high degrees of symmetry. We undertook the present investigation to determine conclusively the stereochemical geometries of dithiocyanate adducts using *erythro*- and *threo*-3,4-dithiocyanatohexanes as the representative models. The stereochemical structures of the *vic*-dithiocyanate adducts were unequivocally confirmed by examination of the chemical shifts and the C-13 satellite spectra of their cyclic derivatives, the salts of 2-imino-1,3-dithiolanes. The coupling constants were also determined for the related erythro and threo isomers of 3-isothiocyanato-4-thiocyanatohexane and the 1,2-dithiocyanato-1-phenylpropane. The assignments were derived by correlation of the constants with the stereochemical conformations.

While our work was in progress, Guy and co-workers[7] reported assignments of several related dithiocyanate adducts. However, they did not report any NMR data or discuss the mode of analysis used that would allow independent confirmation of their assignments.

Results and Discussion

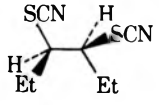
Configuration Assignment. In the earlier stages of this work differentiation of adducts **3** and **4** (eq 2 and 3) by NMR analysis was limited because of symmetry considerations. Therefore, a method of cyclic derivatization of **3** and **4** was developed whereby the stereochemistry of the asymmetric C–S bonds in these compounds was maintained. Cyclization would freeze the structures into a more limited and discrete number of conformations for each configuration. The desired derivatives of the erythro (**3**) and threo (**4**) forms of 3,4-dithiocyanatohexanes were accordingly obtained by facile cyclization to the corresponding 2-imino-1,3-dithiolane salts of methanesulfonic acid (**5** and **6**, respectively; eq 2 and 3).[8] The cyclization was smoothly attained in methanesulfonic acid as solvent–catalyst. No alteration of the precursor's C–S bonds at the point of carbon attachment in the alkane chain occurs since these asymmetric bonds do not participate in the reaction.

Chemical shifts of the salts **5** and **6** were obtained and the stereochemical assignments were proven by comparison with published assignments for known cyclic analogues (Table I). In each example the chemical shift of vicinal methine protons of the trans isomers appear ~0.2 ppm upfield relative to cis isomers. This difference has been noted for many cis–trans isomeric pairs of planar three- to five-membered ring com-

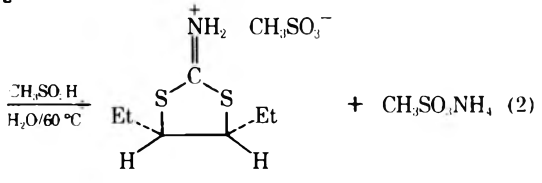
Table I. Chemical Shifts of Substituted 1,3-Dithiolane and 1,3-Dioxolane Derivatives

Compd	δ, ppm (methine protons) cis	trans	c − t
4,5-Diethyl-1,3-dithiolane-2-iminium methanesulfonate[a]	4.50 (4.13)[b]	4.30 (4.07)[b]	0.20 0.06
4,5-Dimethyl-1,3-dithiolane-2-thione[c,a,e]	4.38	4.11	0.27
4,5-Dimethyl-1,3-dioxolan-2-one[e,f]	5.84	5.66	0.18

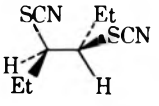
[a] Measured at 60 MHz in D_2O with DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate) as internal standard. [b] Measured in $CSCl_3$. [c] C. G. Overberger and A. Drucker, *J. Org. Chem.*, **29**, 360 (1964). [d] E. J. Corey and R. B. Mitra, *J. Am. Chem. Soc.*, **84**, 2938 (1962), also established the configuration by an independent synthesis of L(−)-*trans*-4,5-dimethyl-1,3-dithiolan-2-one from *trans*-4,5-dimethyl-1,3-dithiolane-2-thione, the latter being the only isomer of the two geometric structures capable of supporting optical activity. [e] Measured at 60 MHz in CCl_4 with Me_4Si as internal standard. [f] Reference 9.



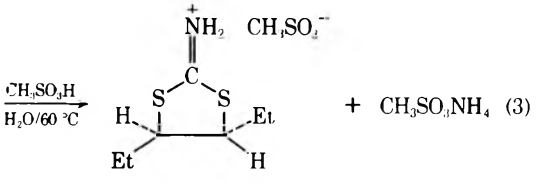
erythro 3



cis 5



threo 4



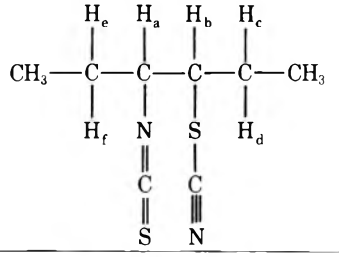
trans 6

pounds.[10] The stereochemical assignment made for the cis isomer **5** confirms the stereochemistry of the precursor erythro dithiocyanate **3**; similarly the established trans stereochemistry of isomer **6** confirms the identity of the threo dithiocyanate **4**.

Configuration of **5** and **6** was further verified through analysis of the corresponding natural abundance ^{13}C proton satellites. Homonuclear decoupling of each of the methylene proton resonances at δ 1.93 yielded a methine singlet whose low-field ^{13}C satellite doublet could be easily analyzed for the methine J_{vic}. The stereochemistry of **5** was established by the large cis coupling J_{vic} = 10.7 Hz for this five-membered ring compound ($J_{^{13}C-H}$ = 164 Hz). Likewise, the trans configuration of **6** was confirmed by J_{vic} = 2.7, $J_{^{13}C-H}$ = 170 Hz.[11] The data also support McGhie's[4] assignments and confirm his proposal of a stereochemical trans addition of thiocyanogen to olefins.

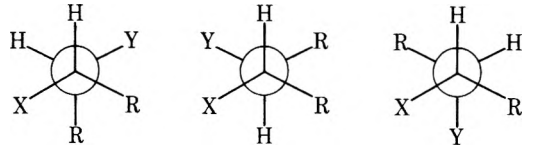
Conformational Assignments. A. 3-Isothiocyanato-4-thiocyanatohexanes. In contrast to symmetrical 3,4-dithiocyanatohexanes, the differences in chemical shift of *vic*-methine protons in the isomeric 3-isothiocyanato-4-thiocyanatohexanes enabled direct conformational analysis of the stereochemical isomers.[12] Table II records the results of a first-order analysis of these isothiocyanatothiocyanate isomers. Newman projections of the threo (**7**) and erythro (**9**) diastereoisomeric conformer are depicted below (exclusive of mirror images for each conformer).

Table II. NMR First-Order Analysis of 3-Isothiocyanato-4-thiocyanatohexanes[a]



Compd	Proton H_a δ, ppm	Coupling constant, Hz	Proton H_b δ, ppm	Coupling constant, Hz
Erytho adduct (from *trans*-3-hexene)	3.95 (double triplets)	J_{ab} = 5.4[b] J_{ae} = 5.4 J_{af} = 7.0	3.2 (double overlapping quartets)	J_{ab} = 5.4[b] J_{bc} = 4.2 J_{bd} = 9.0
Threo adduct (from *cis*-3-hexane)	4.05 (double quartet)	J_{ab} = 3.7[b] J_{ae} = 6.0 J_{af} = 7.2	3.2 (double quartet)	J_{ab} = 3.7[b] J_{bc} = 6.0 J_{bd} = 8.1

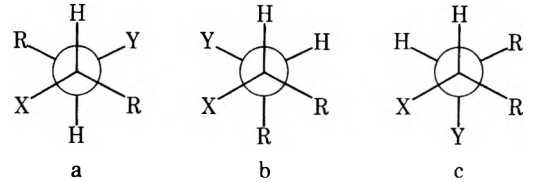
[a] All methine coupling constants were verified by reproduction of the spectra of the methine hydrogens H_a, H_b using LAOCN 3[13] on an ab spin system representing protons a–f. [b] Verified by decoupling of methylene protons.



a b c

threo:

7, R = Et; X = SCN; Y = NCS
8, R = Me; X, Y = Br



a b c

erythro:

9, R = Et; X = SCN; Y = NCS
10, R = Me; X, Y = Br

In general for conformers having trans methine protons, such as **7b** and **9a**, a large J_{vic} value of 10–12 Hz is anticipated whereas the remaining conformers with gauche methine protons are expected to have small J_{vic} values of 1–3 Hz. Our observed J_{HH} of 3.75 Hz for **7** closely approximates the value of 3.15 Hz found by Anet[9] for *dl-threo*-2,3-dibromobutane (**8**). The erythro adduct **9**, however, gave the significantly lower value of 5.4 Hz for J_{vic} in comparison with Anet's[9] 7.85 Hz for the corresponding dibromide **10**. Anet[9] had obtained weighted averages of conformer populations for the latter compounds by considering the steric and electronic effects of adjacent bromines. His studies of the conformer population of threo adduct **8** showed that it contained predominantly **8a**, with a minor **8b** contribution, whereas the erythro adduct **10** was a mixture comprised of 66% conformer **10a** and 34% conformer

Table III. Coupling Constants and Methyl Chemical Shifts of 1,2-Disubstituted 1-Phenylpropanes[a]

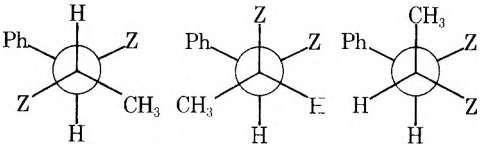
	J_{vic}, Hz		δ_{CH_3}, ppm		
	Erythro	Threo	Erythro	Threo	$\Delta\delta_{CH_3}$
1,2-Dithiocyanato-1-phenylpropane	10.2	9.0	1.9	1.5	0.4
1,2-Dibromo-1-phenylpropane[b]	11.0	5.5	2.0	1.6	0.4
1,2-Dichloro-1-phenylpropane[c]	8.0	5.7	3.6	3.4	0.2

[a] Spectra measured at 60 MHz with CCl_4 as the solvent and Me_4Si as internal standard. [b] Reference 14. [c] Reference 15.

10b. On the other hand, electrostatic interactions in *vic*-isothiocyanatothiocyanates would not be expected to contribute greatly to the establishment of relative conformer populations. Therefore, conformational assignments in this class of adducts would be determined primarily on the basis of steric interactions. The similarity in J_{vic} values for the threo adducts **7** and **8** indicated that the conformer populations were nearly the same. The erythro isomer **9**, however, gave a J_{vic} value 2.4 Hz smaller than that reported for **10**, which indicated that the relative contribution by **9a** decreased and contributions from **9b** and **9c** correspondingly increased. Reduced steric interactions in conformers **9b** and **9c**, relative to the corresponding *vic*-dibromides, would account for the decrease in conformational preferences for **9a** in the erythro isomer **9**.

B. *erythro*- and *threo*-1,2-Dithiocyanato-1-phenylpropanes. In contrast to aliphatic dithiocyanates, the asymmetry in aryl-substituted dithiocyanates made these compounds amenable to direct NMR analysis. Conformational analysis was carried out with dithiocyanate adducts derived from *cis*- and *trans*-1-phenylpropene. For conformational determinations, *vic*-dithiocyanates were compared with the known stereochemical structures of analogous *vic*-dibromides[14] and *vic*-dichlorides.[15] Our data for the thiocyanated adducts were compared with published values for halogenated adducts (Table III).

The Newman projections for the three primary conformations of the erythro adduct **11** are illustrated below. Conformer **11a** was expected to be the rotamer of lowest energy because of the all-trans structure in which the bulky groups are maximally separated (dihedral angle 180°). The observed average



erythro:

Z = –SCN	11a	11b	11c
Z = –Br or Cl	12a	12b	12c

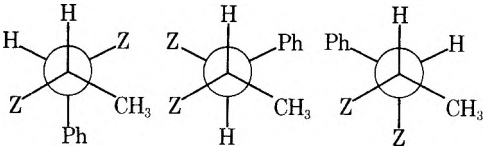
J_{vic} (10.2 Hz) for **11** is comparable to J_{vic} (11.0 Hz) reported for the analogous dibromide adduct **12** and is significantly larger than 8.0 Hz for the erythro dichloride adduct (Table III).

The following conformations for threo-substituted adducts indicate, from the coupling constant (9.0 Hz) for **13**, that the trans rotamer **13b** must contribute significantly to the average population of this isomer. The coupling constants of threo dibromide and dichloride adducts **14** are much lower in value in comparison with adduct **13**. Such a trend indicates that rotamers **14a** and **14c** best represent the conformational population of the two dihalides. The lower values of threo

Table IV. Solvent Effect on Vicinal Coupling Constant of 1,2-Dithiocyanato-1-phenylpropanes

	J_{vic}, Hz	
Solvent	Erythro	Threo
CCl_4	10.2	9.0
Benzene	9.7	9.0
$CDCl_3$	9.5	8.6
Dimethyl sulfoxide	10.7	10.0

dihalide adducts suggest a counterbalance of steric and electronic interactions, the latter attaining paramount importance



threo:

Z = –SCN	13a	13b	13c
Z = –Br or Cl	14a	14b	14c

in determining conformational preference in vicinal dihalide systems.[9] However, in thiocyanate adducts the steric requirement is more important and appears to outweigh polarity effects. The predominance of trans rotamers in **11** and **13** suggests that the spatial interactions of the linear thiocyanate functionality are contributed primarily by the sulfur moiety for which steric repulsions appear similar to those of methyl groups.

The data in Table III for the methyl resonance of each isomer show the same trend observed for the corresponding dihalides; the methyl proton resonances of all threo adducts are observed at higher field relative to the erythro adducts. In a previous study[14] of dibromide adducts, the higher field positions of the $-CH_3$ resonances in the threo adduct were attributed to the shielding effects of the phenyl groups. Should this effect solely account for the higher field position of the $-CH_3$ resonances, the $\Delta\delta CH_3$ (11–13) should be larger than expected since the threo adduct **13** should exist predominantly as conformer **13b**, in which shielding of the $-CH_3$ by phenyl would be maximal.

The unexpectantly large J_{vic} obtained for **13** with $CHCl_3$ prompted a further NMR study of the isomers in several polar and nonpolar solvents. When a solute molecule interacts with solvent, J_{vic} is expected to decrease as the solvent medium is changed from low to high dielectric constant,[9,16] owing to a shift in the conformer population equilibrium, i.e., **11a** → **11b** + **11c** and **13a** → **13b** + **13c**. However, the data in Table IV show an increase in the average J_{vic} for both the erythro **11** and threo **13** adducts upon changing the solvent from CCl_4, benzene, and $CDCl_3$ to Me_2SO, i.e. to solvents of higher dielectric constants. Clearly, these results are inconsistent with the effects normally expected in solvent-dependence studies of vicinal coupling constants. None of the data presently available account for the fact that both isomers **11** and **13** have similar conformational preferences in all the solvents tested.

Experimental Section

Equipment. The thiocyanogen adducts were separated by countercurrent distribution (CCD) in a 200 cell Post Automatic[17] instrument with acetonitrile as stationary phase and hexane as mobile phase.

NMR spectra were obtained with a Jeolco C-60H spectrometer. The chemical shifts of adducts in organic solvents are reported relative to tetramethylsilane whereas shifts obtained in D_2O are relative to DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate). Coupling

constants were confirmed, when necessary, by reconstruction of the spectra using the LAOCN 3 program modified for an IBM 1130 computer. ^{13}C proton satellites were measured on a Brucker WH-90 Fourier transform pulsed NMR spectrometer using block averaging techniques to overcome dynamic range problems. Only the low-field satellites were accessible for measurement. Infrared spectra were recorded on a Perkin-Elmer Model 457 spectrophotometer.

Samples were analyzed with a Model 810 F & M gas chromatograph using the following columns: (A) SS colum 0.25 in. × 6 ft, saturated $AgNO_3$/ethylene glycol on 60/80 mesh Anakrom ABS; (B) SS column 0.25 in. × 8 ft, 10% DEGS on 60/80 mesh Anakrom ABS; (C) Glass column 0.25 in. × 4 ft, 5% DEGS on 60/80 mesh Anakrom ABS.

Reagents. The olefins (*cis*-3-hexene, *trans*-3-hexene, *cis*-β-methylstyrene, and *trans*-β-methylstyrene) were from Chemical Samples Co. The isomeric purity of each sample was determined by GLC with column A. The lead thiocyanate used to generate thiocyanogen was prepared by a previously described method.[18]

Thiocyanation of Olefins. The α,β-dithiocyanate and α-isothiocyanato-β-thiocyanate adducts were prepared as follows. Lead thiocyanate (125 g, 0.38 mol) and acetic acid (2 L) were added to a three-neck flask equipped with a true-bore stirrer and maintained under nitrogen. The mixture was stirred for 10 min, bromine (31 g, 0.19 mol) was added, and stirring was continued until the solution became colorless. Olefin (0.097 mol) was added, and the mixture stirred overnight to ensure complete reaction, then filtered. The filtrate was shaken with water to destroy excess thiocyanogen, and the aqueous layer extracted with ethyl ether. The extract was water washed, dried over anhydrous $MgSO_4$, and concentrated to a thick, amber liquid. The adducts in the mixture were thereby separated by CCD. Individual components were checked for purity by GLC using column B. Elemental analyses were satisfactory for all compounds described. The following compounds were isolated in this manner.

erythro-3,4-Dithiocyanatohexane (**3**) was isolated as a white, crystalline solid: mp 62–63 °C; IR (KBr) 2150 cm^{-1} (SCN).

threo-3,4-Dithiocyanatohexane (**4**) was isolated as an amber-colored, viscous oil, IR (neat) 2150 cm^{-1} (SCN).

threo-3-Isothiocyanato-4-thiocyanatohexane (**7**) from the addition of thiocyanogen to *cis*-3-hexane was recovered as a brown liquid: IR (neat) sharp –SCN peak at 2150 cm^{-1} and broad –NCS peak at 2080 cm^{-1}.

erythro-3-Isothiocyanato-4-thiocyanatohexane (**9**), from the addition of thiocyanogen to *trans*-3-hexene, was separated as a brown, oily liquid: IR (neat) sharp –SCN peak at 2160 cm^{-1} and broad –NCS peak at 2080 cm^{-1}.

threo-1,2-Dithiocyanato-1-phenylpropane (**11**) was isolated as a viscous oil from the addition of thiocyanogen to *cis*-β-methylstyrene. The purity of this sample was checked by GLC using column C, IR (neat) 2160 cm^{-1} (SCN).

erythro-1,2-Dithiocyanato-1-phenylpropane (**13**) from the addition of thiocyanogen to *trans*-β-methylstyrene was isolated as a white, crystalline solid: mp 110–111 °C; IR (KBr) 2160 cm^{-1} (SCN).

cis- and *trans*-4,5-diethyl-1,3-dithiolane-2-iminium methanesulfonate (**5** and **6**) were obtained by cyclization of **3** and **4** in methanesulfonic acid as described in part 3 of this series.[8]

Registry No.—**3**, 30647-63-3; **4**, 61521-96-8; **5**, 61521-98-0; **6**, 61522-00-7; **7**, 61522-01-8; **9**, 61522-02-9; **11**, 60212-01-3; **13**, 60212-00-2; *cis*-3-hexene, 7642-09-3; *trans*-3-hexene, 13269-52-8; *cis*-β-methylstyrene, 766-90-5; *trans*-β-methylstyrene, 873-66-5; methanesulfonic acid, 75-75-2; lead thiocyanate, 592-87-0; thiocyanogen, 505-14-6.

References and Notes

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Pteridines. 40. Some Reactions of 2-Amino-3-cyano-5-bromomethylpyrazine and 2-Amino-3-cyano-5-methylpyrazine[1]

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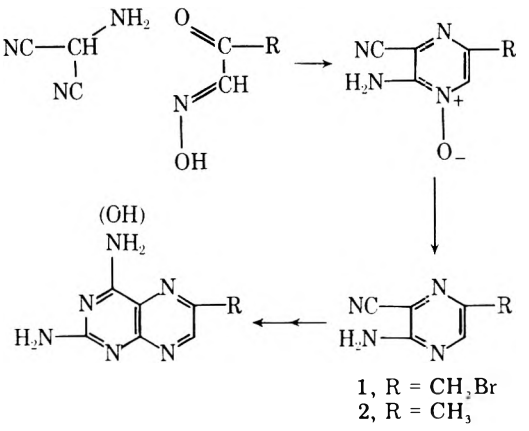
Some chemistry of 2-amino-3-cyano-5-bromomethylpyrazine (**1**) and 2-amino-3-cyano-5-methylpyrazine (**2**) has been explored to determine their usefulness as intermediates for the preparation of C-6 substituted pteridines. In general, new carbon–carbon bonds can be formed at the 5 position of **1** if weakly basic nucleophiles are employed. The synthetic potential of **2** was less than expected, however, owing to the nonacidity of the 5-methyl protons. By contrast, 2-amino-3-cyano-6-methylpyrazine could be alkylated to give 2-amino-3-cyano-6-*n*-propylpyrazine. A general discussion is given of the reactivity of both **1** and **2**.

Previous papers in this series have detailed an unambiguous approach to the synthesis of 6-substituted pteridines (i.e., L-*erythro*-biopterin, xanthopterin, methotrexate, folic acid, Asperopterin B), by guanidine cyclization of a 2-amino-3-cyano- (or carboalkoxy-) pyrazine suitably substituted at position 5. These latter critical intermediates were prepared in turn by an unequivocal cyclization of aminomalononitrile or an ester of α-aminocyanoacetic acid with an α-ketoaldoxime followed by deoxygenation of the resulting pyrazine 1-oxide.[3]

One obvious disadvantage of this procedure for the preparation of pteridines possessing complex side chains at position 6 (pyrazine position 5) was the inaccessibility of the requisite α-ketoaldoxime intermediates. We have therefore investigated the possible utility of two readily accessible pyrazines, 2-amino-3- cyano-5-bromomethylpyrazine (**1**)[4] and 2-amino-



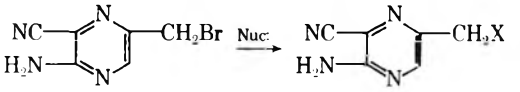
1, R = CH_2Br
2, R = CH_3

3-cyano-5-methylpyrazine (**2**),[5] as possible relay compounds for the construction of complex side chains.

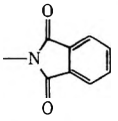
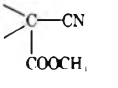
We have already described some reactions of **1** with phosphorus, nitrogen, and sulfur nucleophiles.[4,6,7] Of particular interest would be the utilization in such displacement reactions of carbon nucleophiles for the eventual preparation of pteridines bearing complex carbon side chains at position 6. For example, it was envisioned that the reaction of **1** with an acyl anion equivalent might provide a convenient route to 2,4-diamino-6-acylmethylpteridines, compounds of considerable interest as potential xanthine oxidase inhibitors. Similarly, treatment of **1** with the anion of a β-keto ester should lead eventually to pteridines bearing oxygenated side chains reminiscent of the naturally occurring side chains found in biopterin and neopterin and thus of potential interest as inhibitors of various enzymatic hydroxylation and dehydrogenation reactions. Alternately, the dianion of **2** appeared to be an attractive intermediate for elaboration of more complex side chains at position 5, particularly in view of the reported successful C-alkylation of the dianions of 2-amino-4-methylpyrimidine and 2-methylbenzimidazole.[8]

Because of the susceptibility of the cyano substituent in **1** to attack by strong nucleophiles, our initial attempts to utilize **1** as an intermediate for the formation of new carbon–carbon bonds at position 5 were restricted to investigations with weak nucleophiles. For example, treatment of **1** with a slight excess of sodium cyanide in Me_2SO afforded the cyanomethyl derivative **3** in 65% yield. It is interesting to note that the reaction of cyanide ion with the 1-oxide of **1** was not successful because of a competing reaction involving addition of cyanide ion to position 6 of the pyrazine ring, followed by aromatization by dehydration. Similarly, the sodium salts of diethyl malonate, ethyl acetoacetate, ethyl γ-methoxyacetoacetate, and potassium phthalimide all reacted successfully with **1**; results are summarized in Table I. In a few instances, the desired products were contaminated by some dialkylated product; with the sodium salt of methyl cyanoacetate, only dialkylated material could be obtained.

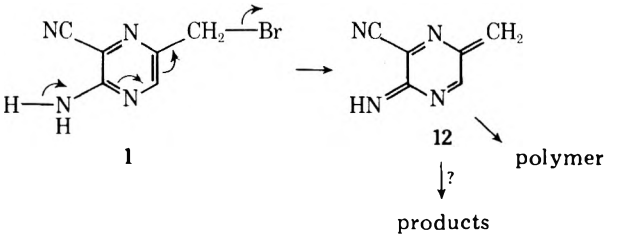
Table I. Reaction of 2-Amino-3-cyano-5-bromomethylpyrazine (1) with Nucleophiles



1

Product	X	Yield, %
3	—CN	65
4	—$CH(COOC_2H_5)_2$	60 + 20% dialkylated product (5)
6	—$CHCOCH_3$ $COOC_2H_5$	65 + 15% dialkylated product (7)
8	—$CHCCH_2OC_2H_5$ $COOC_2H_5$	70 + 20% dialkylated product (9)
10		91
11		67 (dialkylated product)

Unfortunately, reactions of **1** with carbanions derived from weaker carbon acids were not successful. For example, addition of **1** to 2-lithio-1,3-dithiane in THF at −25 °C resulted in the formation of an extremely insoluble black solid which did not melt below 300 °C. Inverse addition led to identical results. The IR spectrum of this solid showed that the nitrile function at position 3 was still present, and we surmise that the strongly basic dithiane anion initiated dehydrobromination of **1** by deprotonation of the amino group, and that the resulting quinoidlike pyrazine intermediate **12** subsequently polymerized. An attempt to remove the acidic protons of the 2-amino grouping of **1** by conversion to its 2-dimethylaminomethylenamino derivative (vide infra) by reaction with dimethylformamide dimethyl acetal led only to decomposition, apparently because reaction also took place at the (activated) 5-bromomethyl group.

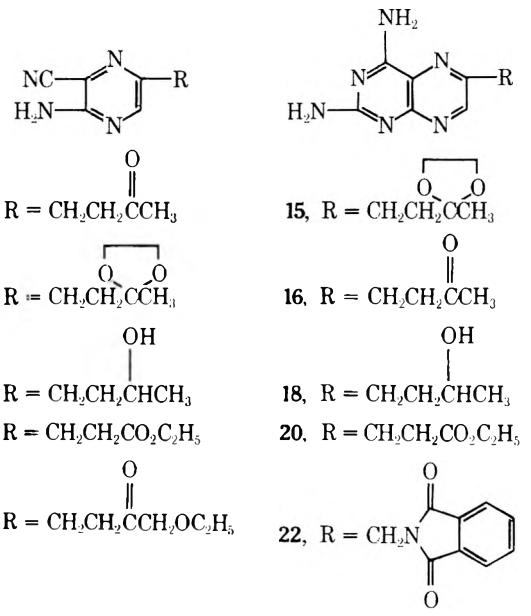


These results with 2-lithio-1,3-dithiane were unfortunately not unique. Thus, treatment of **1** with the anion of methyl methylthiomethyl sulfoxide gave analogous results. Attempts to react **1** with lithium acetonitrile or with the sodium salt of acetophenone also failed.

The above observations do not allow a clear-cut interpretation of the mechanism of the reaction of **1** with nucleophiles. It is clear that anions of compounds with $pK_a > 19$ (acetophenone, acetonitrile, dithiane) do not react successfully with **1**, whereas anions derived from less basic substrates ($pK_a < 13$), such as keto esters and malonates, give excellent yields of displacement products. However, it is not clear whether the unsuccessful results observed in the former cases are due to dehydrohalogenation followed by polymerization of **12**, or to the fact that those anions which bring about polymerization, being very poor Michael donors, fail to capture the intermediate quinoidlike pyrazine intermediate **12**, which could conceivably be formed in all instances where **1** was treated with carbanions. An attempt to prepare a 2,4-diaminopteridine from **3** by reaction with guanidine again gave a black, polymeric solid similar in its general properties to the above black solid isolated from reactions of **1** with highly basic carbanions. Elimination of HCN from **3**, initiated by guanidine acting as a base, would appear to be responsible.

In view of these results, it is clear that synthetic schemes leading from **1** to pteridines carrying complex side chains at position 6 are more limited than originally envisioned. Nevertheless, we have been successful in converting compounds **3**, **4**, **6**, and **10** to various 2,4-diaminopteridines of potential interest as biopterin inhibitors. Thus, decarboethoxylation of the ethyl acetoacetate displacement product **6** was effected

by the method of Krapcho.[9] The resulting ketone **13** was first converted to its ethylene ketal **14** which was then cyclized with



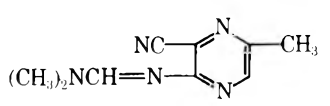
guanidine in the presence of sodium methoxide to the protected 2,4-diaminopteridine **15**. Removal of the protecting group then gave 1-(2,4-diamino-6-pteridinyl)-3-butanone (**16**) in 33.5% overall yield from **6**.

The carbonyl function in the intermediate pyrazine **13** could be reduced in moderate yield with sodium borohydride to give the secondary alcohol **17**, which was then cyclized with guanidine to the 6-hydroxybutylpteridine derivative **18** in 81% yield.

Decarboethoxylation of the malonate displacement product **4** gave 2-amino-3-cyano-5-(2-carboethoxyethyl)pyrazine (**19**) in 77% yield. This was cyclized in moderate yield with guanidine acetate in dimethylformamide to the 2,4-diaminopteridine **20**; a competing reaction was acylation of guanidine either by **19** or by **20**. Curiously, attempts to decarboethoxylate the displacement product **8** (from **1** and ethyl γ-ethoxyacetoacetate) were only moderately successful, and nothing further was done with the derived pyrazine **21**.

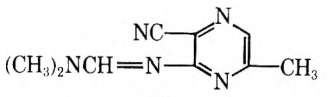
The phthalimidomethylpyrazine **10** was converted to 2,4-diamino-6-phthalimidomethylpteridine **22** in modest yield, but attempts to remove the phthalimido grouping from **22** were unsuccessful, probably because of its insolubility.

We have also briefly investigated the possible intermediacy of 2-amino-3-cyano-5-methylpyrazine (**2**) for the construction of more complex side chains at position 5. Since the above results with **1** appeared to indicate that deprotonation of the amino group at position 2 was possible with strongly basic carbanions, we protected the 2-amino group in **2** by reaction with dimethylformamide dimethyl acetal to give the protected derivative **23**. However, attempts to form a carbanion from **23** were unsuccessful. Thus, treatment of **23** with butyllithium/TMEDA led only to nucleophilic addition to the 3-cyano grouping. Only starting material was recovered after attempted alkylation when a nonnucleophilic base, lithium diisopropylamide, was employed.

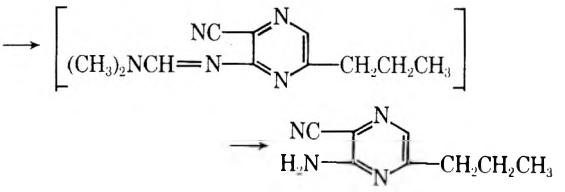


23

The failure of **23** to deprotonate under the above conditions might not be surprising in view of the unfortunate positioning of the dimethylformamidylamino substituent para to the (potentially) acidic methyl group. In order to ascertain whether the failure of **2** to deprotonate was indeed due to this structural feature or to some inherent property of the pyrazine ring, we briefly examined 2-(*N,N*-dimethylformamidylamino)-3-cyano-6-methylpyrazine (**24**), a structural isomer of **23**



24



25

in which an electron-withdrawing nitrile group is now situated para to the methyl group. In fact, deprotonation of **24** with lithium diisopropylamide followed by addition of ethyl iodide, and then removal of the protecting group by acid hydrolysis, gave 2-amino-3-cyano-6-*n*-propylpyrazine (**25**) in 52% yield. The inability of either **2** or its amino-protected derivative **23** to undergo carbon alkylation is thus apparently the result of both the nature and positioning of the substituents on the pyrazine ring.

Experimental Section

2-Amino-3-cyano-5-cyanomethylpyrazine (3). A solution of 0.58 g (11 mmol) of sodium cyanide in 25 ml of Me_2SO was stirred at room temperature in a 50-ml round-bottomed flask fitted with a thermometer and condenser. To this solution was added 2.13 g (10 mmol) of 2-amino-3-cyano-5-bromomethylpyrazine (**1**);[4] the temperature of the reaction mixture rose from 22 to 36 °C. The mixture was heated at 40 °C for 2.5 h and then poured into 100 ml of a saturated solution of sodium chloride. Extraction with methylene chloride (4 × 40 ml) followed by drying of the combined methylene chloride extracts (Na_2SO_4), filtering, and evaporation (to remove traces of Me_2SO) gave an oil which solidified upon trituration with 2-propanol. The solid which separated was collected by filtration, dried, and recrystallized from 2-propanol to give 1.03 g (65%) of **3** as light orange needles, mp 169–170 °C.

Anal. Calcd for $C_7H_5N_5$: C, 52.83; H, 3.17; N, 44.00. Found: C, 52.87; H, 3.46; N, 43.92.

2-Amino-3-cyano-5-(2,2-dicarboethoxyethyl)pyrazine (4). A solution of the sodium salt of diethyl malonate was prepared by adding 1.53 g (11 mmol) of a 50% NaH–paraffin oil dispersion to 20 ml of freshly distilled dry THF and then, under nitrogen at 5 °C, slowly adding a solution of 1.68 g (10.5 mmol) of diethyl malonate in 10 ml of dry THF. This mixture was stirred at room temperature for 1 h and then added dropwise to a solution of 2.13 g (10 mmol) of **1** in 15 ml of dry THF at room temperature under nitrogen. This mixture was stirred for 4 h and poured into 50 ml of saturated sodium chloride solution. The mixture was neutralized with 6 N HCl and extracted four times with 20-ml portions of chloroform. The combined chloroform layers were dried (Na_2SO_4), filtered, and evaporated to give a crude solid which was recrystallized from carbon tetrachloride to give 1.75 g (60%) of **4** as a white, crystalline solid, mp 115–116 °C.[10]

Anal. Calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.24. Found: C, 53.62; H, 5.59; N, 19.01.

1-(2-Amino-3-cyano-5-pyrazinyl)-2-carboethoxy-3-butanone (6). A solution of the sodium salt of ethyl acetoacetate was prepared by adding 3.17 g (0.066 mol) of a 50% NaH–paraffin oil dispersion to 40 ml of freshly distilled dry THF and then adding slowly, under nitrogen at 5 °C, a solution of 8.19 g (0.063 mol) of ethyl acetoacetate in 25 ml of dry THF. The mixture was stirred at room temperature for 1 h and then added dropwise to a solution of 12.78 g (0.060 mol) of **1** in 75 ml of dry THF at room temperature under nitrogen. This mixture was stirred for 4 h and then poured into 150 ml of a saturated solution of sodium chloride. This mixture was neutralized with 6 N HCl and extracted four times with 50-ml portions of chloroform, and the combined chloroform layers dried (Na_2SO_4), filtered, and evaporated to give an oil which solidified on trituration with cyclohexane.

Recrystallization from carbon tetrachloride gave 10.2 g (65%) of **6** as a white, crystalline solid, mp 96–97 °C.

Anal. Calcd for $C_{12}H_{14}N_4O_3$: C, 54.96; H, 5.38; N, 21.36. Found: C, 54.88; H, 5.45; N, 21.36.

The material insoluble in carbon tetrachloride was removed by filtration and recrystallized from ethanol/acetonitrile to give 1.0 g of the dialkylated product (**7**), mp 237–238 °C.

Anal. Calcd for $C_{18}H_{18}N_8O_3$: C, 54.82; H, 4.60; N, 28.41. Found: C, 54.84; H, 4.63; N, 28.24.

2-Amino-3-cyano-5-phthalimidomethylpyrazine (10). A mixture of 2.69 g (12.6 mmol) of **1**, 2.6 g (14 mmol) of potassium phthalimide, and 35 ml of DMF was stirred at room temperature for 30 min. There was an initial mild exothermic reaction with the temperature rising from 18 to 33 °C. The mixture was poured into 50 ml of water and the resulting precipitate collected by filtration, dried, and recrystallized from 350 ml of acetonitrile to give 3.2 g (91%) of a white, crystalline solid, mp 275–276 °C dec.

Anal. Calcd for $C_{14}H_9N_5O_2$: C, 60.21; H, 3.25; N, 25.08. Found: C, 60.58; H, 3.36; N, 24.94.

2-Amino-3-cyano-5-(2-carboethoxyethyl)pyrazine (19). A mixture of 0.58 g (2.0 mmol) of **4**, 0.15 g (2.5 mmol) of sodium chloride, 0.15 ml (8.0 mmol) of water, and 15 ml of Me_2SO was placed in a three-necked 50-ml round-bottomed flask fitted with a thermometer, condenser, and magnetic stirrer. Attached to the condenser was a trap containing a solution of saturated barium hydroxide which was used to monitor CO_2 evolution. The mixture was heated at 155–170 °C for 6 h, cooled, and poured into 50 ml of water. The aqueous solution was extracted five times with 15-ml portions of chloroform. The combined chloroform extracts were dried (Na_2SO_4), filtered, and evaporated to give an oil which solidified upon drying in vacuo for 4 h. Recrystallization from carbon tetrachloride (charcoal) gave 0.34 g (77%) of **19** as a white, crystalline solid, mp 85–86 °C.

Anal. Calcd for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found: C, 53.98; H, 5.29; N, 25.14.

1-(2-Amino-3-cyano-5-pyrazinyl)-3-butanone (13). Using the same procedure as outlined above for the preparation of **19**, 10.2 g (0.039 mol) of the keto ester **6** was decarboethoxylated to give 5.3 g (72%) of **13** as a white, crystalline solid, mp 130–131 °C after recrystallization from benzene.

Anal. Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.98; H, 5.38; N, 29.02.

1-(2-Amino-3-cyano-5-pyrazinyl)-2-carboethoxy-4-ethoxy-3-butanone (8). A solution of the sodium salt of ethyl γ-ethoxyacetoacetate was prepared by adding 0.48 g (10 mmol) of a 50% NaH–paraffin oil dispersion to 25 ml of freshly distilled dry THF followed by addition, under nitrogen at 5 °C, of a solution of 1.74 g (10 mmol) of ethyl γ-ethoxyacetoacetate in 10 ml of dry THF. The mixture was stirred at room temperature for 1 h and then added dropwise to a solution of 2.13 g (10 mmol) of **1** in 25 ml of dry THF at room temperature under nitrogen. This mixture was stirred for 4 h, poured into 50 ml of saturated sodium chloride solution, neutralized with 6 N HCl, and then extracted three times with 40-ml portions of chloroform. The combined chloroform extracts were dried (Na_2SO_4), filtered, and evaporated to give an oil. Trituration with benzene resulted in a separation of a solid which was collected by filtration, dried, and recrystallized from 2-propanol to give 0.60 g (20%) of a white solid, mp 194–195 °C, which appeared from microanalytical data and spectral analysis to be the dialkylated product **9**.

Anal. Calcd for $C_{20}H_{22}N_8O_4$: C, 54.79; H, 5.06; N, 25.56. Found: C, 54.80; H, 5.28; N, 25.51.

Evaporation of the benzene filtrates then gave 2.1 g (70%) of **8** as an oil: NMR ($CDCl_3$) δ 8.18 (s, 1), 5.65 (b, 2), 4.5–3.2 (m, 9), 1.25 (t, 6); IR (neat) 1750 (ester), 1725 (ketone), 2225 (CN), 3250–3450 cm^{-1} (NH_2).

1-(2-Amino-3-cyano-5-pyrazinyl)-4-ethoxy-3-butanone (21). A mixture of 2.1 g (7 mmol) of the keto ester **8**, 0.58 g (10 mmol) of sodium chloride, 0.5 ml of water, and 20 ml of Me_2SO was placed in a 50-ml three-necked round-bottomed flask fitted with a thermometer, condenser, and magnetic stirring bar. The mixture was heated at 150–160 °C for 5 h, cooled, and poured into 100 ml of water. Some black, polymeric material precipitated which was removed by filtration. The aqueous filtrate was then extracted four times with 50-ml portions of chloroform and the combined chloroform extracts dried (Na_2SO_4), filtered, and evaporated. The residual oil crystallized upon trituration with hexane and cooling. Recrystallization from carbon tetrachloride gave 0.30 g (19%) of **21** as a white, crystalline solid, mp 89–91 °C.

Anal. Calcd for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.28; H, 5.89; N, 24.18.

1,3-Bis(2-amino-3-cyano-5-pyrazinyl)-2-cyano-2-carbomethoxypropane (11). A solution of the sodium salt of methyl cyanoacetate was prepared by adding 1.62 g (15.7 mmol) of 97% methyl cyanoacetate in 15 ml of dry THF to a stirred mixture of 0.75 g (15.7 mmol) of 50% NaH–paraffin oil dispersion in 15 ml of THF under nitrogen at 0 °C. After stirring at room temperature for 30 min, this mixture was added to a stirred solution of 3.20 g (15 mmol) of **1** in 30 ml of dry THF at room temperature under nitrogen. The mixture was stirred at room temperature for 4 h, poured into 100 ml of saturated sodium chloride solution, neutralized with 10% HCl, and then extracted with 100 ml of chloroform. The chloroform extracts were dried (Na_2SO_4), filtered, and evaporated to give a crude solid which was partially purified by extraction with hot benzene. The benzene-insoluble material was further purified by dissolving in 60 ml of boiling acetonitrile, decolorizing with charcoal, and then concentrating to a small volume followed by cooling. This gave 1.9 g (67%) of **11** as a yellow solid, mp 213–215 °C dec.

Anal. Calcd for $C_{16}H_{13}N_9O_2$: C, 52.89; H, 3.61; N, 34.70. Found: C, 52.54; H, 3.92; N, 34.79.

1-(2-Amino-3-cyano-5-pyrazinyl)-3-ethylenedioxybutane (14). A mixture of 1.90 g (10 mmol) of **13**, 0.93 g (15 mmol) of ethylene glycol, 50 mg of *p*-toluenesulfonic acid, and 40 ml of benzene was placed in a 100-ml round-bottomed flask fitted with a Dean-Stark trap and condenser, and heated under reflux for 8 h. The reaction mixture was decanted while hot to remove some insoluble tarry material and poured into an equal volume of hexane. Cooling resulted in the separation of yellow needles which were collected by filtration, dried in vacuo, and recrystallized from benzene/cyclohexane to give 1.90 g (82%) of **14**, mp 126–127 °C.

Anal. Calcd for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.59; H, 6.20; N, 24.87.

1-(2,4-Diamino-6-pteridinyl)-3-ethylenedioxybutane (15). To a solution of sodium methoxide [from 0.55 g (24 mmol) of sodium in 30 ml of dry methanol] was added 1.2 g (12 mmol) of guanidine hydrochloride. The mixture was stirred briefly and then filtered into a 100-ml round-bottomed flask containing 1.87 g (8.0 mmol) of **14**. The reaction mixture was heated under reflux for 40 h, cooled, concentrated to 10 ml, and diluted with 40 ml of 2-propanol. Cooling at −20 °C for 1 h resulted in the separation of a solid which was collected by filtration, washed with 2-propanol, dried, and recrystallized (charcoal) from 2:1 acetonitrile/methanol to give 1.53 g (70%) of **15** as a yellow, microcrystalline solid, mp 269–270 °C.

Anal. Calcd for $C_{12}H_{16}N_6O_2$: C, 52.16; H, 5.84; N, 30.42. Found: C, 52.26; H, 5.86; N, 30.28.

1-(2,4-Diamino-6-pteridinyl)-3-butanone (16). To a stirred mixture of 1.9 g (7 mmol) of **15** and 25 ml of trifluoroacetic acid at 0 °C was added 0.5 ml of concentrated H_2SO_4. The resulting solution was stirred for an additional 15 min at 0 °C, poured into 50 ml of ice water, stirred for 15 min, and filtered. The collected solid was stirred with 50 ml of 2 N NaOH for 1 h, collected by filtration, and triturated with hot methanol. Cooling and filtration gave 1.31 g (81%) of analytically pure **16** as a light yellow solid, mp 286–287 °C.

Anal. Calcd for $C_{10}H_{12}N_6O$: C, 51.72; H, 5.21; N, 36.19. Found: C, 51.61; H, 5.25; N, 35.95.

1-(2-Amino-3-cyano-5-pyrazinyl)-3-butanol (17). A mixture of 1.52 g (8 mmol) of **13**, 0.16 g (4.2 mmol) of sodium borohydride, and 50 ml of dry methanol was stirred at 0 °C for 10 min and at room temperature for 1 h, and then evaporated to dryness. The residue was dissolved in 20 ml of water and extracted with four 15-ml portions of chloroform. The combined chloroform extracts were dried (Na_2SO_4), filtered, and evaporated to give 0.98 g of a crude solid which was recrystallized from benzene to give 0.83 g (54%) of **17** as a fluffy, yellow solid, mp 101.5–103 °C.

Anal. Calcd for $C_9H_{12}N_4O$: C, 56.24; H, 6.29; N, 29.15. Found: C, 55.64; H, 6.37; N, 28.42.

1-(2,4-Diamino-6-pteridinyl)-3-butanol (18). To a solution of sodium methoxide [from 0.69 g (20 mmol) of sodium in 40 ml of dry methanol] was added 0.57 g (6.0 mmol) of guanidine hydrochloride. After brief stirring, this mixture was filtered into a 100-ml round-bottomed flask containing 0.77 g (4.0 mmol) of **17**. The resulting mixture was heated under reflux for 40 h, cooled, concentrated to 10 ml by evaporation in vacuo, and diluted with 25 ml of 2-propanol. After thorough cooling, the mixture was filtered and the collected solid washed with cold 2-propanol, dried, and recrystallized from 1-propanol to give 0.76 g (81%) of **18** as a microcrystalline, yellow powder, mp 257–258 °C.

Anal. Calcd for $C_{10}H_{14}N_6O$: C, 51.27; H, 6.02; N, 35.89. Found: C, 51.53; H, 5.99; N, 35.89.

2,4-Diamino-6-(2-carboethoxyethyl)pteridine (20). A mixture of 0.44 g (2 mmol) of **19**, 0.26 g (2.2 mmol) of guanidine acetate, and 20 ml of DMF was heated at 120 °C for 39 h. It was then evaporated

under reduced pressure and the residual solid triturated with 2-propanol. Filtration gave 0.27 g (52%) of a yellow solid which was recrystallized from 2-propanol, mp 266–267 °C dec.

Anal. Calcd for $C_{11}H_{14}N_6O_2$: C, 50.38; H, 5.38; N, 32.04. Found: C, 50.37; H, 5.44; N, 31.91.

2,4-Diamino-6-phthalimidomethylpteridine (22). A mixture of 2.5 g (9 mmol) of **10**, 1.13 g (9.5 mmol) of guanidine acetate, and 50 ml of DMF was heated at 120 °C for 48 h. The reaction mixture was cooled, diluted with an equal volume of methanol, and filtered. The collected solid was washed copiously with methanol and recrystallized from 1:1 DMF/methanol to give 1.5 g of **22** as yellow needles, mp 338 °C dec.

Anal. Calcd for $C_{15}H_{11}N_7O_2$: C, 56.07; H, 3.45; N, 30.52. Found: C, 55.70; H, 3.53; N, 29.55.

2-(*N,N*-Dimethylformamidylamino)-3-cyano-5-methylpyrazine (23). A mixture of 2.68 g (20 mmol) of **2**, 20 ml of dimethylformamide dimethyl acetal, and 30 ml of dry DMF was stirred at room temperature for 12 h. Evaporation in vacuo then gave a residual oil which solidified on trituration with cyclohexane. Recrystallization from cyclohexane then gave 3.48 g (92%) of **23** as white, fluffy needles, mp 102.5–103.5 °C.

Anal. Calcd for $C_9H_{11}N_5$: C, 57.13; H, 5.86; N, 37.01. Found: C, 57.22; H, 5.68; N, 37.01.

2-(*N,N*-Dimethylformamidylamino)-3-cyano-6-methylpyrazine (24) was prepared in 82% yield from 2-amino-3-cyano-6-methylpyrazine[11] as described above for the conversion of **2** to **23**, yellow needles (from benzene), mp 182.5–183 °C.

Anal. Calcd for $C_9H_{11}N_5$: C, 57.13; H, 5.86; N, 37.01. Found: C, 57.24; H, 5.85; N, 33.92.

2-Amino-3-cyano-6-*n*-propylpyrazine (25). A 5.3-mmol solution of lithium diisopropylamide was prepared in a 100-ml round-bottomed flask fitted with a septum, addition funnel, and gas inlet tube, by syringe addition of 2.2 ml of a 2.4 M solution of *n*-butyllithium to 0.54 g (5.3 mmol) of diisopropylamine in 10 ml of dry THF under nitrogen. This was stirred at −78 °C for 30 min and then to it was added a solution of 0.95 g (5 mmol) of **24** in 40 ml of warm THF. After addition was complete, the reaction mixture was stirred for 1 h at −78 °C and a solution of 0.94 g (6 ml) of ethyl iodide in 10 ml of dry THF was added. Stirring was continued as the reaction mixture was allowed to warm to room temperature. After 20 h the solution was quenched with 25 ml of 10% HCl, heated on a steam bath for 15 min, and then extracted with chloroform. The combined chloroform extracts were dried (Na_2SO_4), filtered, and evaporated to give 0.51 g of a crude solid. Sublimation at 100 °C (0.1 Torr) gave 0.42 g (52%) of **25** as a white, crystalline solid, mp 115–116 °C.

Anal. Calcd for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.54. Found: C, 59.13; H, 6.21; N, 34.25.

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Registry No.—**1**, 61267-55-8; **2**, 17890-82-3; **3**, 61267-56-9; **4**, 61267-57-0; **6**, 61267-58-1; **7**, 61303-84-2; **8**, 61267-59-2; **9**, 61267-60-5; **10**, 61267-61-6; **11**, 61288-80-0; **13**, 61267-62-7; **14**, 61267-63-8; **15**, 61267-64-9; **16**, 61267-65-0; **17**, 61267-66-1; **18**, 61267-67-2; **19**, 61267-68-3; **20**, 61267-69-4; **21**, 61267-70-7; **22**, 61267-71-8; **23**, 61303-85-3; **24**, 61267-72-9; **25**, 61267-73-0; diethyl malonate Na salt, 996-82-7; sodium cyanide, 143-33-9; ethyl acetoacetate Na salt, 19232-39-4; potassium phthalimide, 1074-82-4; ethyl γ-ethoxyacetoacetate Na salt, 61267-74-1; methyl cyanoacetate Na salt, 24163-38-0; ethylene glycol, 107-21-1; guanidine HCl, 14317-32-9; guanidine acetate, 34771-62-5; dimethylformamide diethyl acetal, 1188-33-6; 2-amino-3-cyano-6-methylpyrazine, 58091-66-0; lithium diisopropylamide, 4111-54-0.

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Highly Stereospecific Dimerization of 5-Formyl-5-methyl-1-pyrazolines. Preparation and Characterization of Stable Carbinolamines (Amino Hemiacetals)

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The unstable 5-methyl-5-formyl-2-pyrazolines **3**, generated in situ by a 1,3-dipolar additon of α-methylpropenal (methacrolein) to α-diazo esters, dimerize in a highly specific way to *meso*-**4**, which are stable carbinolamines. Surprisingly, the latter show no equilibrium with the monomers (pyrazolines) in solution, even at 90 °C in Me_2SO, but they are cleanly transformed into the aminals **5** by a variety of nucleophiles. The conversion of **4** to **5** occurs with retention of configuration at the reacting center, as established by x-ray diffractometry.

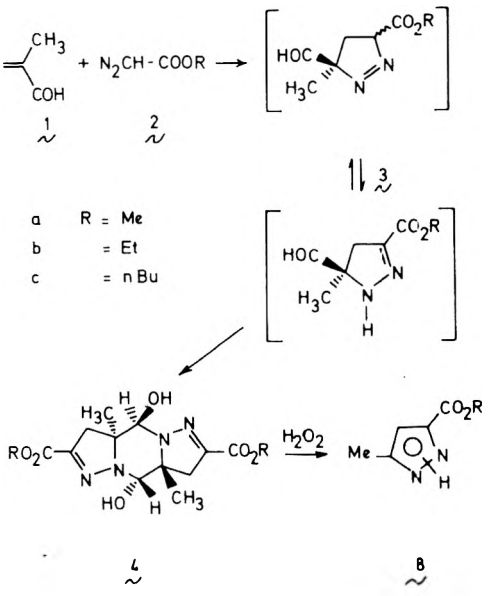
It has been clearly recognized for a long time that the formation of hydrazones, imines, oximes, etc., is a two-step reaction, a carbinolamine being an obligatory intermediate.[1] However, the carbinolamine function itself (also called hemiaminal or amino hemiacetal) has attracted much less attention, although several natural compounds have recently been recognized to possess a stable amino hemiacetal function.[2] From a synthetic point of view, with the exceptions of halogen stabilized molecules,[3] or derivatives of strained cyclopropanones,[4] the dimerization of five-membered heterocycles with a formyl group α to an endocyclic NH constitutes to our best knowledge the only systematic attempts to the synthesis of heterocyclic amino hemiacetals;[5] however, in this case, never was the function clearly and fully characterized, because of nonresolved mixtures and of a dimer–monomer equilibrium in solution. We now report the facile synthesis and characterization of stable carbinolamines from the stereospecific dimerization of substituted 5-formyl-2-pyrazolines.

Results and Discussion

When equimolecular amounts of 2-methylpropenal **1** (methacrolein) and of a diazo ester **2** are mixed in an aprotic solvent at room temperature, a white precipitate begins to appear after about 12 h; its yield, about 45%, is maximum after 2 weeks of standing. Some evolution of nitrogen is also observed; the total amount of gas is proportional to the dilution of the solution, and is quantitative for molar ratios of solvent (CCl_4) to reactants above 50.

The elemental analysis of the precipitates corresponds to equimolecular addition of the starting materials without loss of nitrogen and fits formula **4** (Scheme I) which is further

Scheme I



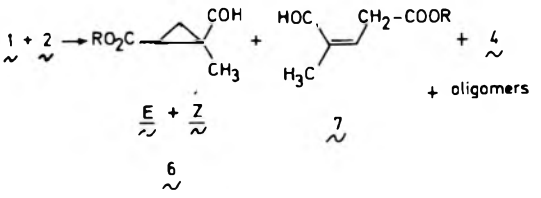
supported by the following spectroscopic characterizations. The main features in the spectra of **4** are, in the infrared, the absence of any peaks due to free hydroxyl group; rather, the sharp and intense absorptions which are seen at about 3500 cm^{-1} indicate hydrogen bonding. Moreover, conjugated azomethine and ester absorptions are seen at respectively 1545 and 1668 cm^{-1}. Although azomethine conjugated esters are quoted to absorb as low as 1680 cm^{-1} in some pyrazolines,[7] such an unusually low frequency is indicative of intermolecular interactions. Indeed, it is shifted up to 1690 cm^{-1} when the –OH function is replaced by $-OCH_3$ (vide infra) or in Me_2SO, while the position of the hydroxyl vibration remains unaffected in the same solvent. On the other hand, the ^1H NMR spectrum shows, beside the AB pattern of the pyrazoline methylene, an uncoupled methyl on a saturated carbon, and an AX system. The latter results from the coupling of the hydroxylic proton with the methine.

Remarkable is the fact that even at 90 °C, no aldehyde (i.e., no equilibrium with **3**) is observed. The AX pattern is still present and indicates a slow exchange in the NMR time scale.

Dipolar additions of diazo compounds to activated double bonds such as **1** are well known and need no further comments, but the stereospecific dimerization of **3** to **4** (Scheme I) which follows the tautomeric equilibrium 1-pyrazoline ⇄ 2-pyrazoline seems to be unique. The mixture complexity made any NMR or IR monitoring of the reaction very difficult. Some points stand out, however. It appeared that the pyrazoline (**3**) concentration is low throughout the reaction (less than an estimated 3–5%, as indicated by integration of the aldehydic region) and, consequently, the dimerization should be fast relative to the pyrazoline formation. The important point in the structure of **4** is the presence of an inversion center, as revealed by the simplicity of both ^1H and ^{13}C NMR spectra. Examination of molecular models did not formally rule out other isomers of **4** on purely steric grounds. However, none of them was observed and that implies a highly stereospecific dimerization of **3**.

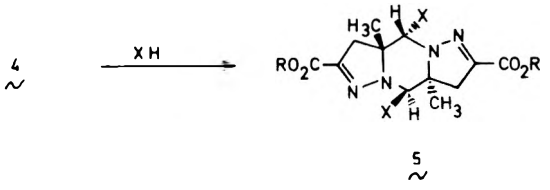
On the other hand, the reaction solution, after filtration of **4** and precipitation by a nonsolvent (hexane), gives a noncrystalline yellow solid, the analysis and spectra of which are indicative of oligomers with a probable polyacetal structure, as described for the reaction of acrolein with ethyl diazoacetate,[7] whereas three additional products are still present in the solution. Their yield increases with dilution and is proportional to the amount of nitrogen evolved. After isolation by VPC, two of them are identified as the *E* and *Z* isomers of cyclopropanes **6**, and the third one is the previously unknown ethyl (*Z*)-4-formyl-3-pentenoate **7** (Scheme II), resulting from

Scheme II



a formal insertion of a carbomethoxycarbene into the CH group of methacrolein. Oxidation of **4** by activated manganese dioxide or hydrogen peroxide allowed the isolation of pyrazoles **8** in moderate yields[8] (Scheme I). Substituting the hydroxyl group of the carbinolamine function appears to have broad synthetic potentialities, that are illustrated in Scheme III by some chosen derivatives resulting from the reaction of

Scheme III



5 a X = $-OCH_3$
b = $-OCH_2-CF_3$
c = $-OC_6H_5$
d = $-NH-C_6H_4F$ (p)
e = 

4 with quite various nucleophiles (e.g., alcohols, phenol, aniline, and pyrazole). A complete retention of configuration obtains in these reactions: crystals of **5a** (R = Me) and of **4b** have been analyzed by x-ray diffractometry and the structure fully confirmed.[9] The central piperazine ring is in a chair conformation with a methoxy group trans to the vicinal methyl, and the ester carbonyl (1695 cm^{-1}) lies in the plane of the conjugated azomethine double bond.

On the other hand, crystals of **4b** have the same overall stereochemistry as **5**, the hydroxyl is also trans to the α-methyl,[10] and the conversion of **4** into **5** occurs with retention of configuration. The above observation ought to reflect some kind of intramolecular participation since purely steric effects should not be large enough to promote a total retention at the reacting center.

Experimental Section

Boiling points and melting points are uncorrected. ^1H NMR spectra were recorded on Varian T60 or HA-100 spectrometers; ^{13}C spectra

on a Brucker HFX 90 instrument at 22.63 MHz. All chemical shifts are measured in parts per million (δ) downfield from Me_4Si or HMDS. The ^{13}C resonance frequencies have been assigned by comparison with a nondecoupled spectrum of **5a** (Alk = CH_3) in $CDCl_3$.

Infrared spectra were obtained on a Perkin-Elmer Model 21 spectrometer and frequencies are given in cm^{-1}.

Preparative VPC was carried out on a Varian 2800 instrument; the columns used were 16 × 0.75 in., 20% SE-30 on Chromosorb W 30–60.

The following descriptions are typical for the preparation of **4** and **5**.

I. Preparation of 2,7-Diethoxycarbonyl-3a,8a-dimethyl-4,9-dihydroxy-3*H*,8*H*-dipyrazolino[1,5-*a*:5',1'-*d*]-4*H*,9*H*-pyrazine (4b). In 5 mL of benzene are added 1.14 g (1 mmol) of ethyl diazoacetate and 0.77 g (1.1 mmol) of 2-methylpropenal. The solution is let without stirring at room temperature for several days and **4** slowly precipitates. After 10 days, the yield is about 40% but some precipitation still occurs during the following weeks. The solid is filtered, washed with benzene, and crystallized in acetone.

4b (R = C_2H_5): mp 219–224 °C dec; IR (OH, COOEt, C=N, respectively) (KBr) 3497, 1668, 1547 cm^{-1}; (Nujol) 3500, 1665, 1547 cm^{-1}; (Me_2SO) 3500, 1690, 1537 cm^{-1}; other absorptions (KBr) 1340 (s), 1292 (m), 1266 (s), 1250 (m), 761 (s), 752 (s), 732 cm^{-1} (m); NMR (Me_2SO-d_6, HMDS, 100 MHz) δ 6.47 (d, 1, J = 3.75 Hz, OH), 5.08 (d, 1, J = 3.75 Hz, CH), 4.10 (q, 2, CH_2CH_3), 3.28 and 2.50 [m, 2, J = 16.75 Hz, CH_2 (AB)], 1.24 (s, 3, CH_3), 1.16 (t, 3, CH_2CH_3); ^{13}C NMR (Me_2SO-d_6, Me_4Si–C_6D_6 with proton noise decoupling) 159.6 (COO), 132.0 (C=N), 82.6 (COH), 65.6 (CCH_3), 39.8 [CH_2 (AB)], 24.9 (CCH_3); ethyl ester 59.0 (CH_2), 13.9 ppm (CH_3). Anal. Calcd for $C_{16}H_{24}N_4O_6$: C, 52.17; H, 6.52; N, 15.22. Found: C, 52.2; H, 6.6; N, 15.2.

4a (R = CH_3), mp 208.5–210 °C dec. Anal. Calcd for $C_{14}H_{20}N_4O_6$: C, 49.41; H, 5.88; N, 16.47. Found: C, 49.5; H, 6.0; N, 16.5.

4c (R = *n*-Bu), mp 181–183 °C dec. Anal. Calcd for $C_{20}H_{32}N_4O_6$: C, 56.60; H, 7.55; N, 13.20. Found: C, 56.7; H, 7.7; N, 13.4.

A. Preparation of Aminoacetal 5a from 4a. **4a** is refluxed in methanol with stirring. After dissolution heating is continued for about 0.5 h. Upon slow cooling, **5a** precipitates: mp 218–224 °C; IR (KBr) 3018 (w), 2850 (w), 1695 (s, $COOCH_3$), 1545 (s, C=N), 1333 (s), 763 (s), 756 (s), 727 cm^{-1} (m); NMR ($CDCl_3$, Me_4Si, 100 MHz) δ 4.91 (s, 1, CH), 3.84 (s, 3, CO_2CH_3), 3.34 (s, 3, $-OCH_3$), 3.62–2.69 [m, 2, J = 17.2 Hz, CH_2 (AB)], 1.41 (s, 3, CH_3). Anal. Calcd for $C_{16}H_{24}N_4O_6$: C, 52.17; H, 6.52; N, 15.22. Found: C, 52.3; H, 6.6; N, 15.3.

B. Preparation of 5b (R = Et). **4b** (2 g) in 15 mL of 2,2,2-trifluoroethanol is heated at 60 °C for 3 h. After cooling, **5b** is precipitated by addition of ether and crystallized from carbon tetrachloride: yield 86%; mp 233–236 °C; IR (KBr) 1720 (s, ester), 1552 (s, C=N), 757 (s), 747, 668 cm^{-1} (m); NMR ($CDCl_3$, HMDS, 60 MHz, only quoted are the absorptions of the substituted part of the molecule) 3.7 (q, 2, J = 8 Hz, $-CH_2CF_3$), 5.03 (s, 1 H, CH methine). Anal. Calcd for $C_{20}H_{26}N_4O_6F_6$: C, 45.11; H, 4.89; N, 10.53. Found: C, 45.0; H, 4.9; N, 10.5.

C. Preparation of 5c (R = Et). **4b** (0.5 g) and 3 g of phenol are heated at 40 °C overnight. The excess of phenol is sublimed under vacuum and the residue crystallized from toluene: yield 61%; mp 231 °C; IR (KBr) no OH, 1693 (s, ester), 1556 (s, C=N), 756 (s), 734 cm^{-1} (m); NMR ($CDCl_3$, HMDS, 60 MHz) δ 7.10 (m, 5, C_6H_5), 5.73 (s, 1, CH). Anal. Calcd for $C_{28}H_{32}N_4O_6$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.5; H, 6.6; N, 10.6.

D. Preparation of 5d. **4b** (2 g) is heated in 5 mL of *p*-fluoroaniline for 3 h at 100 °C, 30 mL of benzene is then added, and the solution is refluxed for 1 h. After evaporation of the solvent, the residue is crystallized from acetonitrile: yield 79%; mp 242 °C; IR (KBr) 3450 (s, NH), 1680 (s, ester), 1540 (m), 1510 (s), 823 cm^{-1} (s). Anal. Calcd for $C_{28}H_{32}N_6O_4F_2$: C, 60.65; H, 5.78; N, 15.16. Found: C, 61.0; H, 5.8; N, 15.2.

E. Preparation of 5e. **4b** (1.5 g) and 2 g of pyrazole are refluxed overnight in 830 mL of acetone. After filtration, the solvent is evaporated under vacuum, the solid kept under vacuum for a few hours, and the residue crystallized from a mixture of benzene–cyclohexane: yield 42%; mp 228–232 °C; IR (KBr) no OH, 1714 (s, ester), 1545 (s, C=N), 1212 (s), 772 (m), 763 (s), 753 cm^{-1} (s); NMR ($CDCl_3$, HMDS, 60 MHz) δ 7.60 (d, 1, J = 2 Hz, pyrazole), 7.45 (large d, 1, H pyrazole), 6.20 (t, 1, H_4 pyrazole), 6.08 (s, CH).

II. Preparation of 3(5)-Carboethoxy-5(3)-methylpyrazole (8). The product **4b** (R = Et) is dissolved with stirring in an excess of hot H_2O_2 (15%) for 5 min. After cooling, the solution is extracted several times with chloroform, the organic solution dried ($CaSO_4$), and the solvent evaporated under vacuum. The oily residue is crystallized twice from hexane (38%): mp 82–83 °C, identical with the literature data;[11] (KBr) 3300–2900 (s, NH), 1725 cm^{-1} (s, COOEt); NMR ($CDCl_3$, HMDS, 60 MHz) δ 11.73 (s, 1, NH), 6.47 (s, 1, H aromatic), 4.25 (q, 2, CH_2CH_3), 2.26 (s, 3, CH_3), 1.22 (t, 3, CH_2CH_3).

III. Reactions in Diluted Medium. Preparation of 6 and 7. To a solution of 1.7 mL (20 mmol) of α-methylacrolein in 25 mL of benzene is added 2.1 mL (20 mmol) of ethyl diazoacetate. The mixture is stirred at 40 °C until the evolution of nitrogen is over (80% in volume). The solid **4** is filtered off, the solvent eliminated, and the crude mixture distilled under vacuum before preparative VPC. The crude yield of **6** and **7** is about 80%.

IV. (*Z*)-1-Formyl-1-methyl-2-carboethoxycyclopropane (6, R = Et): bp 43–46 °C (1 mm); IR (neat) 3060 (w, cycle), 1735 (s, COOEt), 1720 (s, CHO), 1029, 878 cm^{-1}; NMR ($CDCl_3$, Me_4Si, 60 MHz) δ 9.09 (s, 1, CHO), 4.05 (q, 2, OCH_2CH_3), 2.2–1.5 (m, 3, ring), 1.17 (t, 3, OCH_2CH_3), 1.15 (s, 3, CH_3).

V. (*E*)-1-Formyl-1-methyl-2-carboethoxycyclopropane (6, R = Et): NMR ($CDCl_3$, Me_4Si, 60 MHz) δ 8.66 (s, 1, CHO), 2.3–1.8 and 1.6–1.1 (m, 3, ring), 1.25 (s, 3, CH_3).

Anal. (mixture of both isomers of **6**) Calcd for $C_8H_{12}O_3$: C, 61.55; H, 7.69. Found: C, 61.6; H, 7.8.

VI. Ethyl (*Z*)-4-Formyl-3-pentenoate (7): 10%; bp 52–54 °C (1 mm); IR (neat) 1749 (s, COOEt), 1700 (s, CHO), 1030 (s), 812 cm^{-1} (w); NMR ($CDCl_3$, Me_4Si, 60 MHz) δ 9.24 (s, 1, CHO), 6.53 (d of t, 1, ^3J = 7.0, ^4J = 1.4 Hz, H vinyl), 4.11 (q, 2, OCH_2CH_3), 3.23 (d of d, 2, ^3J = 7.0, ^5J = 1.0 Hz, CH_2), 1.66 (m, 3, CH_3).

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Registry No.—**1**, 78-85-3; **2a**, 6832-16-2; **2b**, 623-73-4; **2c**, 24761-88-4; **4a**, 61597-89-5; **4b**, 60323-59-3; **4c**, 61597-90-8; **5a** (R = Me), 55199-74-1; **5b** (R = Et), 61597-91-9; **5c** (R = Et), 61597-92-0; **5d** (R = Et), 61597-93-1; **5e** (R = Et), 61597-94-2; *E*-**6** (R = Et), 13949-97-8; *Z*-**6** (R = Et), 13950-14-6; *Z*-**7** (R = Et), 61597-95-3; **8**, 4027-57-0; methanol, 67-56-1; 2,2,2-trifluoroethanol, 75-89-8; phenol, 108-95-2; *p*-fluoroaniline, 371-40-4; pyrazole, 288-13-1.

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The Thermal β-Cis-Elimination Reaction of Cyclic Sulfoxides and Subsequent Ring Expansion Reactions

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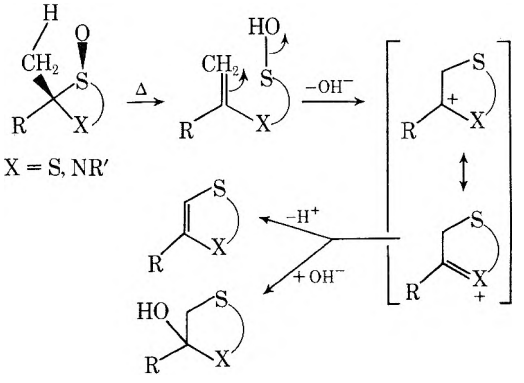
A two-step process has previously been identified for the ring expansion which occurs on heating cyclic and spirocyclic sulfoxides in solution, a β-cis elimination to form sulfenic acid and olefin moieties, followed by an intramolecular electrophilic addition reaction between these functional centers with ring closure yielding a heterocyclic sulfide with one more member than the original sulfoxide. It is found that either step can be rate determining depending on the ground state geometry of the substrate undergoing reaction. The geometric factors that determine the rates of the β-cis elimination step are examined in some detail through variation of the structural features of the sulfoxides. Study of the kinetic deuterium isotope effect by applying the criterion of the temperature dependence of k_H/k_D discloses that tunneling is an important factor in the pseudopericyclic process by which β-cis-elimination is effected in sulfoxides. Moreover, such tunneling is correlated directly with the distance of separation of the carbon and oxygen centers between which hydrogen is transferred in the course of forming olefin and sulfenic acid.

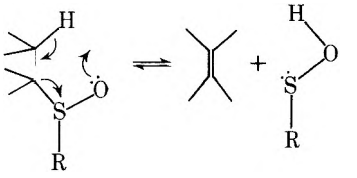
Thermolysis of sulfoxides containing β hydrogen atoms is a well-known method of preparing olefins; the established stereo- and regiospecificity of the reaction[1] is an important feature. The application of this reaction to cyclic sulfoxides, however, has been practiced infrequently in the past. A well-documented example occurs in the penam–cephem conversion of penicillin *S*-oxides;[2] the initial step of this reaction apparently is the thermal ring opening to a sulfenic acid intermediate via an assumed β-cis-elimination process.[1]

The subsequent intramolecular interaction of the sulfenic acid and olefin centers arising from this thermolytic cleavage of a cyclic sulfoxide can take place either through a cis addition which is the reverse of the cleavage reaction, or an electrophilic addition equivalent to the attack of a sulfur cation on the double bond. Typical cases of the cis addition are the ring contraction of thiepane 1-oxide to 2-methylthiane 1-oxide[3] and the thermal isomerization of penicillin *S*-oxides.[4] The electrophilic addition appears to be operative when the cationic intermediate is stabilized by a heteroatom substituent on the olefin center. Two cases of this type have recently been reported[5,6] to take place according to the following scheme.[7]



There are indications that the electrophilic addition mode requires acid catalysis.

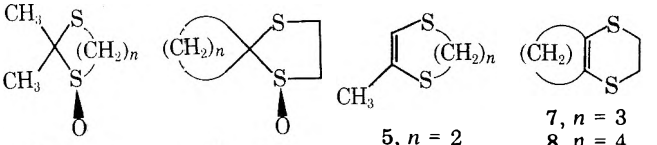
The rearrangement of 1,3-dithiolane 1-oxides into dihydro-1,4-dithiins reported recently[5] was independently characterized by us. However, the valuable synthetic applications of this reaction pointed out by Chen[5] have not been our main concern. Here we have undertaken to elucidate the kinetic characteristics of the sequence of steps involved in the overall rearrangement process. The elimination of sulfenic acid on thermolysis of sulfoxides is generally regarded as a concerted process. Though conceived to have a planar structure, some charge separation in the transition state has been alleged.[8] Since unshared pairs on the heteroatoms must be involved in the synchronism of bond making and breaking it is possible to consider this a pseudopericyclic[9,10] process as represented in the following equilibrium:



The principal focus of our studies has been on the geometry of the sulfoxide ring expansion controlling the kinetic factors of the overall reaction process.

Results and Discussion

The cyclic and spirocyclic sulfoxides **1–4** were prepared from the corresponding sulfides by oxidation with hydrogen peroxide in acetic acid.[11] Upon heating in *o*-dichlorobenzene or Me_2SO at 110–130 °C, **1**, **3**, and **4** rearrange smoothly into the corresponding dithiins **5**, **7**, and **8**, respectively, identified by their NMR and mass spectral features.[12,13] In Me_2SO-d_6



1, *n* = 2
2, *n* = 3

3, *n* = 4
4, *n* = 5

5, *n* = 2
6, *n* = 3

7, *n* = 3
8, *n* = 4

at 110 °C, **1**, **3**, and **4** were converted to the extent of 50% after 13, 2.5, and 20 h, respectively, as monitored by NMR spectroscopy. However, **2** decomposed much more slowly—50% after ~50 h—and less cleanly; dihydrodithiepin, **6**, was formed only in low yield (<20%), and the only other low-boiling product identified was 2,2-dimethyl-1,3-dithiane.

The unexpected course taken in the thermolysis of **2** may be a consequence of both the high $\Delta G^{\ddagger}$ for closure of a seven-membered ring and a ground-state structure which does not completely fulfill the geometric requirements for cis elimination. On the other hand, inspection of models reveals that **1** and **3** possess the geometry that is very favorable for the cis cleavage, with **3** being almost locked into the ideal positioning. It can also be seen with the aid of models that the S–O bond in **2** is disposed equatorially.[14,15] These circumstances, wherein the distance between the oxygen and the methyl is unusually long and coplanarity is difficult to achieve, are decidedly unfavorable for the cis-concerted elimination process. The situation in the spirocyclic sulfoxide **4** is somewhat more

Table I. Kinetic Parameters[a] for the Decomposition of *tert*-Butyl Ethyl Sulfoxide (11) and Its d_9 Analogue (12)

Substrate	$10^5 k^{112.5°C}$, s^{-1}	Temp range, °C	E_a, kcal mol^{-1}	A (10^{-12})
11	3.8[c]	102–135	29.4 ± 0.9	11.7
12	0.74[b]	112–143	32.6 ± 0.7	24

$[\Delta E_a]_D^H$ = 3.2 kcal mol^{-1}; A_H/A_D = 0.07

[a] Calculated from rate data plotted in Figure 1. [b] Data not corrected for incomplete deuteration of <5%. [c] Compare with *tert*-butyl methyl sulfoxide data[10] (toluene solvent) $k_{100°C} = 0.63 \times 10^{-5}$ s^{-1}.

complex, but study of its model construction discloses that its geometry is slightly more favorable for the cis elimination than is the case in **2**. Thus, the observed order of overall rearrangement rates, **3** > **1** > **4** > **2**, appears to parallel the order deduced on the basis of ground-state structural considerations which determine the ease of attainment of the geometric requirements of an essentially planar, cis-concerted elimination process.

The question which then presents itself is whether the ring opening is indeed the rate-determining step of the overall rearrangement, for, if not, it is reversible. To test reversibility and stereospecificity of the ring-opening step under the reaction conditions, substrates **1** and **2** were heated in Me_2SO-d_6 containing a large molar excess of D_2O. If the intermediate sulfenic acid existed for a finite interval prior to the product forming step it must suffer H/D exchange. Assuming its formation to be rapidly reversible, the substrate molecule must become deuterated and, if this step is stereospecific, the deuterium incorporation is to be expected at the cis methyl.[4] Consequently, the uptake of a measurable amount of deuterium in the starting material after a half-life of reaction under these circumstances is indicative of a rate-determining, product-forming step of electrophilic ring closure. The converse result, i.e., no deuterium incorporation into the substrate, is also to be taken as an indication of rate-determining cis elimination to form irreversibly a sulfenic acid which is very rapidly transformed to product.

In the NMR spectra of **1** and **2** the cis methyl groups appear at lower field than the trans. On heating at 100 °C the cis/trans ratio of the methyl groups of **1** is dramatically decreased; the spectrum of **2**, however, remained unchanged after 4 days of such heating. At 120 °C heating, **2** slowly decomposed but the cis/trans ratio of its methyl groups remained essentially unaltered. Clearly sulfenic acid formation is rapidly reversible and stereospecific in the conversion of the cyclic sulfoxide **1** to its rearrangement product **5**, but in the corresponding reaction of **2** this is the slow step. Reversibility of ring opening as shown by deuterium incorporation into the starting material was also demonstrated in the course of conversion of **3** to **7**, whereas there was no significant D incorporation in **4** during its conversion to **8** (see Experimental Section).

The deuterium exchange experiment was also performed in the reverse manner; the 2,2 dimethyl-d_6-1,2-dithiolane 1-oxide (**1**-d_6) was prepared and heated in Me_2SO-d_6 in the presence of H_2O. Some hydrogen was taken into the cis methyl group (i.e., cis to the sulfoxide oxygen) but quite slowly, the overall rate of rearrangement also being considerably slower than that for the nondeuterated substrate **1**. According to the NMR analysis the product contained some vinylic hydrogen but no $-CH_3$ could be detected. The results appear to be consistent with a large kinetic deuterium isotope effect in the initial cis-elimination step, sufficient to reduce the rate differences between the two reaction steps and thereby shorten the lifetime of the sulfenic acid intermediate. Direct evidence

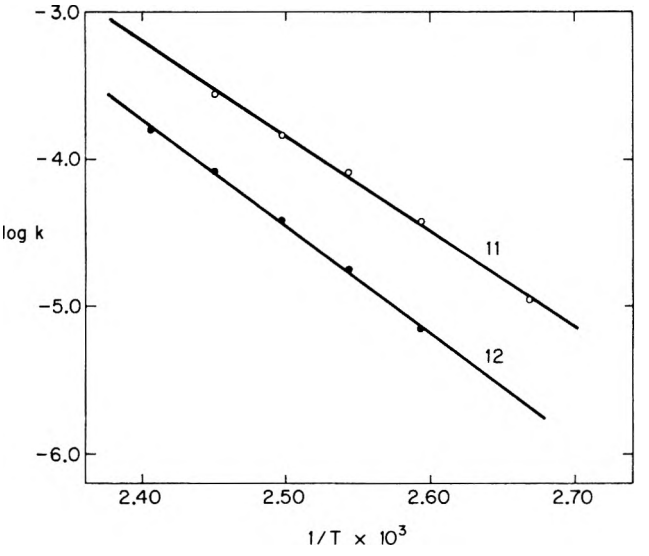
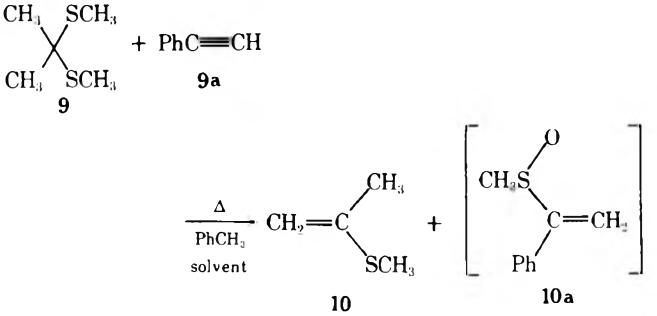


Figure 1. Arrhenius plots, thermolysis of *tert*-butyl ethyl sulfoxide and deuterated analogue.

of a large k_H/k_D in sulfoxide thermolysis is discussed in the following section.

The Kinetic Deuterium Isotope Effect in β-Cis Elimination of Sulfoxides. For these studies 3,3-dimethyl-2,4-dithiapentane 2-oxide (**9**) and its 3,3 dimethyl-d_6 analogue were considered to be suitable model substrates. When **9** was refluxed in toluene (~10 h) in the presence of ethynylbenzene (**9a**) to trap the methylsulfenic acid formed,[16] isopropenyl methylsulfide (**10**) was indeed isolated alongside of the



product (**10a**) of sulfenic acid addition to **9a**. However, the sulfoxide **9**, which is known to be very sensitive toward acids,[17] including probably methylsulfenic acid, proved to be too unstable to permit accurate kinetic analysis. Consequently the isotope effect studies were carried out using a somewhat less attractive model, but one which did not have the limitations of **9**, namely, *tert*-butyl ethyl sulfoxide (**11**) and its d_9 analogue **12**.

The temperature dependence of k_H/k_D (TIC)[18] has proven to be a much more valuable approach to elucidating mechanistic factors in H-transfer reactions than the common practice of estimating the nature of the isotope effect from a single temperature measurement of k_H/k_D. With this understanding the first-order rates of decomposition of **11** and **12** in inert (*n*-decane) solvent were determined over a ca. 30 °C temperature range. These rate data have been plotted in Figure 1 and the computed activation parameters are compiled in Table I. The large kinetic deuterium isotope effect invoked earlier to explain the slow and incomplete exchange of deuterium in **1**-d_6 on reaction in the presence of a large molecular excess of water is verified by these results; $k_H/k_D \approx 5$ at the same temperature.

A number of pericyclic H-transfer reactions, involving a

six-membered transition state structure, exhibit a maximum, (exclusively) zero-point energy controlled isotope effect.[18a,b] No evidence for hydrogen tunneling[19] has been observed in these cases. The (above) results for the five-membered pericyclic transition state involved in sulfoxide thermolysis clearly show a $[\Delta E_a]_D{}^H$ which is much larger than the value (~1.1 kcal mol^{-1}) characteristic for H-transfer from carbon when determined only by zero point energy differences. In fact, the large magnitude of $[\Delta E_a]_D{}^H$ and the correspondingly small value of the frequency factor ratio, A_H/A_D, strongly suggest the incursion of hydrogen tunneling,[19,20] which, as stated earlier, is most unusual among the pericyclic processes studied by application of the TIC.[18a]

Shelton et al.[10] have identified a significant degree of steric strain acceleration by *tert*-butyl substitution on the sulfoxide center, as well as considerable curvature of the activation plot for the decomposition rates of di-*tert*-butyl sulfoxide. Such effects may also be correlated[19] with the occurrence of hydrogen tunneling. A major factor controlling the incidence of tunneling is the thickness of the activation barrier;[18d,19,21] a relatively tall and narrow barrier, of course, creates the most favorable circumstances.[22] In the retroene reactions previously studied,[18a,b] where tunneling is totally absent, the distance between the centers across which the hydrogen is linearly transferred in the course of reaction is quite large. This makes for a barrier top of low curvature and relatively broad width, i.e., a reflection of the ground state geometry from which the double minimum activation curve is structured. However, in the five-membered pseudopericyclic transition state of *tert*-butyl sulfoxides, it can readily be seen with the aid of models that the oxygen atom is always close to one of the β(C–H) bonds. This situation must result in a narrow barrier and the consequent increased possibilities for tunneling.

With regard to cyclic sulfoxides, the results considered above suggest that a small distance of separation between the sulfoxide oxygen and the cis methyl is prerequisite for a low energy, concerted pathway. In **1** and **3**, as well as most penicillin *S*-oxides, where this distance is ~2 Å,[2b] barriers of ≤1 Å thickness are of great likelihood and engender high probability for H tunneling. This also has recently been illustrated for thermal cleavage of *tert*-butyl ethers which take place via a cyclic mechanism.[18d]

Experimental Section[23]

Preparation of Sulfides. Dithioketals were prepared from their corresponding ketones by reaction with the appropriate bismercaptans in the presence of boron trifluoride etherate.[24] Acetone-d_6 (99+ %) was used for the preparation of 2,2-dimethyl-d_6-1,3-dithiolane. *tert*-Butyl ethyl sulfide was prepared from *tert*-butyl alcohol and ethanethiol in sulfuric acid (75%); *tert*-butyl-d_9 ethyl sulfide was prepared from *tert*-butyl alcohol-d_{10} (99%) and ethanethiol in D_2SO_4–D_2O. The latter product was purified by preparative GLC; all other sulfides were purified by simple distillation.

Preparation of Sulfoxides. The general procedure[11] involved oxidation of the corresponding sulfides with approximately 0.9 equiv of 30% hydrogen peroxide in glacial acetic acid at 5–15 °C. After additional stirring for about 30 min at room temperature, the sulfoxide product was worked up by dilution with methylene chloride, neutralization of the acid with sodium carbonate and, after drying, evaporation of the solvent. Unless otherwise indicated, the sulfoxides were purified by distillation under high vacuum.

2,2-Dimethyl-1,3-dithiolane 1-Oxide (1): bp 84 °C (0.015 mm) [lit.[5] 83–84 °C (1 mm); NMR ($CDCl_3$) δ 3.9–3.1 [m, $-CH_2-_2$], 1.7 (s, 3, cis CH_3), and 1.55 (s, 3, trans CH_3).

2,2-Dimethyl-d_6-1,3 dithiolane 1-Oxide (1-d_6): bp 104 °C (0.9 mm); NMR ($CDCl_3$) δ 3.8–3.0 [m, 4, $-CH_2-_2$]; no CH_3 detected.

2,2-Dimethyl-1,3 dithiane 1-Oxide (2): bp 102 °C (0.2 mm) [lit.[14] 98–100 °C (0.15 mm); NMR ($CDCl_3$) δ ~3–2 [m, 6, $-CH_2-_3$], 1.65 (s, 3), and 1.60 (s, 3, CH_3).

1,4-Dithiaspiro[4.4]nonane 1-Oxide (3): bp 122 °C (0.05 mm) [lit.[13] 53.5 °C (8 μ); NMR ($CDCl_3$) δ 3.8–3.1 (m, 4, $-SOCH_2CH_2S-$), ~2.6 (m, 1), and ~1.8 (m, 7) both equivalent to $-CH_2-_4$; the multiplet at ~2.6 ppm probably can be ascribed to the β hydrogen atom in the carbocyclic ring cis–cis with respect to the S=O bond.

1,4-Dithiaspiro[4.5]decane 1-Oxide (4): recrystallized from heptane, mp 83–85 °C (lit.[13] 82.8 °C); NMR ($CDCl_3$) δ 3.7–3.1 (m, 4, $-SOCH_2CH_2S-$) and ~2.2–1.5 [m, 10, $-CH_2-_5$].

3,3-Dimethyl-2,4-dithiapentane 2-Oxide (9): bp 60 °C (0.5 mm); NMR ($CDCl_3$) δ 2.6 (s, 3, $-SOCH_3$), 2.2 (s, 3, SCH_3), 1.60 (s, 3) and 1.55 (s, 3) both CH_3's.

***tert*-Butyl ethyl sulfoxide (11)** was purified by preparative GLC on an SE-30 column at 130 °C: NMR ($CDCl_3$) δ 2.5 (double quartet, 2, CH_2), 1.4 (t, 3 CH_2CH_3), and 1.3 [s, 9, $C(CH_3)_3$]; mass spectrum *m/e* 134 (M^+).

***tert*-Butyl-d_9 ethyl sulfoxide (12)** was also purified by preparative GLC (SE-30, 130 °C): NMR ($CDCl_3$) δ 2.5 (m, 2, CH_2) and 1.4 (t, 3, CH_2CH_3), but no $C-CH_3-_3$; mass spectrum ~94% d_9 and ~6% d_8.

Thermolysis of Cyclic Sulfoxides. **1** was heated in o-dichlorobenzene solution (20%) at 130 °C for 40 h. The formation of 2-methyl-5,6-dihydro-1,4-dithiin (**5**) as the only product was shown by GLC and NMR;[25] **5** was isolated by preparative GLC (SE-30 column). The NMR ($CDCl_3$) showed δ 5.9 (m, 1, C=CH), 3.15 [m, 4, $-CH_2-_2$], and 1.9 (d, 3, CH_3); mass spectrum *m/e* 132 (M^+).

2 was heated in o-dichlorobenzene solution (20%) at 130 °C for ca. 15 h. The resulting dark brown solution was concentrated and the residue distilled under reduced pressure. The isolated fraction consisted of 2-methyl-5,6-dihydro-1,4-dithiepin (**6**) and 2,2 dimethyl-1,3-dithiane in a ~3:1 ratio as indicated by GLC and NMR.[25] GLC/mass spectral analysis, *m/e* 148 (M^+, 2,2 dimethyl-1,3-dithiane) and 146 (M^+, 6)

3 was heated in o-dichlorobenzene solution (8%) at 130 °C for ca. 17 h. Essentially the only product present in the resulting brown solution was 2,3-trimethylene-5,6-dihydro-1,4-dithiin (**7**) by NMR analysis. This was isolated by distillation: bp 85 °C (0.4 mm) [lit.[26] 64 °C (0.2 mm)]. NMR ($CDCl_3$) δ 3.15 (s, 4, $-SCH_2CH_2S-$), ~2.5 (m, 4) and 2.0 (m, 2) carbocyclic protons.

4 was heated in Me_2SO solution (8%) at 110 °C for ca. 17 h. Essentially the only product present in the reaction mixture as indicated by NMR analysis was 2,3-tetramethylene-5,6-dihydro-1,4-dithiin (**8**). This was isolated by extraction with petroleum ether: NMR ($CDCl_3$) δ 3.2 (s, 4, $-SCH_2CH_2S-$), ~2.1 (m, 4) and 1.7 (m, 4) both carbocyclic protons.

Deuterium exchange experiments in **1** and **2** were carried out by heating sealed NMR tubes containing solutions of the sulfoxides (~0.3 M) in Me_2SO-d_6 which was ~8 M in D_2O and also contained an internal standard (benzophenone). The tubes were removed at intervals from a thermostated oil bath and examined in the NMR. Incorporation of deuterium into **3** was studied as follows.

A solution of 300 mg of **3** in a mixture of 5 mL of THF and 1 mL of D_2O was refluxed (bp 65 °C) for 90 h; the resulting solution was concentrated, diluted with acetone/water (1:1), washed with pentane to remove the rearrangement product, and concentrated again. The NMR spectrum showed *decreased* intensity of the 2.6 ppm multiplet; mass spectral analysis showed a strongly *increased* intensity of the M + 1 peak ($M^-/M + 1^+ = 2$)

Compound **4** was also refluxed in THF/D_2O (5:1) for ~150 h; mass spectral analysis showed an essentially unaltered $M^+/M + 1^+$ ratio as compared to an untreated sample of **4**; ($M^+/M^+1^+ = \sim 7$.

Hydrogen exchange experiments in 2,2 dimethyl-d_6-1,3-dithiolane 1-oxide (1-d_6) were carried out in the same manner as the deuterium exchanges described above, only H_2O was used in place of D_2O.

Thermolysis of 3,3-Dimethyl-1,4-dithiapentane 1-Oxide (9). A solution of 1 g of **9** and 2 mL of ethynylbenzene in 10 mL of toluene was refluxed for 5 h. The reaction mixture was then distilled. The fraction bp 90–102 °C consisted of toluene and isopropenyl methyl sulfide **10** (lit.[27] bp 91 °C) confirmed by NMR analysis.

Thermolysis of *tert*-Butyl Ethyl Sulfoxide (11) and Its d_9 Analogue 12. Measurement of k_H/k_D. Thin-walled tubes containing ~0.075 M solutions of the sulfoxide, and *p*-di-*tert*-butylbenzene as the internal standard, in freshly distilled *n*-decane as solvent were heated in a thermostated bath. Samples were removed at regular intervals and analyzed by GLC; column, 10% OV-101 on Gas-Chrom Q, direct on column injection. The relative amounts of sulfoxide present in the samples were calculated from peak areas. Arrhenius plots were constructed using a least-squares method; activation parameters were calculated by standard procedures.

Registry No.—**1**, 59176-95-3; 1-d_6, 61558-89-2; **2**, 41893-06-5; **3**, 59796-90-6; **4**, 59796-91-7; **5**, 5769-49-3; **6**, 5769-50-6; **7**, 35156-14-0; **8**, 23285-17-8; **9**, 35493-34-6; **9a**, 536-74-3; **11**, 25432-20-6; **12**,

61558-90-5; 2,2-dimethyl-1,3-dithiolane, 6008-78-2; 2,2-dimethyl-d_6-1,3-dithiolane 61558-91-6; 2,2-dimethyl-1,3-dithiane, 6007-22-3; 1,4-dithiaspiro[4.4]nonane, 176-39-6; 1,4-dithiaspiro[4.5]decane, 177-16-2; hydrogen peroxide, 7722-84-1.

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Conformational Analysis. 36. Preferred Conformations of 5-Substituted 1,3-Dioxanes with Sulfur-Containing and Ether Functions in the Side Chain[1,2]

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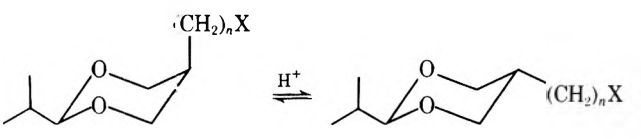
The conformational preferences of 2-isopropyl 5-substituted 1,3-dioxanes in which the 5 substituent is $-(CH_2)_nSCH_3$, $-(CH_2)_nSOCH_3$, $-(CH_2)_nSO_2CH_3$, $-(CH_2)_nS(CH_3)_2^+$, or $-(CH_2)_nOCH_3$ and n = 0, 1, 2 have been determined. The results may be interpreted in terms of the amount of positive charge on the atom attached to C(5) of the ring: the greater the positive charge, the higher the axial preference.

In a previous publication[3] we have reported the conformational preference of compounds of the type shown in Scheme I where n = 0 and X is a polar substituent, such as

Scheme I



SCH_3, $SOCH_3$, SO_2CH_3, or NO_2, or a charged species, such as SMe_2^+, NH_3^+, NMe_2H^+, or NMe_3^+. We have now extended these measurements to the cases where n = 1 or 2 and X is SCH_3, $SOCH_3$, SO_2CH_3, or $S(CH_3)_2^+$. For comparison, the cases where X = OCH_3 are reported also. The results contribute to our as yet meager knowledge of *intra*molecular polar effects.

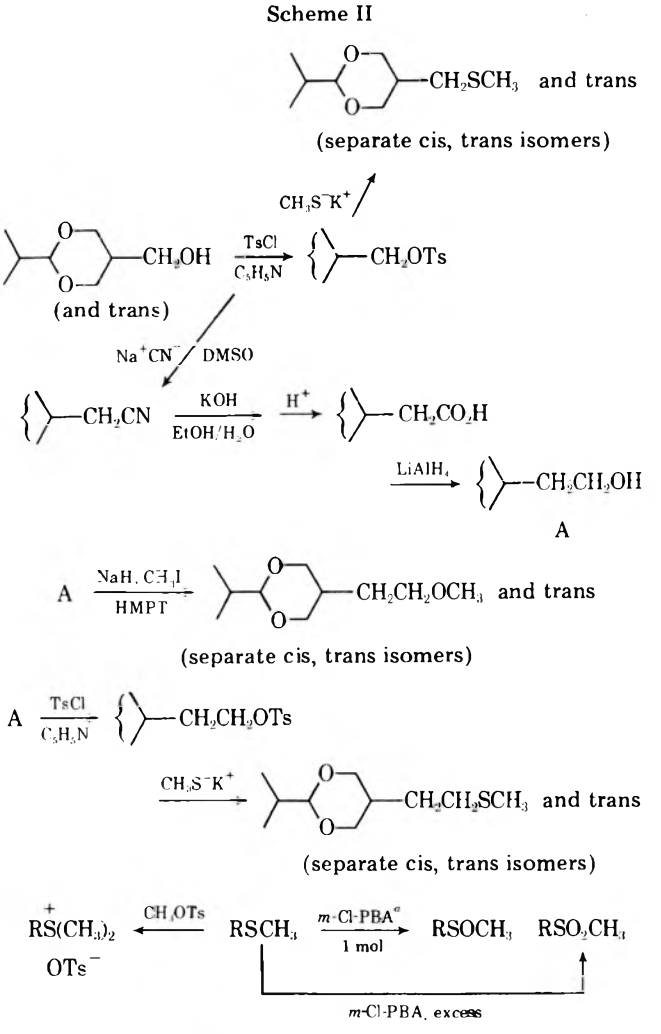
Synthesis, Configurational Assignment, Analysis, and Results. The synthesis of the required compounds from *cis*- and *trans*-5-hydroxymethyl-1,3-dioxane[4] is shown in Scheme II. It was found convenient to start with a mixture of diastereomeric 2-isopropyl-5-hydroxymethyl-1,3-dioxanes and separate the final cis–trans mixtures of ethers or thioethers by gas chromatography. Configurational assignments of the ethers and thioethers rest on the ^1H NMR signals of $H(4)_e$ and $H(4)_a$. In the trans (equatorial) isomers, these protons appeared as a nearly first-order AA'BB'X system, with $H(4)_a$ the upfield, slightly distorted triplet and $H(4)_e$ the downfield, narrow doublet of broad doublets. In the cis (axial) isomers

Table I. Diastereomer Equilibria (Scheme I)[a]

X	n	Solvent	Temp, °C	K	ΔG°[b]
SCH_3	0[3]	C_6H_{12}	26.5	21.3 ± 0.03	−1.82 ± 0.01
		CCl_4	26.5	18.6 ± 0.6	−1.74 ± 0.02
		Ether	26.5	18.3 ± 0.6	−1.73 ± 0.02
		C_6H_6	26.5	13.5 ± 0.5	−1.55 ± 0.02
		CH_3CN	26.5	6.68 ± 0.2	−1.13 ± 0.02
		DCA[c]	25	7.59	−1.20
		TFA[d]	25	4.81	−0.93
SCH_3	1	C_6H_{12}	41	1.08 ± 0.02	−0.05 ± 0.01
		CCl_4	50	1.08 ± 0.02	−0.05 ± 0.01
		C_6H_6	50	1.24 ± 0.02	−0.14 ± 0.01
		$CHCl_3$	50	1.22 ± 0.02	−0.13 ± 0.01
		CH_3CN	50	1.28 ± 0.02	−0.16 ± 0.01
SCH_3	2	C_6H_{12}	41	1.89	−0.40
		CCl_4	41	1.79	−0.36
		C_6H_6	41	2.23 ± 0.03	−0.50 ± 0.01
		$CHCl_3$	41	2.19 ± 0.02	−0.48 ± 0.01
		CH_3CN	41	2.74 ± 0.04	−0.63 ± 0.01
OCH_3	0[6]	C_6H_{12}	25	5.69	−1.03
		CCl_4	25	4.57	−0.90
		Ether	25	4.06	−0.83
		C_6H_6	25	2.71	−0.59
		$CHCl_3$	25	1.31	−0.16
		CH_3CN	25	0.98	+0.01
OCH_3	1	C_6H_{12}	41	0.92 ± 0.01	+0.05 ± 0.01
		Ether	30	1.08 ± 0.01	−0.05 ± 0.01[3]
		C_6H_6	41	0.985 ± 0.015	+0.01 ± 0.01
		$CHCl_3$	41	0.94 ± 0.01	+0.04 ± 0.01
		CH_3CN	41	1.12 ± 0.01	−0.07 ± 0.01
OCH_3	2	C_6H_{12}	41	2.33	−0.53
		C_6H_6	41	2.53 ± 0.03	−0.58 ± 0.01
		$CHCl_3$	41	2.53 ± 0.03	−0.58 ± 0.01
		CH_3CN	41	3.06 ± 0.06	−0.70 ± 0.01
$SOCH_3$	0[3]	CCl_4	54	0.40	~+0.6[e]
		C_6H_6	54	0.32 ± 0.04	+0.74 ± 0.07[e]
		$CHCl_3$	54	0.28 ± 0.05	+0.82 ± 0.11[e]
		CH_3CN	54	0.26 ± 0.04	+0.86 ± 0.09[e]
$SOCH_3$	1	C_6H_6	50	0.80 ± 0.07	+0.14 ± 0.05[f]
		$CHCl_3$	50	0.47 ± 0.04	+0.49 ± 0.05[f]
		CH_3CN	50	1.10 ± 0.09	−0.06 ± 0.05[f]
$SOCH_3$	2	C_6H_6	50	1.86 ± 0.09	−0.40 ± 0.03[f]
		$CHCl_3$	50	1.47 ± 0.07	−0.25 ± 0.03[f]
		CH_3CN	50	2.14 ± 0.06	−0.49 ± 0.02[f]
SO_2CH_3	0[3]	C_6H_{12}	50	0.165 ± 0.025	+1.16 ± 0.10[e]
		C_6H_6	50	0.19 ± 0.03	+1.07 ± 0.10[e]
		$CHCl_3$	50	0.16 ± 0.03	+1.19 ± 0.10[e]
		CH_3CN	50	0.25	~+0.9[e]
SO_2CH_3	1	C_6H_6	50	0.63 ± 0.02	+0.30 ± 0.02[f]
		$CHCl_3$	50	0.44 ± 0.02	+0.53 ± 0.03[f]
		CH_3CN	50	0.84 ± 0.04	+0.11 ± 0.03[f]
SO_2CH_3	2	C_6H_6	50	1.22 ± 0.07	−0.12 ± 0.03[f]
		$CHCl_3$	50	1.08 ± 0.03	−0.05 ± 0.02[f]
		CH_3CN	50	1.68 ± 0.08	−0.33 ± 0.03[f]
$^+S(CH_3)_2$ OTs^-	0	TFA[d]	25	0.034	2.0[e,g,3]
$^+S(CH_3)_2$ PF_6^-	0	CD_3CN	25	0.034 ± 0.004	2.00 ± 0.07[e,g]
$^+S(CH_3)_2$ PF_6^-	1	CD_3CN	25	0.34 ± 0.02; 0.31	0.63 ± 0.03;[f,g] 0.69[e,g]
$^+S(CH_3)_2$ PF_6^-	2	CD_3CN	25	1.27 ± 0.02	−0.14 ± 0.01[f,g]

[a] Catalyst Amberlyst-15 unless otherwise noted. [b] kcal/mol. Analysis by gas–liquid partition chromatography unless otherwise noted. [c] Dichloroacetic acid. [d] Trifluoroacetic acid. [e] Analysis by ^1H NMR. [f] Analysis by ^{13}C NMR. [g] Equilibrated with trifluoroacetic acid.

Scheme II



[a] *m*-Chloroperbenzoic acid.

$H(4)_e$ and $H(4)_a$ were nearly coincident and appeared as a narrow, highly distorted doublet. The sulfoxides, sulfones, and sulfonium salts were prepared from the corresponding sulfides; their configurations follow accordingly and were corroborated by their ^1H NMR coupling constants.

The equilibrium positions are summarized in Table I. Equilibration was brought about either by means of beaded polystyrenesulfonic acid (Amberlyt-15[5]) or by means of trifluoroacetic acid, as shown in Table I. Analysis for the volatile methyl sulfides and methyl ethers was by gas chromatography whereas the involatile sulfoxides, sulfones, and sulfonium salts were analyzed by peak integration of ^1H or ^{13}C NMR spectra (Table II, Experimental Section). It is of interest that the ^{13}C NMR signals of the axial methylene groups attached to C(5) (cis isomers) are, in all cases, *downfield* of the corresponding equatorial methylene group in the trans isomers. Included in

Table II. ^{13}C NMR Chemical Shift Data of 5-Substituted 2-Isopropyl-1,3-dioxanes (Scheme I)[a]

X	Registry no.	n		C_2	$C_{4,6}$	C_5	$CH(CH_3)_2$	$(CH_3)_2CH$	CH_2S	SCH_3	Others
SCH_3	40245-27-0	0	Cis	106.13	70.10	42.18	32.62	(16.99)		14.98	
	40245-28-1		Trans	105.43	70.55	39.63	32.47	16.99		13.26	
$S^+(CH_3)_2$	61543-14-4	0	Cis[a]	107.06	66.25	52.01	33.33	16.87		24.54	
PF_6^-	61522-97-2		Trans[a]	106.62	65.59	46.35	32.79	17.24		23.33	
SCH_3	61522-98-3	1	Cis	106.01	69.09	34.03	32.78	16.78	34.70	15.69	
	61522-99-4		Trans	105.30	70.85	(33.23)	(32.13)	16.64	32.13	15.45	
$SOCH_3$	61523-00-0	1	Cis	106.45	71.11 68.10	29.72	32.73	16.70	55.74	39.29	
	61523-01-1		Trans	105.85	70.84 70.57	30.75	32.53	16.94	53.63	39.50	
SO_2CH_3	61523-02-2	1	Cis	106.36	70.14	29.41	32.70	16.71	54.65	42.20	
	61523-03-3		Trans	105.90	70.47	29.71	32.52	16.94	53.31	41.46	
$S^+(CH_3)_2$	61523-05-5	1	Cis[a]	107.10	69.34	31.70	33.35	16.92	46.39	26.52	
PF_6^-	61523-07-7		Trans[a]	106.61	70.12	31.43	33.15	17.20	42.67	26.16	
SCH_3	61523-08-8	2	Cis	105.96	69.82	33.21	32.76	16.79	32.13	15.23	28.48 ($-CH_2-$)
	61523-09-9		Trans	105.66	71.60	33.79	32.59	17.05	31.15	15.31	27.86 ($-CH_2-$)
$SOCH_3$	61523-10-2	2	Cis	105.93	69.54	33.42	32.66	16.74	52.43	38.47	22.60 ($-CH_2-$)
	61523-11-3		Trans	105.62	71.31 71.20	33.70	32.47	17.01	51.09	38.47	20.95 ($-CH_2-$)
SO_2CH_3	61523-12-4	2	Cis	106.11	69.53	(32.93)	(32.71)	16.77	52.79	40.38	22.81 ($-CH_2-$)
	61523-13-5		Trans	105.82	71.12	33.31	32.53	17.03	51.67	40.49	20.69 ($-CH_2-$)
$S^+(CH_3)_2$	61523-15-7	2	Cis[a]	106.63	69.97	33.97	33.58	17.25	42.42	25.12	24.89 ($-CH_2-$)
PF_6^-	61523-17-9		Trans[a]	106.51	71.37	34.41	33.45	17.62	41.22	25.18	22.96 ($-CH_2-$)
OCH_3	28808-25-5	1	Cis	106.07	67.57	35.18	32.90	16.83	71.80[b]	58.82[c]	
	58619-95-7		Trans	105.81	69.50	35.27	32.76	17.10	71.25[b]	58.87[c]	
OCH_3	61523-18-0	2	Cis	106.13	70.20	31.45	32.91	16.85	70.64[b]	58.43[c]	29.57 ($-CH_2-$)
	61523-19-1		Trans	105.81	72.09	32.74	32.74	17.09	70.39[b]	58.52[c]	28.50 ($-CH_2-$)

[a] In $CDCl_3$ except for sulfonium salts, which were in CD_3CN. [b] CH_2O. [c] OCH_3.

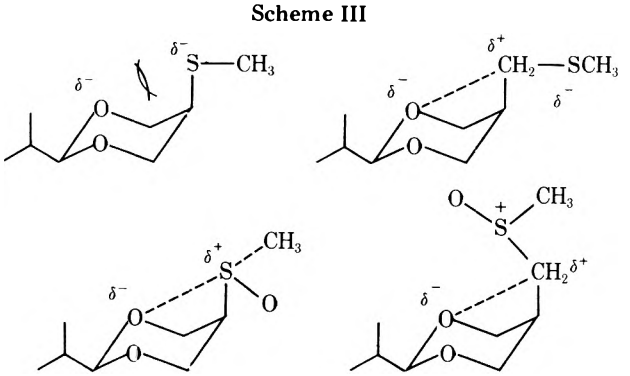
Table I are data for $n = 0$ for the sulfur compounds[3] and for $n = 0$[6] or 1[3] for the ethers, taken from previous papers.[3,6]

Discussion

The following regularities appear to be implied by the data in Table I: (a) When $n = 2$, $\Delta G°$ becomes negative for all X substituents. Presumably $\Delta G°$ converges to the value for an alkane chain (X = H). ($\Delta G°$ is −0.6 kcal/mol for C_2H_5[5] and −0.9 kcal/mol for CH_3.[7]). (b) For the $SOCH_3$ and SO_2CH_3 groups, $\Delta G°$ decreases monotonically as n increases from 0 to 1 to 2. (c) In contrast, for X = SCH_3 and OCH_3 $\Delta G°$ increases substantially as n goes from 0 to 1 and then decreases (presumably converging to the alkyl value) when $n = 2$. (d) The solvent effects for X = SCH_3 and OCH_3 are large when $n = 0$, small or negligible when $n = 1$ or 2. (e) The solvent effects for X = $SOCH_3$ and SO_2CH_3 are small when $n = 0$, if anything slightly larger for $n = 1$, 2. There appears to be a specific preference for the axial position in solvent chloroform.

Scheme III provides the basis for an explanation of these findings.

Scheme III



For SCH_3 and OCH_3 and $n = 0$, the repulsive interaction of the heteroatom with the ring oxygen seems to be dominant. This may alternatively be considered as a repulsive interaction of the dipole of the ring[3] and the XCH_3 dipole. As such, it is subject to a sizable solvent (or solvation[8,9]) effect.[10] (We have previously measured[10] the dipole moments of the stereoisomers with X = OCH_3 and $n = 0$; they are 2.85 D for the axial and 1.30 D for the equatorial isomer.) But when X = SCH_3 or OCH_3 and $n = 1$, the dipole difference between isomers will be small (because of the presence of a number of conformations in each diastereomer) and the dominant effect is now the attraction of the partially positively charged methylene next to O or S and the partially negatively charged ring oxygen. The effect of solvent on this interaction would be largely coulombic,[8] and since the solvent does not effectively penetrate the region, close to the molecules, where the electrostatic interaction is most important, solvent effects are small.[11] For $n = 2$ this (inductive) coulombic effect is dampened by relay through the alkyl chain[12] and $\Delta G°$ approaches the value for that chain.

The situation is otherwise for $SOCH_3$ and SO_2CH_3, $n = 0$. The sulfur atoms in these functions bear a substantial positive charge and are attracted to the ring oxygen. The oxygen atoms are turned toward the outside, even in the sulfone,[3] and are thus more distant from the ring oxygens. Solvent effects on the coulombic attraction are small for the reasons already mentioned and solvation of dipoles is less important than for OCH_3 and SCH_3 because the differences in dipole moment are smaller (e.g., 3.50 D for an axial sulfoxide, 2.46 D for an equatorial one[3]). When $n = 1$ or 2 for the sulfoxide, sulfone, and sulfonium function, the relay of positive charge along the hydrocarbon side chain leads to enough residual charge on the carbon next to the ring to engender substantial attraction (for $n = 1$) or at least to reduce the normal repulsion (for $n = 2$). The fact that solvent effects are appreciable, at least for the sulfoxide and sulfone, when $n = 1$ or 2 suggests some coiling back of the functional group toward the ring (Scheme III). In the conformation shown, some of the coulombic attraction is between side-chain sulfur and ring oxygen, and since the sulfur is now further away from the ring oxygen, solvent penetration into the area of interaction becomes more important so that the effect of the dielectric properties of the

solvent manifests itself. There may, in addition, be a special effect in solvent chloroform which we hope to discuss in more detail in a future publication.

In summary, the data in Table I may all be logically interpreted in terms of charge alternation ($-S^{\delta-}-C^{\delta+}H_2$, $-O^{\delta-}-C^{\delta+}H_2$), attenuation of charge by relay ($O^{-}-S^{+}-C^{\delta+}H_2C^{\delta\delta+}H_2$), coulombic attraction or repulsion and the (generally minor) effect of solvent thereon, and dipole repulsion and dipole solvation. These interpretations are based on the assumption—not absolutely certain—that the ΔG values are dominated by ΔH. They could be vitiated by major differences in ΔS between stereoisomers, either as a result of differences in solvation or as a result of differences in conformational isomerism of the $(CH_2)_nX$ chains (Scheme I).

Experimental Section

Melting points were determined on a Sargent Mel-Temp variable temperature heating block in open capillary tubes. Analytical gas–liquid partition chromatography was carried out with a Hewlett-Packard 5750 research chromatograph, equipped with a thermal conductivity detector, on 0.125-in. columns. Varian Aerograph Series 2700 and Model 960 instruments with matched 0.375-in. aluminum columns were used for preparative GLC. Elemental microanalyses were performed by Galbraith Laboratories, Inc., Knoxville Tenn.

^{1}H NMR spectra were recorded on a Jeolco C-60HL or a Varian XL-100 spectrometer in cw mode. Samples were 20–30% in $CDCl_3$; shifts are reported in parts per million downfield from internal tetramethylsilane and are accurate to ±0.01 ppm. Coupling constants are in hertz and accurate to ±0.5 Hz. ^{13}C NMR spectra were recorded on the XL-100 instrument in 5- or 10-mm tubes in FT mode at 25.16 MHz. The solvent was $CDCl_3$ and an internal deuterium lock and internal Me_4Si reference (2%) were used except in the case of the sulfonium salts. Assignment of ^{13}C spectra (Table II) was achieved by a combination of off-resonance decoupling and parametric reasoning.

5-(2-Isopropyl-1,3-dioxanyl)methyl *p*-Toluenesulfonates. A cold solution of a mixture of *cis*- and *trans*-5-(2-isopropyl-1,3-dioxanyl)methanol[4] (50 g, 0.31 mol) in 150 mL of pyridine was added to a solution of tosyl chloride (63 g, 0.33 mol) in pyridine (250 mL) and the mixture was allowed to stand in the refrigerator for 48 h. The solution was then poured over ice and placed in the refrigerator overnight. The resulting precipitate was collected, washed several times with water, and dried under vacuum to give 84.5 g (87%) of white solid.

NMR ($CDCl_3$) δ 0.90 [d, J = 7 Hz, 6 H, $(CH_3)_2CH$–], 1.16–2.8 (m, 2 H, –CHMe$_2$ and C_5 H), 2.43 (s, 3 H, $-CH_3$), 3.4 (apparent t, 2 H, $C_{4,6}$ H_a), 3.7–4.33 (m, 5 H, $C_{4,6}$ H_e and $-CH_2$ and C_2H_a), 7.3 (AB, J = 9 Hz, 2 H, H_{meta}), 7.73 (AB, J = 9 Hz, H_{ortho}).

***cis*- and *trans*-2-Isopropyl-5-methylthiomethyl-1,3-dioxane.** A solution of the above mixed tosylates (41 g, 0.13 mol) in 700 mL of absolute ethanol was treated with excess CH_3SK [prepared by adding 14.4 g (0.30 mol) of CH_3SH to a solution of 16.8 g (0.30 mol) of KOH in 200 mL of absolute ethanol]. The reaction mixture was stirred at room temperature for 2 h and refluxed for 10 h. The ethanol was removed by distillation, and 400 mL of water was added; the solution was extracted with three 300-mL portions of ether and the combined extracts were dried over $MgSO_4$, filtered, and concentrated (rotary evaporator). Distillation of the residue afforded 18.9 g (75.4%) of clear liquid, bp 53–55 °C (0.01 Torr).

The isomers were separated by preparative GLC techniques employing a 12-ft column packed with 20% Carbowax 20M/10% KOH on 60–80 mesh Chromosorb A at 190 °C.

^{1}H NMR ($CDCl_3$), cis isomer: δ 0.93 [d, J = 7.0 Hz, 6 H, $-CH(CH_3)_2$], 1.3–2.1 [m, 2 H, $-CH(CH_3)_2$, C_5 H_e], 2.06 (s, 3 H, $-SCH_3$), 2.83 (d, J = 7.5 Hz, 2 H, $-CH_2SCH_3$), 2.06 (s, 3 H, $-SCH_3$). 2.83 (d, J = 7.5 Hz, 2 H, $-CH_2SCH_3$), 3.93 (AA′BB′X, J_{gem} = 12 Hz, 4 H, $C_{4,6}$ H), 4.24 (d, J = 4.5 Hz, 1 H, C_2 H_a).

Trans isomer: δ 0.93 [d, J = 6.5 Hz, 6 H, $-CH(CH_3)_2$], 1.4–2.1 [m, 2 H, C_5 H_a, $-CH(CH_3)_2$], 2.08 (s, 3 H, $-SCH_3$), 2.22 (distorted d, 2 H, $-CH_2S$–), 3.34 (apparent t, J = 11 Hz, 2 H, $C_{4,6}$ H_a), 4.14 (d, J = 4.5 Hz, 1 H, C_2 H_a), 4.2 (d of d, J_{gem} = 11–12 Hz, 2 H, $C_{4,6}$ H_e).

***cis*-2-Isopropyl-5-methylsulfinylmethyl-1,3-dioxane.** Preparation from *cis*-2-isopropyl-5-methylthiomethyl-1,3-dioxane by treatment with an equimolar amount of *m*-chloroperoxybenzoic acid proceeded as previously described[3] for the lower homologue. Recrystallization from *n*-hexane afforded white crystals, mp 83.5–86.0 °C, in 70% yield.

^{1}H NMR ($CDCl_3$) δ 0.90 [d, J = 7.0 Hz, 6 H, $-CH(CH_3)_2$], 1.5–2.2 [m, 2 H, C_5 H_e, $-CH(CH_3)_2$], 2.65–2.93 (m, 2 H, $-CH_2SO$), 2.60 (s, 3 H, $-SOCH_3$), 3.93 (m, 4 H, $C_{4,6}$ H), 4.2 (d, J = 4.5 Hz, 1 H, C_2 H_a).

***trans*-2-Isopropyl-5-methylsulfinylmethyl-1,3-dioxane.** This stereoisomer was similarly[3] synthesized from *trans*-2-isopropyl-5-methylthiomethyl-1,3-dioxane in 60% yield, mp 73–75 °C after recrystallization from *n*-hexane.

^{1}H NMR ($CDCl_3$) δ 0.90 [d, J = 7.0 Hz, 6 H, $-CH(CH_3)_2$], 1.0–1.3 [m, 1 H, $-CH(CH_3)_2$], 1.5–2.1 (m, 1 H, C_5 H), 2.46 (distorted d, 2 H, $-CH_2SO$–), 2.60 (s, 3 H, $-SOCH_3$), 3.44 (apparent t, J = 11 Hz, 2 H, $C_{4,6}$ H_a), 4.1–4.4 (m 3 H, $C_{4,6}$ H_e, C_2 H_a).

***cis*-2-Isopropyl-5-methylsulfonylmethyl-1,3-dioxane.** The sulfone was synthesized, by a procedure analogous to that previously described for the lower homologue,[3] from *cis*-2-isopropyl-5-methylthiomethyl-1,3-dioxane by treatment with 2.5 molar excess *m*-chloroperoxybenzoic acid: yield 91%; mp 87–88 °C after recrystallization from *n*-hexane.

^{1}H NMR ($CDCl_3$) δ 0.93 [d, J = 6.5 Hz, 6 H, $-CH(CH_3)_2$], 1.4–2.4 [m, 2 H, C_5 H, $-CH(CH_3)_2$], 2.95 (s, 3 H, $-SO_2CH_3$), 3.43 (d, J = 6 Hz, 2 H, $-CH_2SO_2$–), 4.00 (AA′BB′X, J_{gem} = 12.5 Hz, 4 H, $C_{4,6}$ H), 4.27 (d, J = 4.5 Hz, 1 H, C_2 H_a).

Anal. Calcd for $C_9H_{18}SO_4$: C, 48.62; H, 8.16. Found: C, 48.40; H, 8.18.

***trans*-2-Isopropyl-5-methylsulfonylmethyl-1,3-dioxane.** The trans sulfone was similarly obtained from *trans*-2-isopropyl-5-methylthiomethyl-1,3-dioxane in 76% yield, mp 108.5–110.0 °C after recrystallization from *n*-hexane.

^{1}H NMR ($CDCl_3$) δ 0.93 [d, J = 7 Hz, 6 H, $-CH(CH_3)_2$], 1.4–2.5 [m, 2 H, C_5 H_e, $-CH(CH_3)_2$], 2.53 (d, J = 8 Hz, 2 H, $-CH_2SO_2$–), 2.80 (s, 3 H, $-SO_2CH_3$), 3.38 (apparent t, J = 11 Hz, 2 H, $C_{4,6}$ H_a), 4.2 (d, J = 5 Hz, 1 H, C_2 H_a), 4.32 (d of d, J_{gem} = 11 Hz, 2 H, $C_{4,6}$ H_e).

Anal. Calcd for $C_9H_{18}SO_4$: C, 48.62; H, 8.16. Found: C, 48.48; H, 8.43.

***cis*- and *trans*-Dimethyl-5-(2-isopropyl-1,3-dioxanyl)sulfonium Hexafluorophosphates.** The appropriate *p*-toluenesulfonate[3] was converted to the hexafluorophosphate by treatment with a slight excess of ammonium hexafluorophosphate in water. The solid separated was collected, washed with water, and recrystallized from water to give white, crystalline material, mp cis, 121.5–123 °C; trans, 182–183 °C.

The isomers were equilibrated in CD_3CN solution by means of a catalytic amount of trifluoroacetic acid (TFA). The equilibrated solution was analyzed by integration of the $-S^+(CH_3)_2$ ^{1}H NMR signals. Attainment of equilibrium was marked by cessation of change in the relative signal areas. The NMR spectra were identical with those of the *p*-toluenesulfonate except for absence of the aromatic signals.

Dimethyl-5-(*cis*-2-isopropyl-1,3-dioxanyl)methylsulfonium *p*-Toluenesulfonate. A mixture of 0.85 g (5 mmol) of *cis*-2-isopropyl-5-methylthiomethyl-1,3-dioxane and 2.79 g (15 mmol) of methyl *p*-toluenesulfonate was heated at 35 °C for 3 days. The solid was triturated with ether and filtered. Crystallization from absolute ethanol gave 1.5 g (80%) of white solid, mp 178–179 °C.

^{1}H NMR (D_2O–DSS) δ 0.93 [d, J = 6.5 Hz, 6 H, $-CH(CH_3)_2$], 1.2–2.2 [m, 2 H, C_5 H_e and $-CH(CH_3)_2$], 2.23 (s, 3 H, $-CH_3$), 2.83 [s, 6 H, $-S^+(CH_3)_2$], 3.53 (d J = 6 Hz, 2 H, $-CH_2S$), 3.8 (d, J = 2 Hz, 4 H, $C_{4,6}$ H), 4.2 (d, J = 4.5 Hz, 1 H, C_2 H_a), 7.0 and 7.47 (AB, J = 8 Hz, aromatic protons).

The tosylate was converted to the hexafluorophosphate salt as described above, mp 115–117 °C.

Dimethyl-5-(*trans*-2-isopropyl-1,3-dioxanyl)methylsulfonium *p*-Toluenesulfonate. The trans sulfonium salt was similarly obtained from the corresponding sulfide in 85% yield, mp 185–186 °C.

^{1}H NMR (D_2O–DSS) δ 0.88 [d, J = 7 Hz, 6 H, $-CH(CH_3)_2$], 1.33–2.10 [m, 2 H, C_5 H_e and $-CH(CH_3)_2$], 2.23 (s, 3 H, $-CH_3$), 2.87 [s, 6 H, $-S^+(CH_3)_2$], 3.06 (d, J = 7 Hz, 2 H, $-CH_2S$), 3.53 (t, J = 11 Hz, 2 H, $C_{4,6}$ H_a), 4.17 (d of d, J = 5, J_{gem} = 11.5 Hz, 2 H, $C_{4,6}$ H_e), 4.30 (d, J = 5 Hz, 1 H, C_2 H_a), 7.33 and 7.73 (AB, J = 8 Hz, aromatic protons).

The tosylate was converted to the hexafluorophosphate salt as described above, mp 124–125 °C.

Equilibration of the hexafluorophosphates was effected in CD_3CN by means of TFA as described for the lower homologue. Analysis was by ^{1}H NMR [integration of $(CH_3)_2S^+$ signals] and by ^{13}C NMR (integration of all resolved signals).

2-Isopropyl-5-cyanomethyl-1,3-dioxanes. A mixture of 80 g (0.25 mol) of 2-isopropyl-5-hydroxymethyl-1,3-dioxane tosylates and 18.7 g (0.38 mol) of sodium cyanide in 550 mL of Me_2SO was heated to 90 °C for 5 h under nitrogen. The reaction mixture was cooled to room temperature, diluted with 500 mL of water, and extracted with three 300-mL portions of ether. The combined extracts were washed with

water, dried over $MgSO_4$, filtered, and concentrated (rotary evaporator). Distillation of the residue gave 37.0 g (86%) of the cyanomethyl compound, bp 85–87 °C (0.1 Torr).

^{1}H NMR ($CDCl_3$) δ [d, 6 H, J = 7 Hz, $-CH(CH_3)_2$], 1.46–2.83 [m, 2 H, $-CH(CH_3)_2$, C_5 H], 2.1 (m, 2 H, $-CH_2CN$), 3.4 (apparent t, J = 11–12 Hz, 2 H, $C_{4,6}$ H_a), 3.87–4.3 (m, 3 H, C_5 H, $C_{4,6}$ H_e).

5-(2-Isopropyl-1,3-dioxanyl)acetic Acids. A mixture of 24.2 g (0.14 mol) of the above mixed nitriles and 140 g of NaOH in 600 mL of a 1:1 mixture of water and ethanol was refluxed for 12 h. The reaction mixture was cooled, added to water, and acidified with concentrated HCl. The entire suspension was then extracted with ether, dried over $MgSO_4$, filtered, and evaporated under vacuum to give 25.0 g (93%) of product, mp 65–95 °C.

^{1}H NMR ($CDCl_3$) δ 0.93 [d, J = 7 Hz, 6 H, $-CH(CH_3)_2$], 1.47–2.66 [m, 4 H, C_5 H, $-CH(CH_3)_2$, $-CH_2COOH$], 2.7–3.56 (m, 2 H, $C_{4,6}$ H_a), 3.83–4.33 (m, 3 H, C_2 H_a, $C_{4,6}$ H_e).

2-Isopropyl-5-(2-hydroxyethyl)-1,3-dioxanes. Following a procedure similar to that described for 2-isopropyl-5-hydroxymethyl-1,3-dioxane,[4] the 2-isopropyl-5-(2-hydroxyethyl)-1,3-dioxanes were obtained from the acids in 93% yield, bp 85–90 °C (0.5 Torr).

^{1}H NMR ($CDCl_3$) δ 0.90 [d, J = 7 Hz, 6 H, $-CH(CH_3)_2$], 1.0–2.4 [m, 4 H, C_5 H, $-CH(CH_3)_2$, $-CH_2-$], 3.03–4.3 (m, 8 H, $-CH_2OH$, $C_{4,6}$ H, C_2 H_a).

***cis*- and *trans*-2-Isopropyl-5-methoxymethyl-1,3-dioxane.** These compounds have been previously described.[3]

***cis*- and *trans*-2-Isopropyl-5-(2-methoxyethyl)-1,3-dioxane.** To a well-stirred solution of 2.7 g (15.5 mmol) of the above mixed 2-isopropyl-5-(2-hydroxyethyl)-1,3-dioxanes in 15 mL of dry hexamethylphosphoric triamide (HMPT) at 0 °C was added slowly a 20% excess (0.45 g) of sodium hydride. After 30 min a twofold excess (4.4 g) of methyl iodide was added and the mixture stirred for 3 h at 25 °C.[13] The excess hydride was destroyed by cautious addition of water and the mixture extracted with three 60-mL portions of ether. The combined ether extracts were washed with water, dried over Na_2SO_4, and concentrated to give 1.9 g (66%) of a crude mixture of isomers in approximately 1:1 ratio. The diastereomers were separated by gas chromatography using a 20% Carbowax 20M, 10% KOH on Chromosorb A, 60–80 mesh column at 160 °C.

^{1}H NMR ($CDCl_3$), cis isomer: δ 0.9 [d, J = 6.8 Hz, 6 H, $(CH_3)_2CH-$], 1.3–1.8 (m, 2 H, C_5 H_e and $-CHMe_2$), 1.97 (q, J = 6.5 Hz, 2 H, $-CH_2-$), 3.27 (s, 3 H, $-OCH_3$), 3.43 (t, J = 6.5 Hz, 2 H, $-CH_2O$), 3.83 (d, with a splitting of 2 Hz, 4 H, $C_{4,6}$ $H_{a,e}$), 4.23 (d, J = 4.5 Hz, 1 H, C_2 H_a).

Trans isomer: δ 0.93 [d, J = 6.8 Hz, 6 H, $(CH_3)_2CH-$], 1.27 (q, J = 6.5 Hz, 2 H, $-CH_2-$), 1.4–2.3 (m, 2 H, C_5 H_a and $-CHMe_2$), 3.27 (s, 3 H, $-OCH_3$), 3.03–3.5 (m, 4 H, $-CH_2O$ and $C_{4,6}$ H_a), 3.9–4.23 (m, i.e., d of d and d overlapped, 3 H, $C_{4,6}$ He and C_2 H_a).

Tosylates of 2-Isopropyl-5-(2-hydroxyethyl)-1,3-dioxanes. The tosylates were prepared from the mixed alcohols in 86% yield as described above for the lower homologues. The mixture solidified with difficulty after extended vacuum drying.

^{1}H NMR ($CDCl_3$) δ 0.90 [d, J = 6.5 Hz, 6 H, $-CH(CH_3)_2$], 1.1–2.3 [m, 4 H, $-CH_2-$, C_5 H, $-CH(CH_3)_2$], 2.43 (s, 3 H, $-CH_3$), 3.23 (t, 2 H, $C_{4,6}$ H_a), 3.7–4.3 (m, 5 H, $C_{4,6}$ H_e, C_2 H_a, $-CH_2OTs$), 7.26 (d, 2 H, aromatic), 7.66 (d, 2 H, aromatic).

***cis*- and *trans*-2-Isopropyl-5-(2-methylthioethyl)-1,3-dioxane.** Preparation from the above tosylate followed the earlier procedure for the 2-isopropyl-5-methylthiomethyl-1,3-dioxanes. The mixed isomers were obtained in 90% yield, bp 80–88 °C (0.15 Torr). They were separated by GLC on a 12-ft column packed with 20% Carbowax 20M/10% KOH on Chromosorb A, 60–80 mesh at 190 °C.

^{1}H NMR ($CDCl_3$), cis isomer: δ 0.92 [d, J = 7 Hz, 6 H, $-CH(CH_3)_2$], 1.4–1.95 [m, 2 H, C_5H, $-CH(CH_3)_2$], 2.06 (q, J = 7.5 Hz, 2 H, $-CH_2-$), 2.11 (s, 3 H, $-CH_3$), 2.61 (t, J = 7.5 Hz, 2 H, $-CH_2S-$), 3.9 (d, J = 2 Hz, 4 H, $C_{4,6}$ H), 4.26 (t, J = 4.5 Hz, 1 H, C_2 H_a).

Trans isomer: δ 0.91 [d, J = 7 Hz, 6 H, $-CH(CH_3)_2$], 1.32 (q, J = 7 Hz, 2 H, $-CH_2-$), 1.6–2.2 [m, 2 H, $-CH(CH_3)_2$, C_5 H], 2.09 (s, 3 H, $-SCH_3$), 2.45 (t, J = 7 Hz, 2 H, $-CH_2S-$), 3.30 (apparent t, J = 11.5 Hz, 2 H, $C_{4,6}$ H_a), 4.09 (d of d, J_{gem} = 11.0 Hz, 2 H, $C_{4,6}$ H_e), 4.15 (d, J = 4.5 Hz, 1 H, C_2 H_a).

***cis*-2-Isopropyl-5-(2-methylsulfinylethyl)-1,3-dioxane.** Oxidation of the cis sulfide as described earlier for the lower homologue proceeded in 80% yield, mp 64.5–66.0 °C after recrystallization from *n*-hexane.

^{1}H NMR ($CDCl_3$) δ 0.90 [d, J = 7 Hz, 6 H, $-CH(CH_3)_2$], 1.38–1.98 [m, 2 H, $-CH(CH_3)_2$, C_5 H], 2.18 (q, J = 8 Hz, 2 H, $-CH_2-$), 2.62 (s, 3 H, $-SOCH_3$), 2.84 (t, J = 8 Hz, 2 H, $-CH_2SO-$), 3.94 (d, J = 1.5 Hz, 4 H, $C_{4,6}$ H), 4.26 (d, J = 4.5 HZ= 1 H, C_2 H_a).

***trans*-2-Isopropyl-5-(2-methylsulfinylethyl)-1,3-dioxane.** Similar oxidation of the trans sulfide proceeded in 83% yield, mp 71.0–72.0 °C after recrystallization from *n*-hexane.

^{1}H NMR ($CDCl_3$) δ [d, J = 7 Hz, 6 H, $-CH(CH_3)_2$], 1.53 (q, J = 7.5 Hz, 2 H, $-CH_2-$), 1.65–2.4 [m, 2 H, C_5 H_a, $-CH(CH_3)_2$], 2.59 (s, 3 H, $-SOCH_3$), 2.68 (t, J = 8 Hz, 2 H, $-CH_2SO-$), 3.38 (t, J_{gem} = 11 Hz, 2 H, $C_{4,5}$ H_a), 4.04 (d, J_{gem} = 11 Hz, 2 H, $C_{4,6}$ H_e), 4.18 (d, J = 4.5 Hz, 1 H, C_2 H_a).

***cis*-2-Isopropyl-5-(2-methylsulfonylethyl)-1,3-dioxane.** The compound was prepared from the corresponding sulfide as described for the lower homologue in 79% yield, mp 98.5–100.0 °C after recrystallization from *n*-hexane.

^{1}H NMR ($CDCl_3$) δ 0.91 [d, J = 7 Hz, 6 H, $-CH(CH_3)_2$], 1.5–1.95 [m, 2 H, C_5 H, $-CH(CH_3)_2$], 2.28 (apparent q, J = 7–8 Hz, 2 H, $-CH_2-$), 2.95 (s, 3 H, $-SO_2CH_3$), 3.19 (t, J = 8 Hz, 2 H, $-CH_2S-$), 3.95 (d, J = 2 Hz, 4 H, $C_{4,6}$ H), 4.29 (d, J = 4.5 Hz, 1 H, C_2 H_a).

Anal. Calcd for $C_{10}H_{20}SO_4$: C, 50.82; H, 8.53. Found: C, 50.53; H, 8.41.

***trans*-2-Isopropyl-5-(2-methylsulfonylethyl)-1,3-dioxane.** Similar oxidation of *trans*-2-isopropyl-5-(2-methylthioethyl)-1,3-dioxane proceeded in 86% yield, mp 121.5–122.5 °C after recrystallization from *n*-hexane.

^{1}H NMR ($CDCl_3$) δ 0.90 [d, J = 7 Hz, 6 H, $-CH(CH_3)_2$], 1.45–2.2 [m, 4 H, C_5 H, $-CH(CH_3)_2$, $-CH_2SO_2-$], 2.92 (s, 3 H, $-SO_2CH_3$), 2.9–3.1 (m, 2 H, $-CH_2-$), 3.35 (t, J_{gem} = 11.5 Hz, 2 H, $C_{4,6}$ H_a), 4.11 (two d, J_{gem} = 11.5 Hz, 2 H, $C_{4,6}$ H_e), 4.17 (d, J = 4.5 Hz, 1 H, C_2 H_a).

Anal. Calcd for $C_{10}H_{20}SO_4$: C, 50.82; H, 8.53. Found: C, 50.91; H, 8.46.

Dimethyl-5-(*cis*-2-isopropyl-1,3-dioxanyl)-2-ethylsulfonium *p*-Toluenesulfonate. From 1.02 g (5 mmol) of *cis*-2-isopropyl-5-(2-methylthioethyl)-1,3-dioxane, using the procedure described earlier for the lower homologue, 1.6 g (82%) of sulfonium salt was obtained after recrystallization from ethanol–ether, mp 170–171 °C.

The tosylate was converted to the slightly impure hexafluorophosphate salt by treatment with NH_4PF_6, mp ca. 134–136 °C.

^{1}H NMR (CD_3CN) δ 0.87 [d, J = 6.5 Hz, 6 H, $-CH(CH_3)_2$], 1.3–2.3 (m, 4 H, $-CH_2-$, C_5 H_e, and $-CH(CH_3)_2$0, 2.8 [s, 6 H, $-S^+(CH_3)_2$], 3.2 (m or apparent q, J = 8 Hz, 2 H, $-CH_2S$), 3.87 (d, J = 2 Hz, 4 H, $C_{4,6}$ H), 4.26 (d, J = 4.5 Hz, 1 H, C_2 H_a).

Dimethyl-5-*trans*-2-isopropyl-1,3-dioxanyl)-2-ethylsulfonium *p*-Toluenesulfonate. This isomer was similarly obtained from the trans sulfide in 85% yield after recrystallization from ethanol–ether, mp 180.5–181 5 °C.

The hexafluorophosphate was prepared from the tosylate, mp 175–176 °C.

^{1}H NMR (CD_3CN) δ 0.85 [d, J = 6.8 Hz, 6 H, $-CH(CH_3)_2$], 1.30–2.0 [m, 4 H, $-CH_2-$, C_5 H_a, and $-CH(CH_3)_2$], 2.74 [s, 6 H, $-S^+(CH_3)_2$], 3.0–3.4 (m, 4 H, $-CH_2S$ and $C_{4,6}$ H_a), 4.0 (two d, J = 4.5, J_{gem} = 12 Hz, 2 H, $C_{4,6}$ H_e), 4.10 (d, J = 4.5 Hz, 1 H, C_2 H_a).

Equilibration of the diastereomeric sulfonium salts was brought about as described for the lower homologues; analysis was by ^{13}C NMR.

Equilibrations. Unless indicated otherwise, the compound or mixture to be equilibrated was dissolved in the appropriate solvent, the solution was placed in a thermostat, and a few beads of Amberlyst-15 (beaded polystyrenesulfonic acid) were added. After equilibrium was reached (equal composition starting from cis-rich and trans-rich mixtures) the solutions were decanted, shaken with solid potassium carbonate, filtered, and analyzed by GLC.

Sulfonium salts were equilibrated by adding a few drops of TFA to their solution in CD_3CN in an NMR tube, allowing the tube to stand, and recording the NMR spectrum at intervals. Equilibrium was deemed to be reached when the signal ratio of the diastereomers became constant.

Acknowledgments. This work was supported under NSF Grant 35669X. We are indebted to Dr. David Harris for recording the ^{13}C and some of the ^{1}H NMR spectra.

Registry No.—*cis*-5-(2-Isopropyl-1,3-dioxanyl)methyl *p*-toluenesulfonate, 61523-20-4; *trans*-5-(2-isopropyl-1,3-dioxanyl)methyl *p*-toluenesulfonate, 61523-21-5; *cis*-5-(2-isopropyl-1,3-dioxanyl) methanol, 28808-24-4; *trans*-5-(2-isopropyl-1,3-dioxanyl)methanol, 35113-53-2; tosyl chloride, 98-59-9; CH_3SK, 26385-24-0; dimethyl-5-(*cis*-2-isopropyl-1,3-dioxanyl)methylsulfonium *p*-toluenesulfonate, 61523-22-6; dimethyl-5-(*trans*-2-isopropyl-1,3-dioxanyl)-methylsulfonium *p*-toluenesulfonate, 61523-23-7; methyl *p*-toluenesulfonate, 80-48-8; *cis*-2-isopropyl-5-cyanomethyl-1,3-dioxane, 61523-24-8; *trans*-2-isopropyl-5-cyanomethyl-1,3-dioxane, 61523-

25-9; *cis*-5-(2-isopropyl-1,3-dioxanyl)acetic acid, 61523-26-0; *trans*-5-(2-isopropyl-1,3-dioxanyl)acetic acid, 61523-27-1; *cis*-2-isopropyl-5-(2-hydroxyethyl)-1,3-dioxane, 61523-28-2; *trans*-2-isopropyl-5-(2-hydroxyethyl)-1,3-dioxane, 61523-29-3; *cis*-2-isopropyl-5-(2-hydroxyethyl)-1,3-dioxane tosylate, 61523-30-6; *trans*-2-isopropyl-5-(2-hydroxyethyl)-1,3-dioxane tosylate, 61523-31-7; dimethyl-5-(*cis*-2-isopropyl-1,3-dioxanyl)-2-ethylsulfonium *p*-toluenesulfonate, 61523-32-8; dimethyl-5-(*trans*-2-isopropyl-1,3-dioxanyl)-2-ethylsulfonium *p*-toluenesulfonate, 61523-33-9; *cis*-2-isopropyl-5-methoxy-1,3-dioxane, 28808-16-4; *trans*-2-isopropyl-5-methoxy-1,3-dioxane, 36094-12-9; *cis*-2-isopropyl-5-(methoxymethyl)-1,3-dioxane, 28808-25-5; *trans*-2-isopropyl-5-(methoxymethyl)-1,3-dioxane, 58619-95-7; *cis*-2-isopropyl-5-(methylsulfinyl)-1,3-dioxane, 40245-31-6; *trans*-2-isopropyl-5-(methylsulfinyl)-1,3-dioxane, 40245-32-7; *cis*-2-isopropyl-5-(methylsulfonyl)-1,3-dioxane, 40245-33-8; *trans*-2-isopropyl-5-(methylsulfonyl)-1,3-dioxane, 40245-34-9; dimethyl-5-(*cis*-2-isopropyl-1,3-dioxanyl)sulfonium *p*-toluenesulfonate, 58620-17-0; dimethyl-5-(*trans*-2-isopropyl-1,3-dioxanyl)sulfonium *p*-toluenesulfonate, 58620-19-2.

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Ion Radicals. 38. Reactions of Phenoxathiin and Thianthrene Cation Radicals with Alkyl- and Dialkylamines[1,2]

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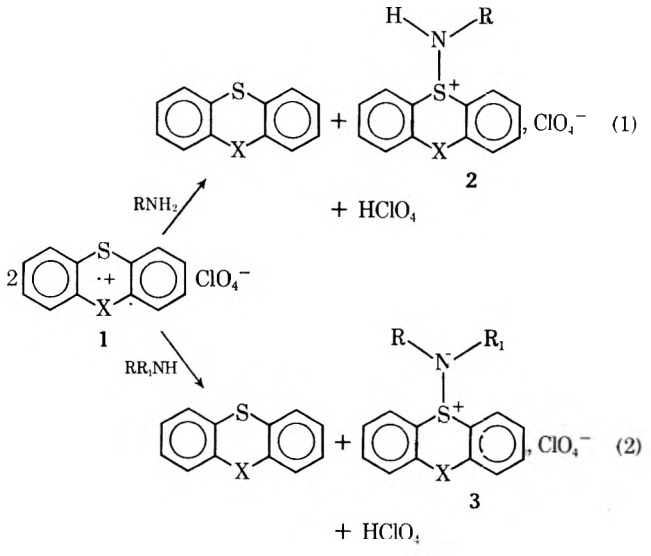
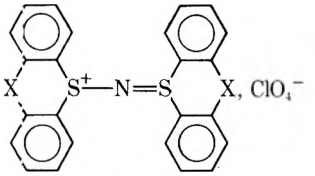
Phenoxathiin cation radical perchlorate (**1c**) reacted with alkylamines to form protonated *N*-alkylsulfilimine perchlorates (**2c**) and with dialkylamines to form *N,N*-dialkylaminosulfonium perchlorates (**3c**). Analogous reactions were obtained with thianthrene cation radical (**1d**), giving products **2d** and **3d**. Reaction of **1d** with alkylamines also gave in every case some 5,5-dihydro-5-(5-thianthreniumylimino)thianthrene perchlorate (**4d**). Only in one case, reaction with propylamine, did **1c** give the analogous **4c**. The salts **2c** were deprotonated to give the *N*-alkylsulfilimines (**5c** and **5d**) and these were methylated with methyl iodide giving *N*-alkyl-*N*-methylaminosulfonium iodides (**6c** and **6d**). Most of the sulfonium salts (**6c** and **6d**) were converted into the corresponding perchlorates (**3c** and **3d**) which were also obtained directly by reactions of **1c** and **1d** with *N*-alkylmethylamines.

It was shown recently that the cation radical perchlorates of 10-methyl-(**1a**, X = *N*-Me) and 10-phenylphenothiazine (**1b**, X = *N*-C_6H_5) react with alkyl- and dialkylamines according to eq 1 and 2.[5] We have found, subsequently, that



phenoxathiin cation radical perchlorate (**1c**, X = O) undergoes analogous reactions. Further, it was reported by Kim and Shine[6] that thianthrene cation radical perchlorate (**1d**, X = S) did not react with alkylamines according to eq 1 except in the case of *tert*-butylamine. That is, reaction of **1d** with ethyl-, propyl-, and cyclohexylamine was reported to give the dimeric product (**4d**, X = S) instead of products **2d** (R = Et, Pr, C_6H_{11}). We have found now that this report is not correct.



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4c. X = O; **4d**. X = S

Reaction of alkylamines with **1d** (eq 1) is not as facile as with the analogues **1a–c**, but it does give the sulfilimine salts **2d** (X = S) although in poor yields. At the same time the dimer byproduct **4d** is formed but not exclusively as was reported earlier.[6]

Separation of products **2d** from the other products of reaction is tedious and apparently was not achieved earlier. Thus, the reactions of eq 1 and 2 are general for the series X = S, O, *N*-Me, *N*-C_6H_5, but yields vary from case to case. Data for reactions of **1c** and **1d** are given in Tables I and II. These data show that the dimer **4d** was obtained from all reactions of **1d** with alkylamines, whereas the dimer **4c** was obtained only in reaction of **1c** with propylamine. Small amounts of phenoxathiin 5-oxide and thianthrene 5-oxide were also obtained presumably from reaction of the cation radicals with water in the reagents or solvents.[7]

Deprotonation of the products **2c** and **2d** was carried out

Table I. Products of Reaction of Phenoxathiin Cation Radical Perchlorate (1c) and Thianthrene Cation Radical Perchlorate (1d) with Alkylamines in Acetonitrile

Cation radical	R in RNH_2	Registry no.	% 2[a]	Parent[b] %[c]	5-Oxide[b] %[c]	% 4[d]	Mp, °C 2
1c	Pr	107-10-8	41	47	1	6	Oil
1c	*t*-Bu	75-64-9	46	44	7		203–204
1c	C_6H_{11}	108-91-8	35	54	8		148–149
1c	$C_6H_5CH_2$	100-46-9	20	63	10		145–146
1d	Me	74-89-5	15	66	3	8	120–122
1d	Et	75-04-7	20	61	4	14	117–118
1d	Pr		21	60	5	5	Oil
1d	C_6H_{11}		19	62	6	3	Oil
1d	$C_6H_5CH_2$		18	65		8	143–144

[a] % yield means the amount of cation radical converted into product. The maximum yield of 2 is 50% (eq 1). [b] Phenoxathiin from 1c, thianthrene from 1d. [c] Equal amounts of parent and 5-oxide are obtained from the reaction of a cation radical with water. [d] % yield means the amount of cation radical converted into 4.

Table II. Products of Reaction of Phenoxathiin Cation Radical Perchlorate (1c) and Thianthrene Cation Radical Perchlorate (1d) with Dialkylamines in Acetonitrile

Cation radical	R	R_1	Registry no.	% 3[a]	Parent[b] %[c]	5-Oxide[b] %[c]	Mp, °C 3
1c	Me	Me	124-40-3	7	73	8	151–152
1c	*i*-Pr	*i*-Pr	108-18-9	13	63	8	180–181
1c	Pr	Me	627-35-0	8	65	8	139–140
1c	C_6H_{11}	Me	100-60-7	11	62	8	200–201
1c	$C_6H_5CH_2$	Me	103-67-3	17	70	8	173–174
1c	$C_6H_5CH_2$	$C_6H_5CH_2$	103-49-1	27	61	11	145–146
1d	Pr	Me		22	70	10	129–131
1d	C_6H_{11}	Me		20	68	5	172–174
1d	$C_6H_5CH_2$	Me		32	67	6	154–156

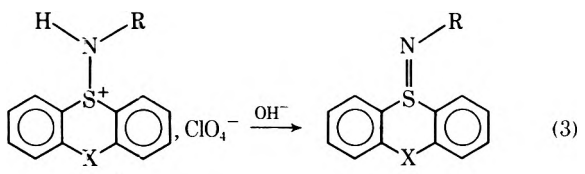
[a] % yield means the amount of cation radical converted into product. The maximum yield of 3 is 50% (eq 1). [b] Phenoxathiin from 1c, thianthrene from 1d. [c] Equal amounts of parent and 5-oxide are obtained from the reaction of a cation radical with water.[7]

Table III. List of Sulfilimines (5) Obtained by Deprotonation of Sulfonium Perchlorates (2), Their Adducts (6) with Methyl Iodide, and the Perchlorates (3) Obtained from 6 by Exchange with $AgClO_4$

Sulfilimine	R in 5	% yield of 5	Mp, °C of 5	% yield of 6	Mp, °C of 6	% yield of 3	Mp, °C of 3[a]
5c	Pr	87	Oil	97	132–133	86	138–139
5c	*t*-Bu	95	74–75	84	168–169	80	183–184
5c	C_6H_{11}	100	172–173	93	142–143	90	201–203
5c	$C_6H_5CH_2$	100	143–144	100	72–75	87	172–173
5d	Me	95	44–46	93	110–112	93	139–141[b]
5d	Pr	96	Oil	87	107–109	94	128–130
5d	C_6H_{11}	98	119–120	84	122–124	98	170–172
5d	$C_6H_5CH_2$	97	Oil	56	130–132	95	154–156

[a] Cf. melting points of 3c and 3d obtained directly, Table II. [b] Product by direct reaction, mp 139–140 °C.[6]

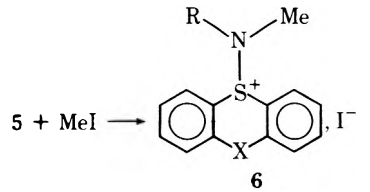
in most cases, leading to the free sulfilimines 5c and 5d (eq 3). Data for these reactions are given in Table III. Methylation



2 5

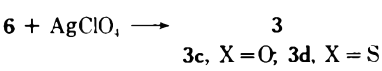
5c, X = O; 5d, X = S (3)

of the sulfilimines with methyl iodide in dry ether gave the *N*-methylsulfonium iodides 6c and 6d (eq 4) in good yields, and conversion of the iodides to perchlorates was carried out (eq 5) in all cases. Thus, the compounds 3c and 3d (R_1 = Me)



6

6c, X = O; 6d, X = S (4)



3c, X = O; 3d, X = S (5)

were obtained both directly (eq 2) and indirectly (eq 5). Data for reactions 4 and 5 are also given in Table III.

The way in which the dimeric products 4c and 4d are formed in reactions of 1c with propylamine and 1d with all of the alkylamines is not known. Attempts to obtain 4d by re-

Table IV. Absorption and NMR Spectra of Products: Sulfilimines (5), Protonated Sulfilimines (2) and Dialkylsulfonium Perchlorates (3), and Dialkylsulfonium Iodides (6)

Compd	R	R_1	λ_{max}, nm (10^{-4} ϵ)[a]	^{1}H NMR, δ (J, Hz)	Solvent
2c	Pr			8.17 (d of d, J = 7, J = unres, 2 H)[b] 8.03–7.50 (m, 6 H, arom), 6.30 (s, 1 H, –NH), 2.47 (t, 2 H, $-CH_2CH_2CH_3$), 1.33 (m, 2 H, $-CH_2CH_2CH_3$), 0.67 (t, 3 H, Me)	$CDCl_3$
2c	$C_6H_5CH_2$		234 (2.44), 299 (0.52)	7.95 (d of d, J = 8, J = unres, 2 H),[b] 7.82–7.46 (m, 6 H, arom), 7.2–7.04 (m, 5 H, $C_6H_5CH_2$), 3.68 (s, 2 H, $C_6H_5CH_2$)	$(CD_3)_2C{=}O$
2c	*t*-Bu		235 (3.47), 302 (0.50)	8.02 (d of d, J = 8.5, J = 2, 2 H),[b] 7.80 (m, J = 8.5, J = 7, J = 2, 2 H)[c] 7.43 (m, 4 H, arom), 1.20 (s, 9 H, *t*-Bu)	$(CD_3)_2C{=}O$
2c	C_6H_{11}		231 (1.72), 302 (0.48)	8.17 (d, J = 8, 2 H),[b] 7.94 (m, 2 H),[c] 7.64 (m, 4 H, arom), 1.70–0.9 (m, 10 H, C_6H_{11})	$(CD_3)_2S{=}O$
2d	Me		221 (2.30), 253 (1.19), 294 (0.81), 328 (0.43)	8.22 (d of d, $J \simeq 7$, 2 H),[b] 7.89–7.57 (m, 6 H, arom), 6.24 (bd s, 1 H, removed with D_2O, –NH), 2.57 (d, becomes s with D_2O, 3 H, Me)	$CDCl_3$
2d	Et		222 (2.02), 252 (1.21), 293 (0.90), 326 (0.38)	8.19 (d of d, $J \simeq 7$, $J \simeq 2$, 2 H),[b] 7.93–7.57 (m, 6 H, arom), 2.96 (q, J = 7.5, 2 H, $-CH_2-$) 1.02 (t, J = 7.5, 3 H, Me)	CD_3CN
2d	Pr			8.25 (d, 2 H),[b] 7.98–7.60 (m, 6 H, arom), 6.07 (s, 1 H, removed with D_2O, –NH), 2.84 (q, becomes t with D_2O, J = 6, 2 H, $-CH_2-$), 1.44 (sext, 2 H, $-CH_2-$), 0.73 (t, J = 7, 3 H, Me)	$CDCl_3$
2d	C_6H_{11}			8.27 (m, 2 H),[b] 7.72 (m, 6 H, arom), 4.73 (bd s, 1 H, removed with D_2O –NH), 3.20 (bd s, 1 H, α-C_6H_{11}), 1.88–0.96 (bd m, 10 H, C_6H_{11})	$CDCl_3$
2d	$C_6H_5CH_2$			8.16 (d of d, 2 H),[b] 7.70–7.52 (m, 6 H, arom), 7.20–7.02 (m, 5 H, C_6H_5), 4.10 (s, 2 H, $-CH_2-$)	$CDCl_3$
3c	Me	Me	239 (1.26), 279 (0.43), 304 (0.68)	8.29 (d of d, J = 8, J = unres, 2 H),[b] 8.05 (m, 2 H, arom),[c] 7.76 (m, 4 H, arom), 2.02 (s, 3 H, Me)	CD_3CN
3c	Pr	Me	238sh (1.41), 278 (0.44), 304 (0.68)	8.08 (d of d, 2 H),[b] 7.90–7.50 (m, 6 H, arom), 3.12 (t, 2 H, $-CH_2CH_2CH_3$), 2.52 (s, 3 H, –NMe), 1.53 (m, 2 H, $-CH_2CH_2CH_3$), 0.80 (t, 3 H, Me)	$(CD_3)_2C{=}O$
3c	C_6H_{11}	Me	238 (1.90), 279 (0.41), 304 (0.57)	8.33 (d of d, J = 8, J = unres, 2 H),[b] 8.05 (m, 2 H, arom),[c] 7.95–7.61 (m, 4 H, arom), remaining peaks overlapped with solvent impurity $(CH_3)_2S{=}O$	$(CD_3)_2S{=}O$
3c	$C_6H_5CH_2$	Me	239sh (1.95), 306 (0.63)	8.32 (d of d, J = 8.5, J = 2, 2 H),[b] 8.1 (m, 2 H, arom),[c] 7.75 (m, 4 H, arom), 7.42 (m, 5 H, C_6H_5), 4.56 (s, 2 H, $-CH_2-$), 2.57 (s, 3 H, Me)	$(CD_3)_2C{=}O$
3c	*i*-Pr	*i*-Pr	238sh (1.41), 275 (0.48), 303 (0.69)	8.18 (d of d, J = 8, J = 2, 2 H),[b] 8.01 (m, 2 H, arom),[c] 7.74 (m, 4 H, arom), 3.67 (hept, J = 7, 2 H, –CH–), 1.27 (d, J = 7, 12 H, Me)	$(CD_3)_2C{=}O$
3c	$C_6H_5CH_2$	$C_6H_5CH_2$	239 (2.02), 309 (0.68)	8.04 (d of d, J = 8, J = 2, 2 H),[b] 7.92 (d of d, J = 8, J = 2, 2 H, arom),[c] 7.65 (t, J = 8, 4 H, arom), 7.40–7.06 (m, 10 H, C_6H_5), 4.23 (s, 4 H, $-CH_2-$)	$(CD_3)_2S{=}O$
3d	Me	Me	222 (2.81), 255 (0.97), 298 (0.78), 330 (0.45)	8.34 (m, 2 H),[b] 7.80 (m, 6 H, arom), 2.83 (s, 6 H, Me)	$CDCl_3$
3d	Pr	Me	226 (2.74), 256 (1.32), 298 (0.85), 335 (0.43)	8.27 (d of d, J = 8, J = unres, 2 H),[b] 7.80 (s, 6 H, arom), 3.24 (t, J = 8, 2 H, $-CH_2-$), 2.65 (s, 3 H, –NMe), 1.57 (sext, 2 H, $-CH_2-$), 0.84 (t, J = 8, 3 H, Me)	$CDCl_3$
3d	C_6H_{11}	Me	225 (2.64), 258 (1.23), 296 (0.83), 334 (0.42)	8.36 (m, 2 H),[b] 7.75 (m, 6 H, arom), 2.60 (s, 3 H, Me), 2.0–1.0 (bd m, 10 H, C_6H_{11})[d]	$CDCl_3$
3d	$C_6H_5CH_2$	Me	225 (3.61), 257 (1.35), 298 (0.90), 329 (0.64)	8.15 (d of d, J = 7, J = unres, 2 H),[b] 7.87 (s, 6 H, arom), 7.51–7.27 (m, 5 H, C_6H_5), 3.33 (s, 2 H, $-CH_2-$) 2.55 (s, 3 H, Me)	$CDCl_3$–CD_3CN
5c	*t*-Bu		236 sh (1.52), 277 (0.39), 297 (0.39)	7.84 (d of d, J = 7, j, 2, 2 H),[b] 7.5–7.12 (m, 6 H, arom), 0.98 (s, 9 H, *t*-Bu)	$CDCl_3$
5c	C_6H_{11}		237 sh (1.61), 274 (0.36), 298 (0.37)	7.86 (d of d, J = 8, 2 H),[b] 7.66–7.20 (m, 6 H, arom), 1.70–0.70 (m, 11 H, C_6H_{11})	$CDCl_3$
5c	$C_6H_5CH_2$		239 sh (1.68), 276 (0.46), 294 (0.49)	7.83 (d of d, 2 H),[b] 7.68–7.04 (m, 11 H, arom), 3.46 (s, 2 H, $-CH_2-$)	$CDCl_3$
5d	Me		216 (2.64), 259 (1.93), 285 sh (1.62), 325 sh (0.36)	7.90 (d of d, $J \simeq 6$, $J \simeq 2$, 2 H),[b] 7.66–7.25 (m, 6 H, arom), 2.78 (s, 3 H, Me)	$CDCl_3$
5d	Pr			7.95 (d of d, J = 7, J = 2 H),[b] 7.59–7.33 (m, 6 H, arom), 2.98 (t, J = 7.5, 2 H, $-CH_2-$), 1.70 (sext, J = 7.5, 2 H, $-CH_2-$), 0.95 (t, J = 7.5, 3 H, Me)	$CDCl_3$
5d	C_6H_{11}		242 (1.38), 285 (0.43), 333 (0.08)	8.07 (d, J = 8, 2 H),[b] 7.66–7.32 (m, 6 H, arom), 3.05 (bd s, 1 H, α-C_6H_{11}), 3.04–1.0 (bd m, 10 H, C_6H_{11})	$CDCl_3$
5d	$C_6H_5CH_2$			7.90 (d of d, 2 H),[b] 7.69–7.17 (m, 11 H, arom), 4.23 (s, 2 H, $-CH_2-$)	$CDCl_3$

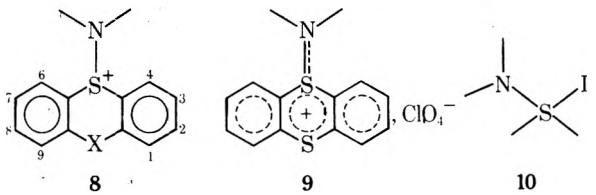
Table IV (*Continued*)

Compd	R	R_1	λ_{max}, nm (10^{-4} ϵ)[a]	^{1}H NMR, δ (J, Hz)	Solvent
6d	Me	Me		8.67 (m, 2 H),[b] 7.82 (s, 6 H, arom), 2.90 (s, 3 H, Me)	$CDCl_3$
6d	Pr	Me	225 (3.50), 244 (2.77), 298 (0.98), 334 (0.53)	8.53 (d of d, J = 8, J = unres, 2 H),[b] 7.95–7.71 (m, 6 H, arom), 3.31 (t, 2 H, $-CH_2-$), 2.71 (s, 3 H, -NMe), 1.59 (sext, J = 7, $-CH_2-$), 0.85 (t, J = 7, Me)	$CDCl_3$
6d	C_6H_{11}	Me	223 (2.87), 242 (2.27), 296 (0.80), 332 (0.41)	8.61 (d of d, J = 8, J = unres, 2 H),[b] 7.78 (s, 6 H, arom), 4.0 (bd s, 1 H, α-C_6H_{11}), 2.63 (s, 3 H, -NMe), 2.06–1.06 (bd m, 10 H C_6H_{11})	$CDCl_3$

[a] Solvent CH_3CN in all cases. [b] This assignment is to the two protons in the 4,6 positions (S is at position 5 of the ring). Each proton undergoes coupling with its ortho and meta protons. In some cases the coupling pattern was well resolved, while in others resolution was poor. [c] This assignment is to the two protons in the 3,7 positions. Each proton undergoes coupling with two ortho protons and one meta proton. [d] The α-H could not be detected.

action of **1d** with one of the protonated sulfilimine perchlorates (**2d**, R = Pr) were not successful. However, some of **4d** (3%) was obtained by reaction of the free sulfilimine **5d** (R = Me) with **1d** in acetonitrile. In this reaction the solid **1d** was added in small portions to a stirred solution of the sulfilimine, and initially the purple color of **1d** disappeared rapidly with each addition, but long before 1 equiv of **1d** was added the color of the cation radical persisted. That is, reaction between **1d** and **5d** ceased after a while. The **1d** which persisted in solution was destroyed by adding water. A recovery of 70% of the **5d** in the protonated form (i.e., **2d**, R = Me) was obtained. The amounts of thianthrene (82%) and its 5-oxide (31%) obtained indicate that some of the **5d** was also converted into thianthrene and/or its 5-oxide. The origin of **4d** in reactions of cation radicals with alkylamines may thus be from reactions of the free sulfilimines with cation radical. Although the protonated sulfilimine and perchloric acid are formed in reaction of **1d** with an alkylamine (eq 1), there is always an excess of alkylamine present, so that free sulfilimine (although a strong base) is likely to be present. However, why **1d** is converted into **4d** more easily than **1c** into **4c** (and than **1a,b** into **4a,b**),[5] and what may be the fate of the alkyl group (R), are in any event still unknown.

Given in Table IV are the ^{1}H NMR data for most of the products **2, 3, 5,** and **6.** In every case the most downfield signals are assignable to the two protons in the 4,6 positions (8). In



8 **9** **10**

a number of cases, particularly of phenoxathiin derivatives (X = O), the spectra were well enough resolved to give the doublet of doublets for these equivalent protons, with J values of about 8 and 2 Hz. These doublets centered at δ values of 8.16–8.28 for compounds **2,** 8.04–8.36 for compounds **3,** and 7.83–8.07 for the unprotonated compounds **5,** illustrating the deshielding effect of the formal positive charge in compounds **2** and **3.** Some variation due to the use of different solvents may have been experienced, but it is not marked. The same pattern for the 4,6 protons is seen in phenoxathiin 5-oxide (δ 7.89, J = 8 and 2 Hz) and thianthrene 5-oxide (δ 7.96) in $CDCl_3$. Thus, the deshielding effect of the S=NR group is about as great as that of the S=O group. The high value of δ 8.07 for **5d** (R = C_6H_{11}) is unusual and is not seen in the corresponding **5c** (δ 7.86).

The very interesting effect of the anion in compounds **3d** and **6d** is seen. That is, for **3d** (R = Me, Pr, C_6H_{11}) δ values for $H_{4,6}$ are 8.34, 8.27, and 8.36, respectively. The corresponding values for **6d** are 8.67, 8.53, and 8.61, resulting in downfield shifts of 0.33, 0.26, and 0.25 δ, respectively, by changing the anion from ClO_4^- to I^-. Downfield shifts of the N-methyl group in each of these compounds amounted to 0.07, 0.06, and 0.03 δ when changing from ClO_4^- to I^-, and a similar shift of 0.07 δ is seen in the α-CH_2 of the propyl groups. The data suggest that in the compounds **3** the ClO_4^- ion is separated from the charge-delocalized cation as in **9,** while in compounds **6** the iodide ion may, in fact, be well attached to sulfur (**10**) and through its inductive effect cause even greater deshielding of nearby protons.

Experimental Section

Phenoxathiin[8] and thianthrene[7a] cation radical perchlorates (**1c** and **1d**) were prepared as described earlier. The potential hazard of explosiveness of these compounds should be noted.[9] Reactions of **1c** and **1d** with amines were carried out in Eastman anhydrous grade (<0.05% water) CH_3CN stored over molecular sieve in septum-capped bottles. Solvents used for column chromatography were dry, reagent grade. The column material was E. Merck silica gel 60, ASTM 30–70 mesh. The several types of reactions are illustrated with examples and all results are tabulated in Tables I–IV. Elemental analyses were obtained on a number of products, while some were characterized by parent peak mass spectrum. Analytical data are given in Table V. All compounds were characterized by ^{1}H NMR (Table IV). Ultraviolet spectra data for most of the compounds are also given in Table IV. A Varian XL-100 NMR spectrometer and a Beckman DK-2A spectrophotometer were used.

Reaction of 1c with *tert*-Butylamine. To a stirred solution of 532 mg (1.78 mmol) of **1c** in 30 mL of CH_3CN was added 0.5 mL (~4.75 mmol) of *tert*-butylamine. The purple solution became pale yellow immediately. After 15 min the solvent was removed in a rotary evaporator, and the residue was washed well with water, dissolved in dry acetone, and dried over K_2CO_3. The acetone solution was concentrated and placed on a silica gel column. Elution with petroleum ether (bp 30–60 °C) gave 156 mg (0.78 mmol, 44%) of phenoxathiin. Elution with ether gave 26 mg (0.118 mmol, 6%) of phenoxathiin 5-oxide, and elution with acetone gave 303 mg (0.81 mmol, 46%) of **2c** (R = *t*-Bu), mp 203–204 °C (from aqueous methanol), infrared (Nujol) ClO_4^- band at 9.1–9.3 μ.

Reaction of 1d with Methylamine. Methylamine was bubbled into a solution of 601 mg (1.93 mmol) of **1d** in 50 mL of CH_3CN causing very rapid disappearance of the purple color of the cation radical. The solution was worked up as above. Elution with benzene gave 275 mg (1.27 mmol, 66%) of thianthrene. Elution with ether gave 12 mg (0.05 mmol, 2.6%) of thianthrene 5-oxide, and elution with acetone gave a mixture of **2d** (R = Me) and **4d.** These were separated with ethanol, in which **4d** is sparingly soluble, giving 43 mg (0.079 mmol, 8.2%) of **4d** and 100 mg (0.289 mmol, 15%) of **2d,** mp 120–122 °C (from CH_2Cl_2–ether).

Deprotonation of 2c. Formation of 5c (R = t-Bu). A mixture of

Table V. Analytical Results[a,b]

Compd	R	R_1	Formula	C	H	N	S	Cl
2c	*t*-Bu		$C_{16}H_{18}NSClO_5$	51.7	4.88	3.77	8.63	9.54
			Found	51.4	4.72	4.02	9.20	9.87
2d	Me		$C_{13}H_{12}NS_2ClO_4$	45.2	3.49	4.05	18.5	10.3
			Found	44.8	3.49	4.06	18.8	10.6
2d	Et		$C_{14}H_{14}NS_2ClO_4$	46.7	3.92	3.89	17.8	9.85
			Found	46.6	4.22	4.03	17.9	10.6
2d	$C_6H_5CH_2$		$C_{19}H_{16}NS_2ClO_4$	54.1	3.82	3.31	15.2	8.40
			Found	54.4	3.98	3.50	15.4	8.56
3c	*t*-Bu	Me	$C_{17}H_{20}NSClO_5$	52.9	5.22	3.63	8.31	9.21
			Found	52.8	5.38	3.50	8.25	
3c	Pr	Me	$C_{16}H_{18}NSClO_5$	51.7	4.88	3.92	8.95	9.54
			Found	51.6	4.84			9.53
3c	C_6H_{11}	Me	$C_{19}H_{22}NSClO_5$	55 4	5.38	3.40	7.78	8.63
			Found	55.4	5.40	3.63	7.79	
3c	$C_6H_5CH_2$	$C_6H_5CH_2$	$C_{26}H_{22}NSClO_5$	62 9	4.47	2.82	6.46	7.15
			Found	63 6	4.41	3.11	6.27	7.73
3d	Pr	Me	$C_{16}H_{18}NS_2ClO_4$	49 6	4.67	3.61	16.5	9.13
			Found	49 9	4.74	3.46	16.6	
3d	C_6H_{11}	Me	$C_{19}H_{22}NS_2ClO_4$	53 3	5.18	3.27	15.0	8.28
			Found	53 9	5.48	3.75	14.9	8.45
3d	$C_6H_5CH_2$	Me	$C_{20}H_{18}NS_2ClO_4$	55.1	4.16	3.21	14.7	8.13
			Found	55.1	4.51	3.46	14.8	8.20
5c	C_6H_{11}		$C_{18}H_{19}NSO$	72.7	6.44	4.71	10.8	
			Found	72.5	6.49	4.89	10.7	

[a] Schwarzkopf Laboratories, Woodside, N.Y. [b] Most of the sulfilimines were characterized by mass matching of the parent peak. For **5c**, R = *t*-Bu, 271.06 (calcd, 271.103); R = Pr, 257.075 (calcd, 257.085); R = $C_6H_5CH_2$, 305.078 (calcd, 305.087). For **5d**, R = Me, 245.035 (calcd, 245.034); R = C_6H_{11}, 313.096 (calcd, 313.096); R = $C_6H_5CH_2$, 321.066 (calcd, 321.065).

502 mg (1.35 mmol) of **2c** (R = *t*-Bu) in 15 mL of ethanol and 2 mL of 20% NaOH was stirred for 2 h, and concentrated to give a white solid. This was filtered, washed with water, and dried to give 346 mg (1.28 mmol, 95%) of **5c** (R = *t*-Bu), mp 74–75 °C (from aqueous ethanol).

Deprotonation of 2d. Formation of 5d (R = Me). After being stirred for 30 min a solution of 500 mg (1.45 mmol) of **2d** (R = Me) in 50 mL of ethanol and 2 mL of NaOH was poured into 300 mL of water. Extraction with ether gave 335 mg (1.37 mmol, 95%) of **5d** (R = Me), mp 44–46 °C (from ether–petroleum ether).

Methylation of 5c. Formation of 6c (R = *t*-Bu). To a suspension of 346 mg of **5c** (R = *t*-Bu) in 25 mL of dry ether was added 1 mL of CH_3I. The **5c** dissolved immediately, and after stirring for 1 h the solution began depositing white crystals. Filtration after 2 h gave 443 mg (1.07 mmol, 84%) of **6c** (R = *t*-Bu), mp 168–169 °C (from $CHCl_3$–ether).

Conversion of 6c into 3c (R = *t*-Bu; R_1 = Me). Reaction with $AgClO_4$. To a stirred solution of 103 mg (0.25 mmol) of **6c** (R = *t*-Bu) in 10 mL of acetone was added an excess of $AgClO_4$. After 15 min the precipitate of AgI was filtered through Celite filter aid. Concentration of the filtrate gave 77 mg (0.20 mmol, 80%) of **3c** (R = *t*-Bu; R_1 = Me), mp 183–184 °C dec (from ethanol).

Reaction of 1c with *N*-Methylbenzylamine. Formation of 3c (R = Benzyl; R_1 = Me). To a stirred solution of 1.11 g (3.7 mmol) of **1c** in 40 mL of CH_3CN was added 0.5 mL (≃4.10 mmol) of *N*-methylbenzylamine. Workup gave 516 mg (2.58 mmol, 70%) of phenoxathiin, 63 mg (0.29 mmol, 8%) of phenoxathiin 5-oxide, and 260 mg of **3c** (R = benzyl; R_1 = Me), mp 173–174 °C dec (from acetone–ether).

Reaction of 1d with 5d (R = Me). Formation of 4d. To a solution of 200 mg (0.816 mmol) of **5d** (R = Me) in 5 mL of CH_3CN was added 258 mg (0.816 mmol) of **1d** in small portions. The first few portions added disappeared very quickly (color), but the rate of disappearance slowed up and eventually stopped well before all of the **1d** was added. After 1 h the unreacted **1d** was destroyed by adding water, and the solution was worked up in the usual way, giving 145 mg (0.67 mmol, 82% based on **1d**) of thianthrene, 58 mg (0.25 mmol, 31%) of thianthrene 5-oxide, 12 mg (0.022 mmol, 2.7%) of **4d**, and 198 mg (0.57 mmol, 70%) of **2d**. It is noticeable that the conversion of **1d** into thianthrene and thianthrene 5-oxide totals 111%, indicating that some of the **5d** was probably converted into one or both of these compounds. In separate reactions it was found that **2d** (R = Pr) did not react with **1d**.

Registry No.—**1c**, 55975-63-8; **1d**, 35787-71-4; **2c** (R = Pr), 61558-38-1; **2c** (R = *t*-Bu), 61558-40-5; **2c** (R = C_6H_{11}), 61558-42-7; **2c** (R = $C_6H_5CH_2$), 61558-44-9; **2d** (R = Me), 61558-46-1; **2d** (R = Et), 61558-48-3; **2d** (R = Pr), 61558-50-7; **2d** (R = C_6H_{11}), 61558-52-9; **2d** (R = $C_6H_5CH_2$), 61558-54-1; **3c** (R = Me; R_1 = Me), 61558-56-3; **3c** (R = R_1 = Pr), 61558-58-5; **3c** (R = Pr; R_1 = Me), 61558-60-9; **3c** (R = C_6H_{11}; R_1 = Me), 61558-62-1; **3c** (R = $PhCH_2$; R_1Me), 61558-64-3; **3c** (R = R_1 = CH_2Ph), 61558-68-7; **3c** (R = *t*-Bu; R_1 = Me), 61558-66-5; **3d** (R = Rr; R_1 = Me), 61558-70-1; **3d** (R = C_6H_{11}; R_1 = Me), 60896-37-9; **3d** (R = $PhCH_2$; R_1 = Me), 61558-72-3; **5c** (R = Pr), 61558-73-4; **5c** (R = *t*-Bu), 61558-74-5; **5c** (R = C_6H_{11}), 61558-75-6; **5c** (R = $PhCH_2$), 61558-76-7; **5d** (R = Me), 61558-77-8; **5d** (R = Pr), 61558-78-9; **5d** (R = C_6H_{11}), 61558-79-0; **5d** (R = $PhCH_2$), 61558-80-3; **6c** (R = Pr), 61558-81-4; **6c** (R = *t*-Bu), 61558-82-5; **6c** (R = C_6H_{11}), 61558-83-6; **6c** (R = $PhCH_2$), 61558-84-7; **6d** (R = Me), 61558-85-8; **6d** (R = Pr), 61558-86-9; **6d** (R = C_6H_{11}), 61558-87-0; **6d** (R = $PhCH_2$), 61558-88-1.

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Reaction of 1,3-Dithiolium Cation with Xanthate and Dithiocarbamate Anions[1]

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The reactivity of 4-aryl-1,3-dithiolium cation (**1**) toward sulfur nucleophiles was investigated. The initial adduct obtained from reaction of **1** with ethyl xanthate (**2**) was found to react further with **2** in an appropriate solvent. Dithiocarbamate anion (**3**) reacted with **1** to give the 1,3-dithiol-2-yl ester derivative (**8**), which is unstable in solution even at room temperature and undergoes thermal decomposition into the 2-disubstituted amino-1,3-dithiole derivative (**10**) with loss of carbon disulfide. Except for the acyl ester (mixed carboxylic dithiocarbamic anhydride), ester **8** is the first example for which the decomposition mechanism has been elucidated. The facile decomposition is due to the existence of concurrent product-catalyzed decomposition. The presence of an electron-donating group at the para position of the 4-phenyl of **8** enhances decomposition, which is accelerated ninefold in EtOH compared with the rate in CH_3CN. Activation parameters for the first-order decomposition of **8m** in EtOH and MeCN are $\Delta H^{\ddagger}$ = 16.5 and 22.0 kcal/mol and $\Delta S^{\ddagger}$ = −21.5 and −6.11 eu, respectively. The decomposition mechanism is discussed in the light of these data.

1,3-Dithiolium cation (**1**) is a 6-π-electronic system in a positively charged five-membered ring and is highly stabilized by delocalization of the π electrons. The positive charge is also delocalized over all of the ring atoms by valence expansion of the sulfur atoms. A high positive charge density on C-2 leads to high reactivity toward nucleophilic reagents, and a C-2 adduct (2-substituted 1,3-dithiole) can be obtained with ease.[2] Thus, in view of their nonbenzenoid aromaticity and reactivity, 1,3-dithiolium cations form an interesting class of versatile compounds.

We have previously studied the behavior of **1** toward a variety of nucleophiles,[3] and have investigated its heteroaromaticity.[4] Continuing this work, we studied the nucleophilic reaction of **1** with xanthate (**2**) and dithiocarbamate (**3**) anions. The initially produced C-2 adducts of **2** reacted further with nucleophiles, **2** or benzylmercaptide anion, in an appropriate solvent, and the C-2 adducts of **3** decomposed easily in solvents with loss of carbon disulfide.

Results

Reaction of 4-Phenyl-1,3-dithiolium Perchlorate (1a) with Potassium Ethylxanthate (2). Reaction of **1a** with 2 mol of **2** (excess of nucleophile) in acetone afforded sulfide **4a**, and not the expected C-2 adduct. NMR of **4a** showed C-2 and C-5 protons of the 1,3-dithiole ring in addition to phenyl protons. The mass spectrum of **4a** showed dithiolium cation (4-phenyl, *m/e* 179) as the base peak, a common decomposition pattern for C-2 adduct. The structure of **4a** was thus ascertained by spectral and analytical data. Treatment of **4a** with perchloric acid yielded 4-phenyl-1,3-dithiolium cation (**1a**) with evolution of hydrogen sulfide. Compound **4a** was also identified as the product of the reaction of **1a** with sodium sulfide in water (Figure 1).

When this reaction was carried out in acetonitrile with an equimolar amount of **2**, C-2 adduct (**5a**) was obtained as an oil; its structure was ascertained by NMR and analytical data. To confirm the formation of **4** by further reaction of **5** with **2**, **5** was treated with **2** in acetone, giving **4a** in high yield. Furthermore, reaction of **5a** with sodium benzylmercaptide afforded **4a** in addition to a transesterified product (**6**). Also, reaction of **5a** with alkoxide ion in the corresponding alcohol gave 2-alkoxy-4-phenyl-1,3-dithiole (**7**).

Reaction of 1 with Sodium N,N-Disubstituted Dithiocarbamate (3). Nucleophilic reaction of **3** toward **1** gave C-2 adduct (**8**) in moderate yield. The structure of **8** was assigned with spectral and analytical data (Table I).

When 2-dialkylamino-4-aryl-1,3-dithiolium perchlorate (**9**) was treated with **3**, a yellow solid not soluble in many solvents (Me_2SO, CH_3CN, EtOH, $CHCl_3$) was isolated. A saturated solution of **9** in ethanol and acetone showed a UV maximum at 380 and 386 nm, respectively, and the analytical data suggested it to be a 1:1 adduct of a cation and anion species (Table I). These data indicate that **9a–d** are anion-exchange products. The visible absorption is due to a charge-transfer band, such as has been reported for pyridinium dithiocarbamate.[5]

In contrast to the reactivity of **5** toward nucleophiles, **8** and **9a–d** are stable in the solid state, though the former is less stable. However, a displacement reaction of **8** takes place with secondary amine or dithiocarbamate anion. And, in solution, **8** undergoes unusually rapid decomposition into 2-disubstituted amino-4-aryl-1,3-dithiole (**10**) with essentially quantitative evolution of carbon disulfide. The appropriate **10** was isolated in good yield by thermolysis of **8** in solvent (see Experimental Section). Decomposed product (**10**) was also obtained by the reaction of **1** with the corresponding amine,[3] or reduction of 2-disubstituted amino-4-aryl-1,3-dithiolium cation with $NaBH_4$ (Figure 2).[20]

Dithiocarbamate esters are in general unstable in solution, decomposing into amine derivatives and CS_2 photochemically[6] or thermally.[7] To elucidate the mechanism of decomposition of **8** in solution, we studied the kinetics spectroscopically. The rate constant for thermolysis of **8** was estimated by the decrease in the absorption coefficient at 257 nm, where the absorption of carbon disulfide did not overlap. The first-order plot, which was obtained from UV data, deviates upward from linearity with the progress of decomposition. The plot, in which the product-catalyzed term was taken into consideration,[8]

$$dx/dt/(a - x) \text{ vs. } x^2$$

has a good linear relationship as shown in Figure 3. This indicates that the second-order catalytic term with respect to **10** takes place. The intercept of the plot in Figure 3 is the first-order decomposition rate constant, k_0, and the slope is the catalyzed rate constant, k_2. With the progress of decomposition (>75%), the plot of Figure 3 deviates upward further from linearity. Table II summarizes k_0 and k_2 which were evaluated from Figure 3.

The k_0 values in EtOH, which has strong ionizing power, are about nine times larger than those in MeCN. The substituent R_1, which has an electron-donating character, accelerates the decomposition. On the other hand, the substituent effect of the aromatic ring attached to nitrogen is the reverse of that of R_1. The existence of the k_2 term in addition to the k_0 term is the main reason for the facile decomposition

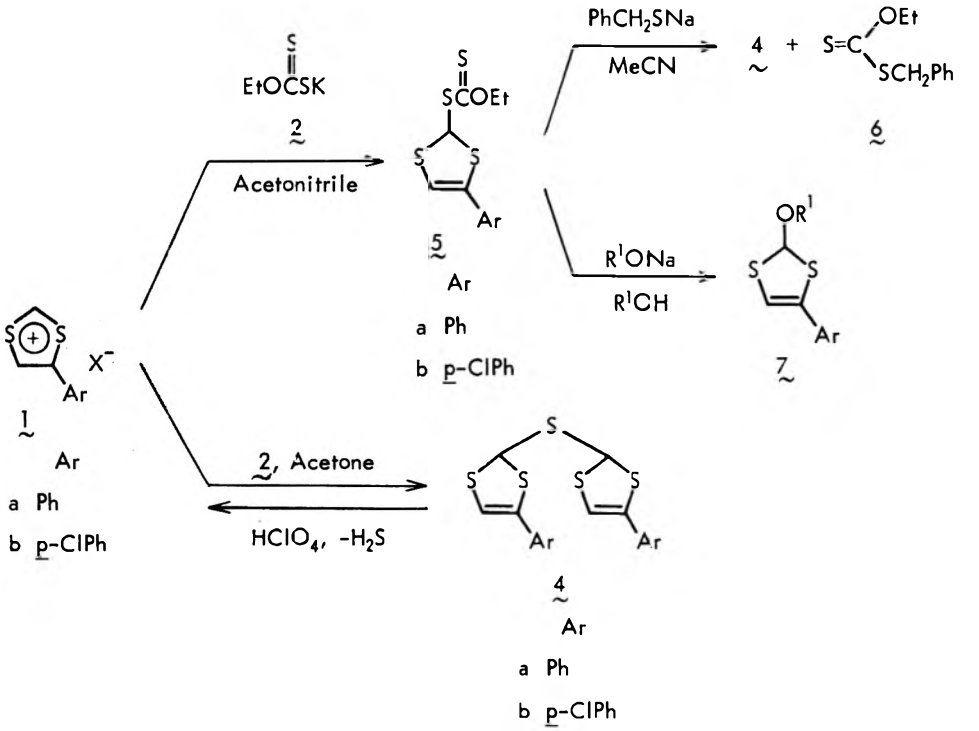


Figure 1. Reaction of 4-phenyl-1,3-dithiolium cation (**1**) with xanthate anion (**2**).

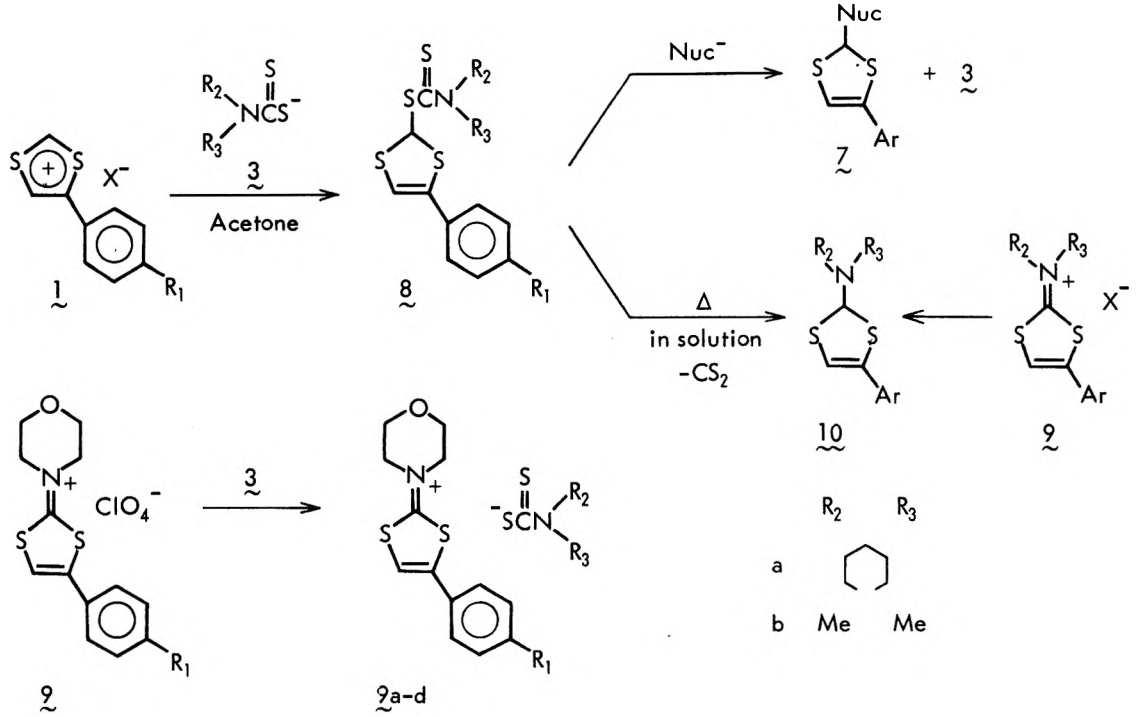


Figure 2. Reaction of 4-phenyl-1,3-dithiolium cation (**1**) with dithiocarbamate anion (**3**).

of **8**. The activation parameters obtained from the plot of log k_0 against $1/T$ are shown in Table III. The large difference in k_0 and $\Delta S^{\ddagger}$ between the solvents EtOH and MeCN indicates that the decomposition mechanisms are not the same.

From the Hammett plot toward σ^+ from the data of runs 11–14 in Table II, we obtained $\rho = -0.57$ and -0.38 for k_0 and k_2, respectively. The data of run 15 deviate downward from this slope. Decomposition did not occur in the presence of base (OH^-); substitution at C-2 of the dithiole ring took place instead.

Discussion

Although the positive charge of 1,3-dithiolium cation can be delocalized over all ring atoms, no report on the nucleophilic attack taking place at other than the C-2 carbon has appeared.[9] Initial adducts obtained from nucleophilic reaction of **1** with nucleophile are generally stable. However, **5** has several reactive sites for futher nucleophilic attack, which took place at one of its reaction centers in a suitable solvent.[10] The reaction route for the formation of **4** is shown in Figure 4.

Refluxing **5** in acetone does not yield **4**, indicating that another reagent is necessary and the reaction is not a Chugaev-type pyrolysis.[11] As shown in Figure 4, in the reaction between **1** and **2** in acetone, **2** attacks as a nucleophile at the thion carbon of adduct **5** to release R^0S^- (R^0 = 4-aryl-1,3-dithiol-2-yl) anion (if benzylmercaptide anion was used instead of **2**, transesterified xanthate ester was obtained). The R^0S^- thus formed further attacks the C-2 carbon of the five-membered

Table I. *S*-(4-Aryl-1,3-dithiol-2-yl) N,N-Disubstituted Dithiocarbamates (8)[a] and 4-Aryl-2-morpholino-1,3-dithiolium N,N-Disubstituted Dithiocarbamates (9)[a]

Compd 8	R_2	R_3	R_1	Mp, °C	Yield, %
a	Me	Me	H	80–81	89
b	Me	Me	Br	124–125	85
c	Me	Me	Cl	106–108	85
d	Me	Me	OCH_3	112–114	82
e	Me	Me	CH_3	119–122	85
f	Me	Me	OH	106–108	69
g	Et	Et	H	81–83	87
h	*n*-Pr	*n*-Pr	H	82–83	86
i	*i*-Pr	*i*-Pr	H	94–96	85
j	*n*-Bu	*n*-Bu	H	61–62	63
k	$PhCH_2$	$PhCH_2$	H	87–88	53
l	$-(CH_2)_5-$		H	120–122	82
m	$CH_2CH_2OCH_2CH_2$		H	121–122	51
n	$CH_2CH_2OCH_2CH_2$		OMe	114–115	73[b]
o	$CH_2CH_2OCH_2CH_2$		Br	116–117	74
p	Me	Ph	H	129–131	30
q	Me	Ph	OMe	146–147	47
r	Me	Ph	Br	121–124	38
s	Me	*p*-MeOPh	H	127–128	28
t	Me	*p*-MeOPh	Cl	138–140	41

9				Mp, °C dec	
a	H	Ph	H	130–131	72
b	$-CH_2CH_2OCH_2CH_2-$		H	152–153	81
c	$-CH_2CH_2OCH_2CH_2-$		OMe	160–165	86
d	$-CH_2CH_2OCH_2CH_2-$		Cl	158–160	68

[a] Satisfactory analytical values (±0.3% for C, H, N, and S) were submitted for all compounds except **8n**. [b] Exact analytical data were not obtained for **8n** owing to its thermal instability.

ring of **5**, and substitution reaction leads to the formation of **4**. At this point, xanthate anion is reproduced. Thus for the reaction of **5** with **2** an equimolar amount of **2** is not necessary, a catalytic amount being sufficient. In fact, sulfide formation from **5** in the presence of 0.1 mol of **2** proceeds smoothly. Reaction of alkoxide ion with **5** proceeds via substitution at C-2 of the dithiole ring analogous to that of R^0S^- with **5**. The different reactive site between R^0S^- and R^1O^- can best be interpreted in terms of the soft base (R^0S^-)–soft acid (thion carbon of **5**) and hard base (R^1O^-)–hard acid (C-2 carbon of **5**) correspondence in the HSAB principle.[12]

The reaction between **1** and **2** is summarized stoichiometrically as follows. The solvent effect in this reaction can be

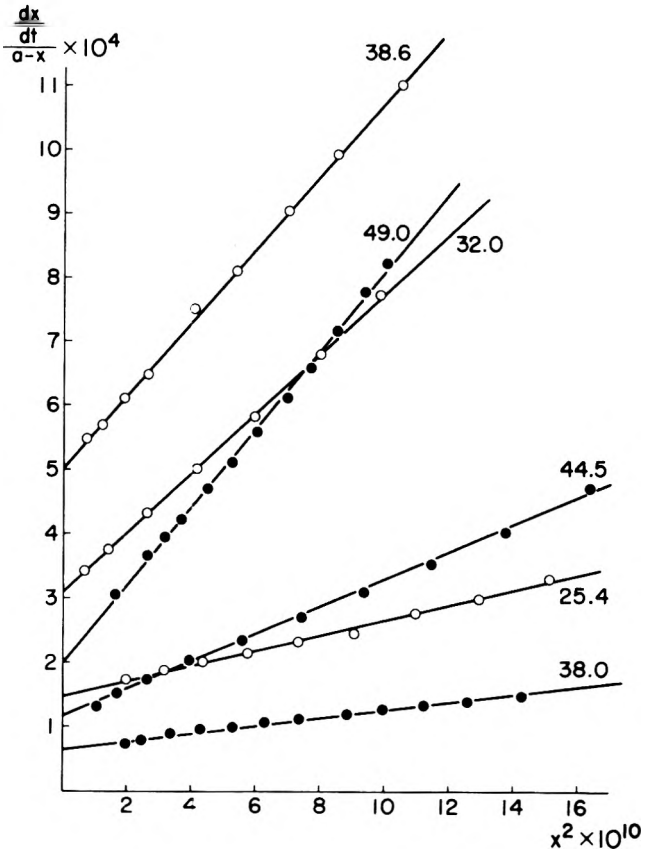
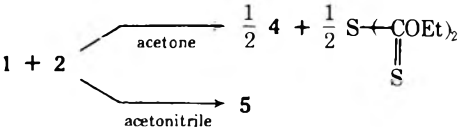


Figure 3. Plot of $dx/dt/(a - x)$ vs. x^2: ●, MeCN; ○, EtOH. Temperatures are shown in the figure.



explained by solvation of the nucleophile which depends on the dielectric constant (21.5 for acetone and 37.5 for acetonitrile). Poorer solvation of nucleophile (xanthate anion) in acetone in comparison to that in acetonitrile results in higher reactivity of the former system. This tendency can be also observed in the N_+ parameters defined by Ritchie.[13] If we compare the nucleophilicity of a given nucleophile in different solvents, confining the comparison to that of N_+ values in dipolar aprotic solvents, then the larger the N_+ values are, the smaller the dielectric constants, i.e., the lesser the solvation the larger N_+ value and the greater the nucleophilicity.

Table II. Rate Constants for the Decomposition of 8 Obtained from Figure 3 with $dx/dt/(a - x) = k_0 + k_2x^2$

Run no.	R_1	R_2	R_3	Solvent	Temp, °C	Concn, $\times 10^5$ M	k_0, $\times 10^4$ s^{-1}	k_2, $\times 10^{-5}$ $M^{-2}\,s^{-1}$
1	H		Morpholino	EtOH	25.4	6.46	1.47	1.19
2	H		Morpholino	EtOH	32.0	4.86	3.13	4.62
3	H		Morpholino	EtOH	38.6	6.15	5.03	5.69
4	H		Morpholino	MeCN	38.0	7.69	0.539	0.819
5	H		Morpholino	MeCN	44.5	6.12	1.15	2.08
6	H		Morpholino	MeCN	49.0	4.65	1.93	6.04
7	OMe		Morpholino	MeCN	44.5	4.47	1.45	4.78
8	Br		Morpholino	MeCN	44.5	8.14	0.865	0.829
9	H	Me	Ph	EtOH	52.5	4.22	1.07	1.74
10	H	Me	*p*-MeOPh	EtOH	52.5	6.72	0.870	0.486
11	Br	Me	Me	EtOH–MeCN	50.0	3.68	2.19	6.15
12	Cl	Me	Me	(9:1 v/v)	50.0	3.68	2.33	6.40
13	Me	Me	Me	EtOH–MeCN	50.0	3.68	3.80	9.69
14	OMe	Me	Me	EtOH–MeCN	50.0	3.68	7.54	17.6
15	OH	Me	Me	EtOH–MeCN	50.0	3.68	5.38	16.1

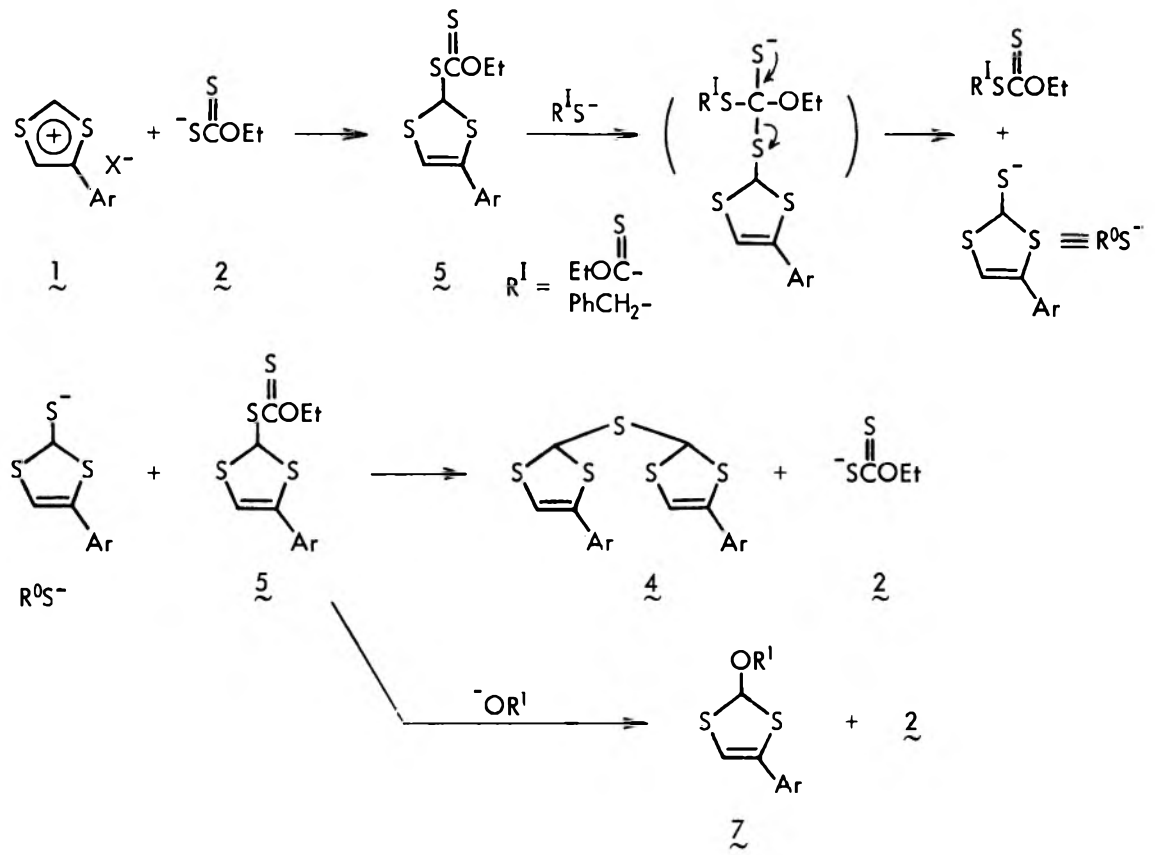


Figure 4. Reaction pathway for the formation of sulfide (4) from the reaction of 1 with 2.

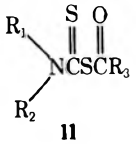
Table III. Activation Parameters for the First-Order Decomposition of 8

Solvent	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
EtOH	16.5	−21.5
MeCN	22.0	−6.11

Decomposition of 8. Many studies have been made on the mechanism of acid- or base-catalyzed decomposition of dithiocarbamate salt[14] and base-catalyzed decomposition of thiolcarbonate or xanthate esters.[15] However, no attempt has been made to explain the mechanism of decomposition of dithiocarbamate esters, except for the acyl esters.[6,7]

There are three mechanisms that can be considered to explain the decomposition mechanism of 8, that is, (a) cyclic four-membered ring transition state, (b) stepwise mechanism, and (c) simultaneous two-bond heterolysis mechanism (Figure 5).

Decomposition of dithiocarbamate acyl esters (11) proceeds via pathway a, and the presence of an electron-withdrawing



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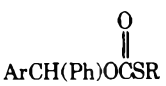
group attached to the acyl carbon, which makes it more positive, accelerates the decomposition. In this case, decomposition takes place via intramolecular nucleophilic attack of the amine moiety. The reverse is the case with the substituent effect of the decomposition of 8. Rate enhancement of the decarboxylation of thiolcarbonic carboxylic anhydride (12) is observed in polar solvent,[16] but the rate ratio does not vary largely with the polarity. Furthermore, the $\Delta S^{\ddagger}$ value of the

12

decarboxylation of 12 is large negatively with increase in solvent polarity. These facts indicate that the decomposition of 11 and 12 proceeds via path a, and the difference in $\Delta S^{\ddagger}$ due to the alternation of solvent polarity is due to that in the solvation of the incipient species. The rate of the decomposition of 8 is slower in the more polar solvent, MeCN, than in EtOH and the $\Delta S^{\ddagger}$ is more negative in the less polar but more powerful ionizing solvent, EtOH, than in MeCN. This result is the reverse of that of 12. Accordingly, mechanism a can be ruled out for the decomposition of 8.

Mechanism b proceeds via the heterolysis of 8 into the dissociated ion pair and the dithiocarbamate anion (2) formed further decomposes into CS_2 and $N^-R_2R_3$. Acid-catalyzed decomposition of 2 or xanthate anion has been described to proceed via the corresponding acid, and not the anion.[14] Protonation occurs between S and X (O or N) in the transition state. The dithiocarbamate anion is stable and no crossover product has been found for the decomposition of 8. From these results, we can conclude that the decomposition of 8 does not proceed via mechanism b.

Noncatalyzed decomposition of aralkyl thiocarbonate (13)



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is accelerated in a solvent having strong ionizing power,[17] and the plot of log k vs. pK_a (pK_a of mercaptans) deviates from a linear relationship with a decrease in pK_a. This fact shows that in the transition state, both C–O and C–S bonds cleave, the degree being smaller for the latter. Solvent dependence of the decomposition rates of 8 is the same as that of 13. From

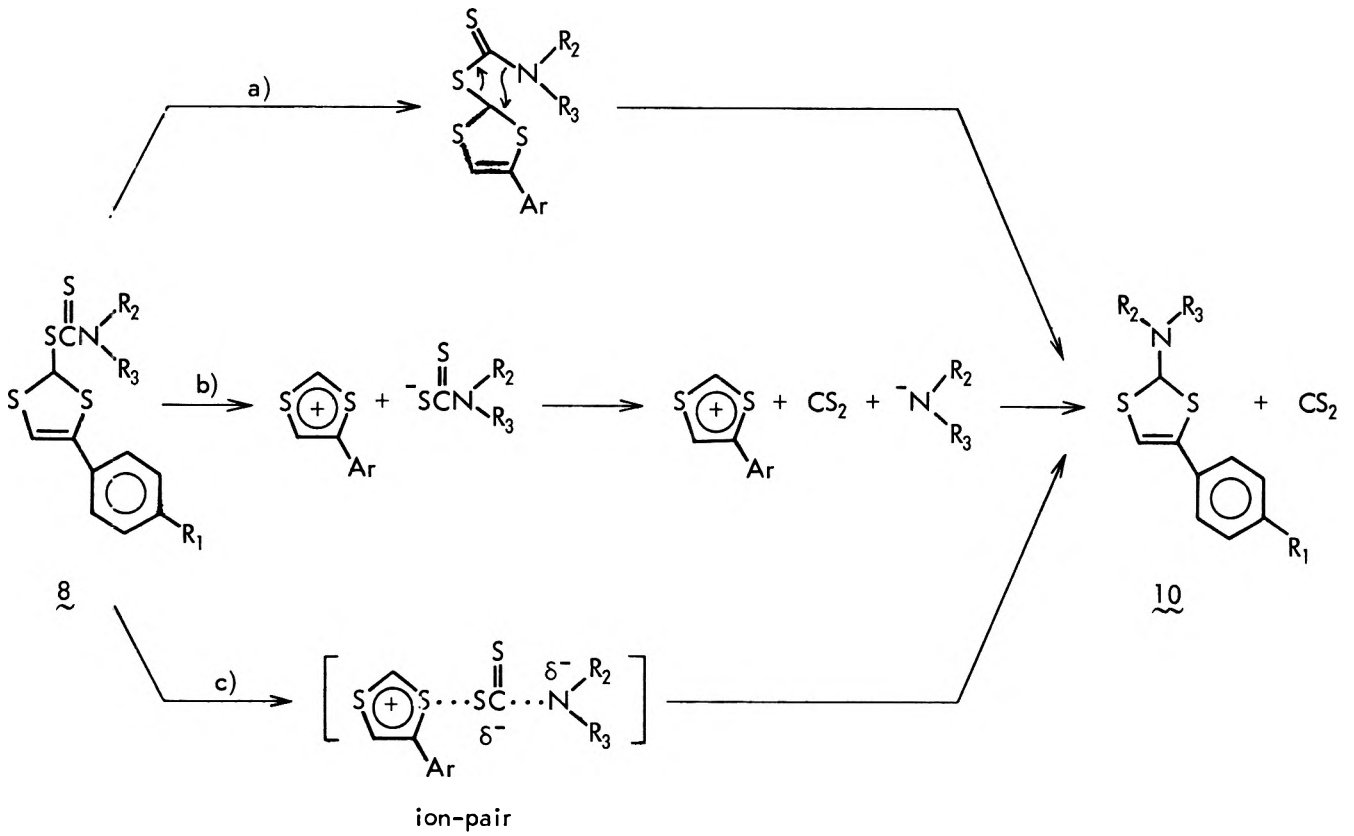

Figure 5. Three possible mechanisms for the thermal decomposition of dithiocarbamate ester (8) into aminodithiole (10) and CS_2.

these consideration, we can conclude that the decomposition of 8 (with regard to k_0) proceeds via mechanism c. This is further supported by the presence of both substituent effects of R_2, R_3, and R_1.

Decomposition of 8 is accelerated in a solvent having strong ionizing power (EtOH) and the degree of dissociation of the C–S and C–N bonds is affected by the nature of the substituents. The enhanced reactivity of *N*-alkyl derivatives (runs 1–8 in Table II) in spite of the larger extent of dissociation of the C–N bond in the transition state of *N*-aryl derivatives (runs 9 and 10) is ascribed to the larger nucleophilicity of the former. On the other hand, the presence of the electron-donating group on nitrogen destablizes the developing negative charge resulting from dissociation of the C–N bond. This results in lesser dissociation of the *N*-methoxyphenyl derivative than that of the *N*-phenyl one. The difference in the decomposition rate between phenyl and *p*-methoxyphenyl derivatives is thus estimated by comparing the stabilizing effects of the developing negative charge from the electron-donating *p*-methoxyphenyl groups.

A linear relationship of the Hammett plot of the substituent effect of R_1 against σ^+ is obtained. The same correlation of the substituent effect on σ^+ has also been seen for pK_{R^+} of **1**[18] and for the decomposition of *tert*-butyl arylperacetate with which decarboxylation proceeds via mechanism c.[19]

The difference in $\Delta S^{\ddagger}$ in EtOH and MeCN can be explained as that in the solvation for the charge-separated transition state. The degree of dissociation of the C–S and C–N bonds in EtOH was larger than in MeCN. The solvent was needed to stabilize the developed polar transition state in EtOH. Hence the large negative $\Delta S^{\ddagger}$ value in EtOH.

Thiocarbonate esters are reported to be subject to base-catalyzed decomposition, which is first order with respect to the base, and the reaction might be intermolecular.[15] With regard to the second-order catalytic term of the product, the electron-donating atoms of the product associate with the positive charge of 8, which stabilizes 8.

Experimental Section

Melting points are uncorrected. UV spectra were measured with a Hitachi EPS-2 spectrometer, NMR spectra with a Varian A-60 instrument in $CDCl_3$ with Me_4Si as an internal standard, and mass spectra with a Hitachi RMU-6E mass spectrometer.

Preparation of Cation. Starting cations (1, 4-aryl-1,3-dithiolium and 2-substituted amino-4-aryl-1,3-dithiolium perchlorates) were prepared by a method described previously.[20]

4-Phenyl-1,3-dithiol-2-yl Sulfide (4a). A mixture of 0.56 g (2.0 mmol) of **1a** and 0.64 g (5.0 mmol) of **2** in 20 mL of acetone was refluxed for 2 h, then concentrated in vacuo. The residue was partitioned between chloroform and water. The organic layer was separated, dried over sodium sulfate, and evaporated to give the crude product. Recrystallization from chloroform yielded 0.28 g of **4a**: mp 167–169 °C dec; yield 73%; NMR δ 6.32 (s, 1), 6.37 (s, 1), 7.20–7.50 (m, 5, ArH); UV λ_{max} (EtOH) 232.5 nm (log ε 4.40), 255 (sh, 4.21), 314 (4.04), 345 (sh, 3.86); mass spectrum *m/e* 356 [15%, bis(4-phenyl-1,3-dithioledene), 210 (35%, 2-thioxo-4-phenyl-1,3-dithiole), 180 (79%, 4-phenyl-1,3-dithiole), 179 (100%, 4-phenyl-1,3-dithiolium cation), 134 (69%, phenylthirene), 121 (18%, thiobenzoyl cation), 102 (85%, phenylacetylene), 89 (19%), 77 (14%, Ph or CS_2H^+), 45 (21%, CSH^+).

Anal Calcd for $C_{18}H_{14}S_5$: C, 55.34; H, 3.61; S, 41.05. Found: C, 55.82; H, 3.57; S, 40.81.

An authentic sample of **4a** was prepared as follows. To an ice-cooled solution of 0.36 g (1.5 mmol) of sodium sulfide nonahydrate in 5.0 mL of water was added 0.84 g (3.0 mmol) of **1a** with efficient stirring. The mixture was stirred for 1 h, then extracted with chloroform. The chloroform layer was dried over sodium sulfate, then evaporated to give 0.39 g (66%) of 4a, the IR spectrum of which was identical with that for the product obtained in the above reaction.

Treatment of a small amount of **4a** with aqueous $HClO_4$ in acetronitrile gave the characteristic odor of hydrogen sulfide. Addition of excess ether gave a colorless precipitate with an IR spectrum identical with that of **1a**.

***S*-4-Phenyl-1,3-dithiol-2-yl *O*-Ethylxanthate (5a).** To a solution of 0.56 g (2.0 mmol) of **1a** in 10 mL of acetonitrile was added 0.32 g (2.5 mmol) of **2** at room temperature. The mixture was stirred for 2 h, then filtered. The filtrate was concentrated and excess ether was added. The precipitate which formed was filtered off, then concentrated to give 0.58 g (97%) of **5a** as an oil: NMR δ 1.43 (t, 3, Me), 4.66 (q, 2, CH_2), 6.40 (s, 1), 7.50–7.17 (m, 5, ArH); UV λ_{max} (EtOH) 231 nm (log ε 4.09), 240 (sh, 4.02), 307 (3.92), (CH_3CN) 227 (4.27), 245 (sh, 4.14), 283 (4.07), 330 (3.78).

Anal. Calcd for $C_{12}H_{12}OS_4$: C, 47.96; H, 4.03; S, 42.68, Found: C, 47.81; H, 4.01; S, 42.74.

By the same method, **5b** was obtained as an oil: yield 91%; NMR δ 1.43 (t, 3, Me), 4.67 (q, 2, CH_2), 6.41 (s, 1), 6.68 (s, 1), 7.30 (s, 4, ArH).

Anal. Calcd for $C_{12}H_{11}ClOS_4$: C, 43.03; H, 3.31; S, 38.30; Cl, 10.58. Found: C, 43.30; H, 3.41; S, 38.18; Cl, 10.86.

Reaction of 5a with 2. A solution of 0.78 g (2.9 mmol) of **5a** in 25 mL of acetone was refluxed for 2 h. TLC showed the presence of **5a** only at this stage. To this solution 0.032 g (0.25 mmol) of **2** was added, and the mixture was refluxed for a further 3 h, then allowed to stand overnight. The reaction mixture was concentrated to dryness and the residue was partitioned between chloroform and water. Workup as described in the reaction between **1a** and **2** in acetone yielded 0.37 g (73%) of **4a**, which was confirmed by comparing the IR spectrum with that of an authentic sample.

By the same method, **4b** was obtained in 64% yield after recrystallization from chloroform: mp 153–155 °C; NMR δ 6.30 (s, 1), 6.37 (s, 1), 7.32 (s, 4, ArH); UV λ_{max} (EtOH) 244 nm (log ϵ 4.34), 323 (4.17).

Anal. Calcd for $C_{18}H_{12}Cl_2S_5$: C, 47.05; H, 2.63; S, 34.89; Cl, 15.43. Found: C, 47.36; H, 2.60; S, 34.70; Cl, 15.27.

Reaction of 5a with Benzyl Mercaptide. To an ice-cooled solution of 0.25 g (5.0 mmol) of sodium hydroxide in 25 mL of acetonitrile was added 0.62 g (5.0 mmol) of benzyl mercaptan. The mixture was stirred for 5 min, then 1.50 g (5.0 mmol) of **5a** in 10 mL of acetonitrile was added. Stirring was continued for 3 h with ice cooling. Then the mixture was concentrated and partitioned between chloroform and water. Undissolved material was filtered off to give 0.12 g of **4a**. The organic layer was concentrated and the residue was washed with ether, the residue being 0.47 g of **4a**. The filtrate was again concentrated and the residue was washed with *n*-hexane. Here 0.082 g of **4a** (for a total 0.67 g of **4a**) was separated. Evaporation of the solvent afforded 0.60 g of *S*-benzyl *O*-ethylxanthate (**6**) as an oil: NMR δ 1.38 (t, 3, Me), 4.64 (q, 2, CH_2), 4.36 (s, 2, CH_2), 7.28 (s, 5, ArH).

An authentic sample of **6** was prepared as follows.[21] A mixture of 0.63 g (5.0 mmol) of benzyl chloride and 0.80 g (5.0 mmol) of potassium xanthate in 15 mL of acetonitrile was stirred for 1 h at room temperature; then the mixture was concentrated and the residue partitioned between ether and water. Concentration of the ether solution gave 0.93 g of ester (**6**), which was identified by spectral comparison with the above product.

Reaction of 5a with Alkoxide. To a solution of 0.046 g (2.0 mmol) of sodium in 5.0 mL of ethanol was added 0.60 g (2.0 mmol) of **5a**. The reaction mixture was refluxed for 1.5 h, then allowed to stand overnight. The residue obtained from evaporation of the solvent was partitioned between chloroform and water. The organic layer was separated, dried over sodium sulfate, and concentrated to yield 0.32 g (72%) of 2-ethoxy-4-phenyl-1,3-dithiole (**7**) as an oil. The identity of **7** was confirmed by comparing its spectra with that of an authentic sample.[3]

By using methanol instead of ethanol the 2-methoxy derivative of **7** was obtained in 94% yield (oil).

Sodium Dithiocarbamate (3). N,N-Disubstituted dithiocarbamates were prepared by the method of Heyningen and Brown.[22]

***S*-(4-Aryl-1,3-dithiol-2-yl) N,N-Disubstituted Dithiocarbamate (8).** The general procedure for synthesis of **8** has been described.[3] The results are summarized in Table I.

Reaction of 8a with Piperidine. A mixture of 599 mg (2.0 mmol) of **8a** and 340 mg (2.0 mmol) of piperidine in 20 mL of EtOH was stirred for 2.5 h at room temperature. The solvent was removed in vacuo and the residue was dissolved in ether, washed with water, separated, and dried. Concentration of the solvent, followed by recrystallization from EtOH, yielded 320 mg (80%) of 2-piperidino-4-phenyl-1,3-dithiole (**10a**), mp 87–88 °C. The IR of the product agreed with that of the authentic sample.[20]

Reaction of 8a with Sodium Piperidinodithiocarbamate (3). A solution of 599 mg (2.0 mmol) of **8a** and 876 mg (2.0 mmol) of **3** dihydrate in 20 mL of EtOH was stirred for 2 h at 50 °C, then concentrated. The residue was extracted with AcOEt, washed with water, separated, and dried. The solvent was removed in vacuo, and the residue was washed with ether to afford 297 mg (44%) of *S*-(4-phenyl-1,3-dithiol-2-yl)piperidinodithiocarbamate (**8l**), which had an IR spectrum identical with that of the authentic sample (see Table I).

Thermolysis of 8 into 10. Thermolysis of 8l. A suspended solution of 340 mg of **8l** in 10 mL of EtOH was stirred for 2 h at 60 °C, then concentrated in vacuo. The residue was triturated with ether. The residue was separated by filtration to give 137 mg (40.5%) of undecomposed **8l**. Evaporation of filtrate afforded 152 mg (57.5%) of 2-piperidino-4-phenyl-1,3-dithiole (**10a**), which had an IR spectrum identical with that of the authentic sample.[20]

Thermolysis of 8a. A solution of 300 mg of **8a** in 15 mL of methylene chloride was refluxed for 75 h. Evaporation of the solvent followed by washing with petroleum ether and recrystallization from EtOH gave 215 mg (96.5%) of 2-dimethylamino-4-phenyl-1,3-dithiole (**10b**). The structure of the product was confirmed by comparing its spectral data with those of the authentic sample.[20] Thermolysis of **8a** in EtOH (the same conditions as for **8l**) gave 83% decomposed product.

Kinetics. Decomposition of **8** was characterized by a decrease in absorption due to substrate at 267 nm and a simultaneous growth in absorption at 315 nm characteristic of the decomposed product, with isosbestic points at 304 and 325 nm being maintained throughout the course of decomposition. The rate of decomposition was determined spectrophotometrically at 257 nm. Rate constants were then calculated from the plot of

$$dx/dt/(a - x) \text{ vs. } x^2$$

where a is the initial quantity of **8** and x is the quantity of the product (**10**) at time t. Usually, the plot of x vs. t gave a straight line (< about 75% decomposition), and $dx/dt = x/t$ was approximated. Because the decomposition of **8** takes place immediately after its contact with solvent, the initial absorbance was estimated graphically from the plot of absorbance vs. t, and the absorbance of the product at time infinity was obtained by allowing the sample to stand overnight.

Registry No.—**1a,** 24396-11-0; **1b,** 24372-89-2; **2,** 140-89-6; **3,** 873-57-4; **4a,** 61522-70-1; **4b,** 61522-71-2; **5a,** 61522-72-3; **5b,** 61522-73-4; **6,** 2943-26-2; **8a,** 24395-63-9; **8b,** 61522-74-5; **8c,** 61522-75-6; **8d,** 61522-76-7; **8e,** 61522-77-8; **8f,** 61522-78-9; **8g,** 61522-79-0; **8h,** 61522-84-7; **8i,** 61522-80-3; **8j,** 61522-81-4; **8k,** 61522-82-5; **8l,** 24395-62-8; **8m,** 24395-13-9; **8n,** 61522-83-6; **8o,** 61522-85-8; **8p,** 61522-86-9; **8q,** 61522-87-0; **8r,** 61522-88-1; **8s,** 61522-89-2; **8t,** 61522-90-5; **9a,** 61522-91-6; **9b,** 61522-92-7; **9c,** 61522-94-9; **9d,** 61522-96-1; benzylmercaptide, 100-53-8; sodium ethoxide, 141-52-6; piperidine, 110-89-4.

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Dipole Moment, Nuclear Magnetic Resonance, and Infrared Studies of Phosphorus Configurations and Equilibria in 2-R-2-Oxo-1,3,2-dioxaphosphorinanes

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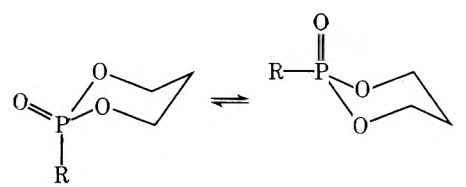
Substantial dipole moment differences (1.3–2.2 D) permit assignment of the stereochemistry at phosphorus in isomeric pairs of 2-R-2-oxo-4,6-dimethyl-1,3,2-dioxaphosphorinanes wherein R = Me (**3a,b**), H (**4a,b**), OMe (**5a,b**), and NMe_2 (**6a,b**) where a and b denote axial R (equatorial P=O) and equatorial R (axial P=O) relationships, respectively. Analogous assignments were obtained from similar measurements on the isomeric pairs of 2-R-2-oxo-4-methyl-1,3,2-dioxaphosphorinanes wherein R = Me (**7a,b**), H (**8a,b**), OMe (**9a,b**), and NMe_2 (**10a,b**). LIS experiments on **7–10** confirm these assignments. The **a** isomers of **3, 5, 6** and **7, 9, 10** exhibit $\delta^{31}P$ values upfield of those of the **b** isomers whereas the opposite is true for **4a,b** and **8a,b.** Doubling (ca. 19 cm^{-1}) of the phosphoryl stretching frequencies in **5b** and **9b** is attributed to rotational isomerism of the MeO groups while the lack of such doubling in the **a** isomers is attributed to steric restrictions. A more pronounced doubling (ca. 40 cm^{-1}) of this frequency in **6a** and **10a,** on the other hand, may be due to the presence of a second conformer arising as a result of the severe 1–3 steric interactions. The μ and $\delta^{31}P$ values and the extinction coefficients of the P=O stretching frequencies associated with **a** and **b** isomers of the rigid-ring model compounds **3–6** were compared to those of the analogous compounds which were free to attain conformational equilibrium by virtue of the absence of the 4,6-dimethyl substituents. All the data are in accord with a substantial axial R (equatorial P=O) group preference when R = H and MeO, although this preference is slightly reversed for R = Me and strongly opposite when R = Me_2N at room temperature in benzene.

Phosphorus stereochemistries and ring conformations of phosphorinanes, especially the 1,3,2-dioxaphosphorinanes reported here, have received considerable attention in recent years. Several instrumental techniques have been employed, from which conflicting conclusions have been occasionally drawn (vide infra). The purpose of this paper is to report a new approach to the use of solution techniques which eliminates some of the ambiguities.

The investigations reported in the literature for 2-R-2-oxo-1,3,2-dioxaphosphorinanes fall into two broad categories: (1) studies of phosphorus configurations and ring conformational equilibria of conformationally mobile systems such as **1**, and (2) assignments of phosphorus configurations of rings with conformationally reduced mobility such as **2a** and **2b.** It



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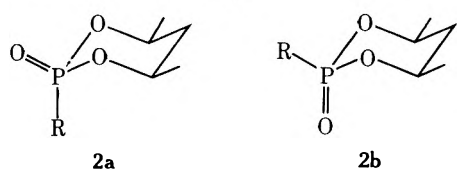


2a **2b**

should be noted that 5,5-dimethyl derivatives are not expected to influence the mobility significantly and they are therefore in the same class with **1.** On the other hand, 4-methyl and 5-*tert*-butyl substituted rings resemble **2** in being more conformationally rigid.

Five instrumental techniques (^1H NMR, ^{13}C NMR, ^{31}P NMR, infrared, and dipole moment experiments) have been used for determinations of phosphorus stereochemistries and ring conformations in solution as is briefly outlined below.

Coupling constants among ring hydrogens and between phosphorus and ring protons have been found to be valuable both for conformer distribution determinations in type **1** compounds and for phosphorus stereochemical assignments.[1] Thus, it has been reported that $^3J_{POCH_{eq}}$ coupling constants are larger for compounds with equatorially oriented substituents in trivalent 1,3,2-dioxaphosphorinanes than for the axial analogues.[2] However, this criterion has been incorrectly applied to 2-oxo analogues[3] which in fact do not exhibit such behavior.[4] Because of this problem in 2-oxo compounds, lanthanide induced shift (LIS) experiments on protons in the molecule become very useful. Mosbo and Verkade have demonstrated that the C4 and C6 axial protons are shifted considerably further downfield in compounds with the **2b** configuration than in those with **2a.**[5] Dale[6] has reported conformer distributions determined from type **1** compounds employing LIS experiments, but the results must be viewed with caution since Bentrude and co-workers[7] have found that the presence of a lanthanide shift reagent can cause conformational changes.

The use of ^{13}C NMR spectra has been reported in only a few instances to identify type **2** isomers. It has been demonstrated that the chemical shift of a carbon atom γ to an axial phosphorus substituent (**b** isomer) is upfield of the **a** isomer.[2b,c]

This technique has not been applied to determinations of conformer distributions in type 1 compounds.

^{31}P NMR data have indicated that chemical shifts of **2a** isomers are generally upfield of the **2b** analogues.[2b,5] A reversal has been found, however, when R = H.[5b,8] No correlations between conformer distributions of type 1 compounds and ^{31}P chemical shifts have been previously reported.

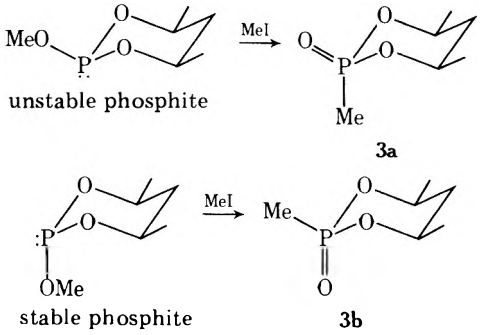
Kainosho et al.[9] first reported that infrared phosphoryl stretching frequencies were indicative of the disposition of the P=O link in the ring. The absorption for the equatorial P=O orientation (**2a**) was found to be at higher energy than that for the axial orientation (**2b**). This technique has been extensively employed for both identification of phosphoryl orientations and determinations of conformer equilibria.[10,11]

Dipole moment data were employed by Kainosho and Shimozawa[12] to deduce phosphorus configurations in type 1 compounds. Their conclusions were tenuous, however, because they were based on comparisons of calculated and observed moments and this method has led to some erroneous assignments by later workers.[11] More recently, dipole moment measurements have been employed to identify the phosphorus configurations of type 2 isomers, where the equatorially oriented P=O of the **a** isomers caused considerably larger molecular moments than the axial P=O[5,13] orientations.

With the exception of infrared spectroscopy, none of the above techniques have been used with any reliability for the determination of both phosphorus configurations and ring conformer distributions of type 1 compounds. In this paper we report quantitative conformer distributions of type 1 compounds, where R = Me, H, OMe, and NMe_2, based primarily on ^{31}P and dipole moment measurements and secondarily on infrared analysis of the P=O region. A new approach to the problem is developed in which ^{31}P chemical shifts and dipole moment measurements of the mobile (type 1) compounds are compared to those of the **2a** and **2b** isomers. The results of these experiments suggest that the infrared phosphoryl stretching frequency criterion is more ambiguous than previously supposed. The 4,6-dimethyl compounds were chosen as excellent representations of conformationally rigid molecules since the presence of the methyl groups renders a second chair form essentially inaccessible.

Results and Discussion

Configurational Assignments of Rigid Compounds. The previously unreported methyl phosphonates **3a** and **3b** were

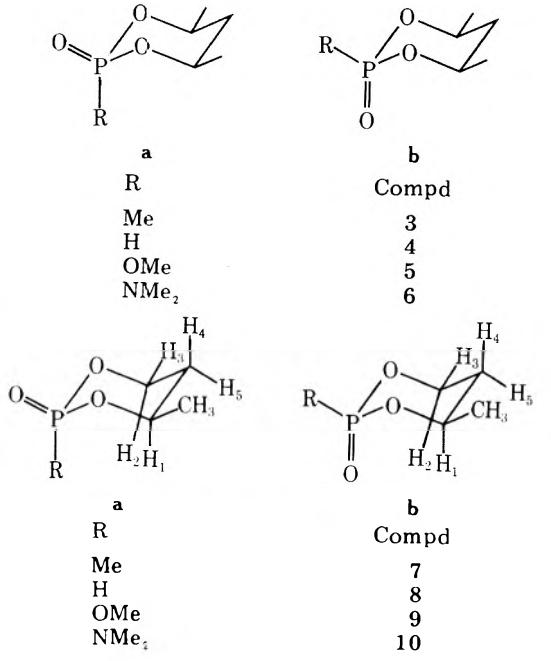


obtained by the reaction of unstable and stable phosphites, respectively, with methyl iodide. The analogous Michaelis–Arbusov reaction to form the 4-methyl compounds **7a** and **7b** has been shown to occur with complete retention of phosphorus configuration.[14] That the 4,6-dimethyl compounds are also obtained through retention of configuration is indicated by the dipole moments of the 4,6-dimethyl substituted compounds **3a,b, 4a,b, 5a,b,** and **6a,b** and the 4-methyl substituted compounds **7a,b, 8a,b, 9a,b,** and **10a,b** which were derived from the appropriate experimental data (see supplementary material in Table I) and are presented in Table II. Those isomers with equatorial phosphoryl oxygens (**a** isomers)

Table II. Dipole Moments, ^{31}P Chemical Shifts, and Phosphoryl Stretching Frequencies of 4-Methyl- and 4,6-Dimethyl-1,3,2-dioxaphosphorinanes[a]

Compd	μ[b]	^{31}P[c]	$\bar{\nu}$(P=O)[d]
3a	6.42	−19.4	1285 s (138)
3b	4.15	−28.0	1251 s (143)
4a	6.37	−2.9	1296 s (79)
4b	5.07	+1.3	1294 vw, 1267 s
5a	6.11	+7.1	1304 s (143)
5b	4.69	+5.0	1289 m, 1271 m
6a	5.80	−3.5	1301 m, 1260 s
6b	4.05	−6.6	1257 s (88)
7a	6.13	−20.4	1284 s (88)
7b	4.07	−27.7	1254 s (110)
8a	6.02	−2.8	1298 s (84)
8b	5.24	+1.7	1293 vw, 1270 s
9a	5.78	+6.8	1309 s (94)
9b	4.93	+5.2	1288 m, 1270 m
10a	5.33	−3.5	1301 m, 1260 s
10b	4.00	−6.6	1257 s (94)

[a] All measurements were made on benzene solutions. [b] Given in Debye units with a precision of ±0.05 D. [c] Given in parts per million relative to external 85% H_3PO_4. Negative and positive signs denote downfield and upfield shifts, respectively, from the standard. [d] Given in cm^{-1}, s = strong, m = medium, w = weak, v = very. The numbers appearing in parentheses are calculated extinction coefficients.



are expected to exhibit larger dipole moments than those with axial phosphoryl oxygens (b isomers) as has been discussed previously.[5] Lanthanide induced shift (LIS) data for the 4-methyl substitute compounds **8–10** have been presented and rationalized previously[5] and the larger C4 and C6 axial proton shifts (H_1 and H_2) observed for the b isomer of **3** (Table III) are consistent with the isomeric phosphorus configurations as shown.

The ^{31}P chemical shifts of the isomeric compounds **3, 5, 6, 7, 9,** and **10** (Table II) are consistent with the previously reported observation that isomers with axially oriented R groups (**a** isomers) have chemical shifts upfield of the equatorial isomers.[2b,5] Because the reverse behavior has been reported

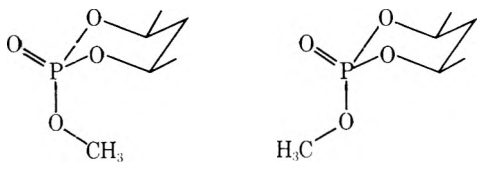
Table III. LIS ^{1}H NMR Shift Data $\Delta\delta^a$ for 2-R-2-Oxo-4-methyl-1,3,2-dioxaphosphorinanes

Compd	R	H_1	Me	H_2	H_3	H_4	H_5
7a	3.64	1.9	1.61	1.9	1.9	1.6	2.6
7b	3.50	4.5	1.09	4.5	1.6	1.4	2.3
8a	*b*	1.6	1.2	1.6	1.6	1.4	2.2
8b	*b*	4.6	1.3	4.1	1.7	2.0	2.6
9a	4.58	3.3	1.30	3.0	2.2	1.5	2.4
9b	3.94	5.1	1.37	4.5	2.2	1.6	2.6
10a	2.64	2.3	1.90	2.3	1.6	1.5	2.6
10b	3.73	5.3	1.19	4.6	2.2	1.4	2.8

^{a} $\Delta\delta$ refers to the chemical shift in the presence of $Eu(fod)_3$ minus that in the absence of $Eu(fod)_3$. ^{b} A very large shift occurred which was out of instrumental range.

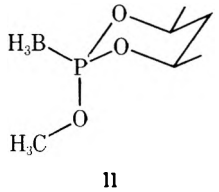
for **8a,b** and **4a,b**,[5b] this criterion must be used with some caution.

The infrared phosphoryl stretching frequencies listed in Table II illustrate that this technique can be misleading unless used with care. Two absorptions of nearly equal intensity for the phosphates **5b** and **9b** and the phosphoramidates **6a** and **10a** were observed even though all four compounds were isomerically pure. The origin of phosphoryl frequency doubling in trialkyl phosphates has been reviewed by several authors.[15] In some cases where the splitting is relatively small (e.g., 15 cm^{-1} for trimethyl phosphate) rotational isomerism has been postulated. However, in other instances a much larger splitting of up to 50 cm^{-1} is observed. In these cases the doubling has been attributed to Fermi resonance of the P=O band with an overtone.[15c] Since splittings for compounds **5b** and **9b** (18 and 19 cm^{-1}, respectively) are similar to that of trimethyl phosphate, it seems reasonable to postulate rotational isomerism of the methoxy group. The apparent absence of such rotational isomers in **5a** and **9a** seems reasonable since Dreiding models of these compounds reveal severe 1-3 steric interactions of the C4 and C6 axial protons when in the folded conformations. The single phosphoryl frequency can thus be attributed to the extended form. Structural support for the extended form of phosphate **5a** comes from the x-ray diffraction study of **11** in which the methyl group was found to be exocyclic to the ring.[16]



folded configuration extended configuration

5a



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For the phosphoramidates the ambiguities in the phosphoryl stretching region are more pronounced. The single frequencies for the **b** isomers of **6** and **10** are very similar in energy to the stronger of the two absorptions of the **a** isomers. This is in contrast to the large difference expected for axial vs. equatorial phosphoryl groups as observed for **3a,b** and **7a,b**. There is much evidence that a nitrogen directly bonded

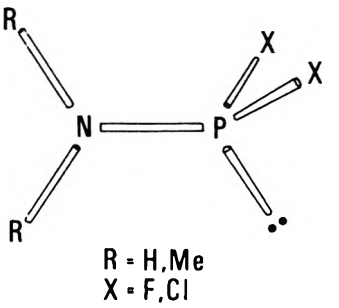
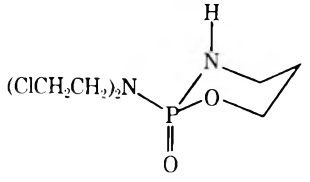


Figure 1. Conformation of compounds of the type R_2NPX_2.

to phosphorus assumes a planar configuration which bisects the X-P-X angle and eclipses the phosphorus lone pair vector[17] in trivalent phosphorus compounds (Figure 1). The crystal structure determinations of cyclophosphamide[18] (**12**)



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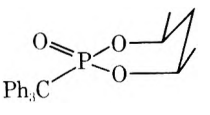
showed a similar phenomenon in the phosphorinane system since the exocyclic nitrogen plane nearly bisects the ring N-P-O angle and eclipses the P=O bond. This apparently stable coplanar relationship of the nitrogen configuration and the phosphorus substituent (oxygen or lone pair) presumably also holds for the phosphoramidates **6a,b** and **10a,b.** The presence of only one type of *N*-methyl group as shown from room temperature ^{1}H NMR spectra indicates rapid rotation about the P-N bond on the NMR time scale in both isomers of each compound. From the structural studies mentioned bove, however, the preferred NR_2 orientation would be as indicated in Figure 1. The single phosphoryl stretching frequency for the **b** isomers could be due to a comparatively low concentration of other rotameric contributions. The situation for the **a** isomers is complicated, however, by the fact that in a chair conformation with the preferred nitrogen orientation [Figure 2(a)], severe steric interactions occur between the *N*-methyl protons and the C4 and C6 axial protons. Two conformational changes could alleviate this problem: (1) rotation about the P-N bond by 90° to produce a stable chair conformation with a disfavored nitrogen configuration [Figure (2(b)] and (2) formation of a half-chair or "chaise longue" (as is found from the x-ray structural determination of **13**[19]). The relatively unstable ring conformation produced by the latter process would preserve the preferred nitrogen conformation [Figure 2(c)]. The presence of two such rotational conformers in isomer **a** of compounds **6** and **10** would be consistent with the appearance of two phosphoryl stretching frequencies. Indeed, the higher energy frequency for each **a** isomer is in the region expected for equatorial P=O and the low energy frequencies are very nearly the same as that observed for **13.**[1a]



13

Although temperature variation might be expected to cause a change in such rotamer ratios, this was not observed in the infrared spectra of **7a** in the range of 30-60 °C.

Two phosphoryl stretching frequencies are listed for both **4b** and **8b,** but their origin is not certain. It is not unreasonable to believe that the higher energy peak in the **b** isomers is due

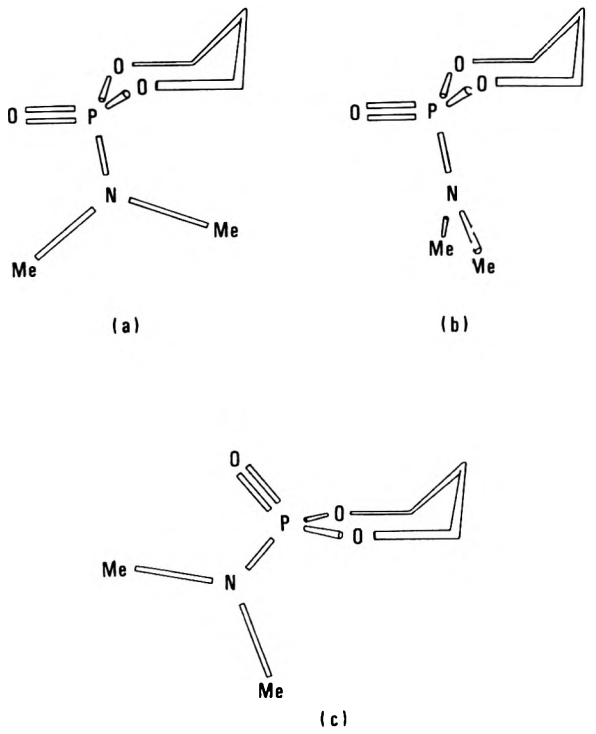
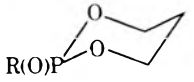


Figure 2. Possible conformations of the a isomer of 2-oxo-2-dimethylamino-4,6-dimethyl-1,3,2-dioxaphosphorinane and its 4-methyl analogue.

to a conformer which possesses a more equatorial P=O disposition arising from a twist or boat conformation. Such a conformer could also explain the rather large dipole moment observed for the **b** isomers. As noted in the introduction, it has been postulated that compounds with equatorial phosphoryl oxygens exhibit stretching frequencies at higher energy than those with axial phosphoryl oxygens. The results reported here, however, indicate that care must be exercised in using this criterion for assignment of phosphorus stereochemistry since isomerically pure compounds may display more than one phosphoryl frequency.

Conformational Equilibria. Conformational distributions of the compounds lacking ring carbon substituents were determined by comparison of dipole moments, ^{31}P chemical shifts, and infrared stretching frequencies of compounds **14–17** to those of the analogous isomeric 4,6-dimethyl compounds. The latter served as rigid models of the two chair conformations in the conformationally mobile systems.



R	Compd
Me	14
H	15
OMe	16
NMe_2	17

The first compound considered is the hydrogen phosphonate **15** since the preferred stereochemistry and equilibrium distribution are known for compounds **4a** and **4b** from thermodynamic data.[5b] The dipole moments, ^{31}P chemical shifts, and infrared phosphoryl stretching frequencies are listed in Table IV.

For calculation of the conformer distribution from dipole moment data, the equation $(Y)(\mu_A)^2 + (1 - Y)(\mu_B)^2 = (\mu)^2$ was employed. It was assumed that the dipole moment of **4a** (μ_A) was identical with the dipole moment of the conformer of **15** containing the equatorial P=O orientation, and that the dipole moment of **4b** (μ_B) was the same as that of the opposite

Table IV. Dipole Moments, ^{31}P Chemical Shifts, and Phosphoryl Stretching Frequencies of 2-R-2-Oxo-1,3,2-dioxaphosphorinanes[a]

Compd	μ[b]	$\delta^{31}P$[c]	$\bar{\nu}$(P=O)[d]
14	4.98	−24.2	1288 m, 1255 s
15	5.86	−2.26	1303 s, 1281 vw
16	5.63	6.7	1310 s
17	3.95	−6.22	1255 s

[a] All measurements were made on benzene solutions. [b] Given in Debye units with a precision of ±0.05 D. [c] Given in parts per million relative to external 85% H_3PO_4. [d] Given in cm^{-1}, s = strong, m = medium, w = weak, v = very.

Table V. Conformer Fractions of 2-R-2-Oxo-1,3,2-dioxophosphorinanes[a]

Compd	From μ	From $\delta^{31}P$	From $\bar{\nu}$(P=O)
14	0.32 (0.05)	0.43 (0.02)	0.4 (0.1)[b] 0.35 (0.1)[c]
15	0.58 (0.08)	0.85 (0.1)	0.8 (0.2)
16	0.63 (0.09)	0.8 (0.1)	0.8 (0.2)
17	0.0 (no estimate)	0.12 (0.06)	0.19 (0.09)

[a] The method of calculation is described in the text. The data refer to the fraction of equatorial conformer in solution. The numbers in parentheses are the errors calculated from precision limits. [b] Calculated assuming the extinction coefficient of **3b** to be the same as the lower energy peak of **14**. [c] Calculated assuming the extinction coefficient of **3b** to be the same as the higher energy peak of **14**.

conformation. Knowledge of the measured moment of **15** (μ) therefore allowed calculation of the fraction (Y) of **15** containing equatorial phosphoryl oxygen. The results are given in Table V with estimated precisional errors in parentheses. Since the ring methyl groups of **4a** and **4b** are symmetrically substituted, no ring distortions affecting the dipole moments are expected for these compounds. (Compounds with a single exocyclic methyl group such as **9a,b** were not used in these calculational studies since distortion is more likely and ring conformation changes by way of flipping are sterically less disfavored.) Substitution of a methyl group for a hydrogen does not introduce a significant change in the local dipole moment since the group moment is $(3 \cos 70.5°)(\mu_{C-H}) = (1.004)(\mu_{C-H})$, which is well within the experimental error of the carbon–hydrogen moment. Introduction of the methyl substituents may cause a change in ring angles which would slightly alter dipole moments, but no corrections were made for this possibility. Another possible source of error is the assumption that **4a** and **4b** are conformationally pure. Although there is no reason to believe that this is not the case for **4a**, **4b** apparently displays two phosphoryl stretching frequencies indicative of more than one conformation (vide supra). The reasonable assumption that no intermediate conformer of **15** makes a significant contribution to the dipole moment has also been made.

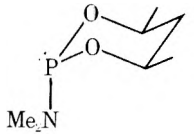
The conformational distribution of **15** was calculated from ^{31}P chemical shift data using the equation $(Y)(\delta_A) + (1 - Y)(\delta_B) = \delta$ (Table V) with similar assumptions to those made for the dipole moment data. The chemical shift of **4a** (δ_A) was assumed to be the same as that of the conformer of **15** containing equatorial P=O, and $\delta^{31}P$ for **4b** (δ_B) was taken to be equal to the axial P=O conformer of **15**. The same two error considerations present in the dipole moment studies also apply here since both are expected to influence the ^{31}P chemical shifts.

The infrared spectrum of **15** displayed two phosphoryl

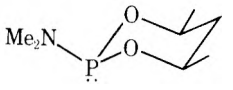
stretching frequencies (Table IV), indicative of two ring conformations. The higher energy absorption was assigned to the equatorial P=O and was assumed to have the same extinction coefficient as that calculated for **4a**. The concentration of this conformer was calculated and the fraction of total compound in that conformation determined (Table V). Any error introduced by assuming identical extinction coefficients is probably overshadowed by the large error in the determination of the absorbances from the nonlinear baselines of the spectra. The equilibrium distribution for **4a** and **4b** at 40 °C is about 90% **4a** and 10% **4b**,[5b] in much better agreement with the results of the ^{31}P and IR methods than with the dipole moment method. All three procedures, however, give the same qualitative result that equatorial phosphoryl is preferred for **15** and this also is consistent with a previous IR study.[10b]

Conformer distributions were calculated for the phosphate **16** (Table V) from the data in Table IV by the same procedures described for **15**. All three methods yield data which qualitatively corroborate the conclusion previously reported for analogous compounds, namely, that equatorial phosphoryl oxygen is preferred.[1c,4g,10c-e,11] Furthermore, the quantitative fractions calculated from ^{31}P and $\bar{\nu}$(P=O) data are in good agreement with those calculated by other workers from phosphoryl stretching frequency data of methyl, ethyl, and phenyl phosphates.[10g]

The dimethylamino substituent in **17** induces a behavior opposite to that of the hydrogen or methoxy compounds in that axial P=O is preferred (Table V). This difference can be ascribed to the same steric problems associated with an axial NMe_2 group in **18a** as described previously.[5a] The tentative



18a

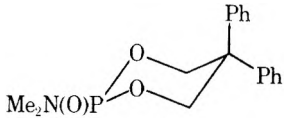


18b

evidence for axial preference of the P=O group from hydrolysis data on **6a,b**[5a] is thus substantiated by the dipole moment, ^{31}P chemical shift, and $\bar{\nu}$(P=O) data for **17**.

An indication of the presence of error in calculating conformer ratios derived from P=O stretching frequency data is now demonstrated with **16** as an example. Only one peak was observed in the spectrum of **16** indicating 100% equatorial P=O. Using the extinction coefficient determined from the P=O mode in **5a** for the analogous peak in **16**, the conformer fraction given in Table V was obtained. Either the peak from the other conformer is so weak as to be unobserved, or the calculations are inaccurate.

Axial P=O preference was initially reported by Majoral and co-workers[10c,e,f,11] for the amino compounds **19** and **20**, but



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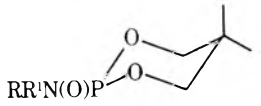


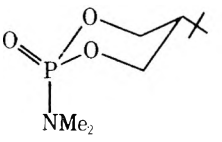
R	R'	Compd
Me	Me	20
n-Pr	H	21
t-Bu	H	22
n-Pent	H	23

they later questioned this conclusion[11] in view of dipole moment studies reported by Kainosho et al.[12] for compounds **20–23** from which the latter authors inferred an equatorial P=O preference. Bentrude and Tan have obtained NMR evidence for the greater stability of axial P=O from compounds **24a,b**[2b,c] and our own results definitely support this conclusion for R_2N substituted derivatives.

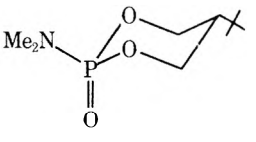
Table VI. Thermodynamic Data for the Conformer Equilibria of 2-Methyl-2-oxo-1,3,2-dioxaphosphorinane (14)[a]

Temp, °C	K_{eq}[b]	Temp, °C	K_{eq}[b]
5	0.76	50	0.53
15	0.68	60	0.52
31	0.62	68	0.47
40	0.57		

[a] Benzene solutions. [b] K_{eq} equals the amount of equatorial phosphoryl conformer divided by the amount of axial phosphoryl conformer.



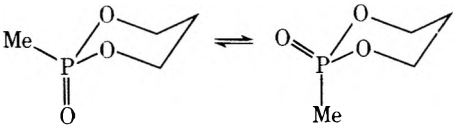
24a



24b

Phosphonates do not appear to display a strong conformational preference[10c,g,11,19,20] and the distributions calculated for the methyl phosphonate **14** (Table V) are consistent with these findings. Two values are calculated from the P=O stretching frequency data; for one it is assumed that the extinction coefficient of **2a** is the same as that of the equatorial P=O conformer of **14** and for the other it is ssumed that the extinction coefficient of **3b** is the same as that of the axial P=O conformer of **14**. All the calculations indicate a somewhat favored axial phosphoryl orientation, which is consistent with previosly reported results.[10g,20]

It is important to note that all of the calculations are based on distributions at or near room temperature with benzene as the only solvent. Indeed, infrared P=O intensities have been reported to be temperature and solvent dependent.[10b,c,g,11] Although benzene was the sole solvent used in the present studies, variable temperature infrared spectra have been obtained for compound **14**. From the data listed in Table VI, values of ΔH and ΔS were calculated to be −1.34 kcal/mol and −5.38 cal/mol·deg, respectively, for the interconversion indicated below, with $\Delta G° = +0.16$ at 25 °C. These



17

values are in reasonable agreement with those reported for phenyl phosphonates calculated from NMR and IR data.[10g] Formation of the equatorial P=O conformer is therefore favored at lower temperature, but the solvent did not permit investigations at temperatures below 5 °C. Low-temperature ^{31}P chemical shifts were essentially unchanged from those measured at 25 °C. The high polarity of $CFCl_3$ as a solvent in this experiment could cause the more polar equatorial P=O conformer to predominate in the low temperature range.

Conclusions

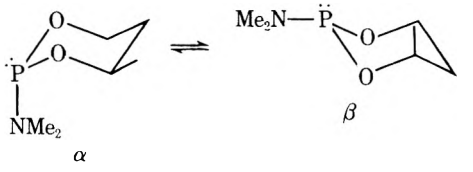
From the results given here, we conclude that the most appropriate instrumental techniques for the determination of phosphorus stereochemistries of conformationally rigid 2-R-2-oxo-1,3,2-dioxaphosphorinanes are dipole moment measurements and LIS experiments. ^{31}P chemical shift and

Table VII. $J(POCCH_3)$ Data for 4-Methyl- and 4,6-Dimethyl-1,3,2-dioxaphosphorinanes

Compd	$J(POCCH_3)$, Hz	Compd	$J(POCCH_3)$, Hz
3a	1.7	**7a**	1.6
3b	1.6	**7b**	1.6
4a	1.7	**8a**	1.9
4b	1.8	**8b**	1.3
5a	2.2	**9a**	2.5
5b	2.2	**9b**	1.9
6a	2.2	**10a**	1.6
6b	2.2	**10b**	2.2

infrared phosphoryl stretching frequency criteria are more ambiguous and can lead to erroneous conclusions. However, for the semiquantitative determination of conformational distributions in equilibria of mobile phosphorinanes, ^{31}P chemical shifts and infrared stretching frequencies may be more accurate if the phosphorous stereochemical assignments have been correctly made. This conclusion is based on the similarity of the thermodynamic data for the equilibrium of **4a** and **4b** and the results for compound **15.**

The isomeric 4,6-dimethyl ring carbon substituted compounds appear to be better representations of conformationally pure compounds than the corresponding 4-methyl compounds for the following reasons. The coupling constants $J(POCCH_3)$ given in Table VII range from 1.6 to 2.5 Hz for all 4,6-dimethyl isomers investigated (**3a,b–6a,b**), for the 4-methyl isomers containing preferred phosphorus configurations (**7b, 8a, 9a,** and **10b**), and also for **7a,** which probably differs little in energy from **7b.** The 4-methyl isomers with unstable phosphorus configurations (**8b, 9b,** and **10a**), however, all have coupling constants which are 0.6 Hz smaller. Although a difference of 0.6 Hz is too small for a meaningful quantitative analysis, it may be indicative of a significant contribution from other conformers arising from ring flipping or twisting. Some evidence for this possibility stems from the recent report of Cogne et al. who found that the trivalent compound **25** exists in the two conformations depicted below



25

with an α/β ratio of 85:15.[2d] The dipole moment data are reasonably consistent with this postulate since compounds **6b** and **10b** have measured moments within experimental error of each other, whereas those of the unstable configurations **6a** and **10a** differ substantially. The same is also true for **3b** and **7b** compared to **3a** and **7a,** although the smaller preference for a specific phosphorus configuration might be expected to produce a smaller difference in moment for **3a** and **7a.** For the hydrogen phosphonates and the phosphates, the 4,6-dimethyl isomers represent dipole moment *extrema* with the 4-methyl isomers intermediate in value. Thus in general, the 4,6-dimethyl isomers are probably better model compounds for axial and equatorial substituents than are the 4-methyl compounds, since the latter are more apt to exist as ring flipped or twisted conformers. Comprehensive NMR spectral analyses of compounds **7a,b–10a,b** are currently underway to determine the extent of chair–chair and chair–nonchair interconversions in 4-methyl compounds.

Experimental Section

The syntheses of the starting materials (*meso*-2,4-pentanediol and 2-chloro-4,6-dimethyl-1,3,2-dioxaphosphorinane) have been described previously.[21] Isomers of the 4,6-dimethyl substituted compounds [2-methoxy-,[5a,20] 2-methoxy-2-oxo-[5a] (**5a,b**), 2-dimethylamino-2-oxo-[5a] (**6a,b**), and 2-hydro-2-oxo-1,3,2-dioxaphosphorinanes[5b] (**4a,b**)] were prepared as previously described. The corresponding 4-methyl-1,3,2-dioxaphosphorinane isomers, as well as the 1,3,2-dioxaphosphorinanes lacking ring substituents, were prepared in a similar manner.

2β-Methyl-2α-oxo-4α,6α-dimethyl-1,3,2-dioxaphosphorinane (3a) and 2α-Methyl-2β-oxo-4α,6α-dimethyl-1,3,2-dioxaphosphorinane (3b). These compounds were synthesized from the equatorial and axial methyl phosphite analogues, respectively. Approximately three times the phosphite volume of methyl iodide was added and the solutions were stirred overnight. The products, obtained in nearly quantitative yields, were sublimed at 55 and 40 °C, respectively (ca. 0.5 mm). Anal. Calcd for $C_6H_{13}O_3P$: C, 43.90; H, 7.98; P, 18.87. Found for **3a:** C, 43.50; H, 8.09; P, 18.44. Found for **3b:** C, 44.23; H, 7.90; P, 18.81.

These compounds were reported earlier[22] as a mixture resulting from the reaction of $OPMeCl_2$ and diol.

2β-Methyl-2α-oxo-4α-methyl-1,3,2-dioxaphosphorinane (7a) and 2α-Methyl-2β-oxo-4α-methyl-1,3,2-dioxaphosphorinane (7b). Syntheses of these compounds were analogous to those described above except that purification was facilitated by vacuum distillation at 93 °C (0.3 mm) and 57 °C (0.15 mm), respectively. Yields were essentially quantitative.

2-Methyl-2-oxo-1,3,2-dioxaphosphorinane (14). This compound was prepared in nearly quantitative yield in the manner described above from the appropriate phosphite and sublimed at 50 °C (0.5 mm). Its melting point (98–99 °C) is in good agreement with that reported earlier for this compound (98–99.5 °C) prepared by reacting $OPMeCl_2$ with 1,3-propanediol.

^{31}P Chemical Shifts. The shifts observed in benzene solution were obtained by standard INDOR techniques employing a Varian Associates HR-60 NMR spectrometer operating at 60 MHz. Positive shifts were assigned to those resonances which appeared at higher field than the external standard, which was 85% H_3PO_4.

Infrared Spectra and Phosphoryl Stretching Frequency Assignments. A Beckman IR-12 operated at sweep speeds of 40 cm^{-1}/s was employed to obtain ambient temperature spectra which were all calibrated with polystyrene. Benzene solutions ca. 0.05 M in solute were used in cells with a 0.1-mm path length and benzene in a 0.1-mm cell was employed in the reference beam. The phosphoryl stretching frequencies of the hydrogen phosphonates were assigned by comparison of samples 80 atom % ^{18}O-enriched in phosphoryl oxygen to normal isotope abundance cmmpounds prepared by the same procedure (vide supra). These were further compared to samples of pure isomers of normal isotope distribution. The phosphoryl stretching frequencies of the other 15 compounds were assigned by comparison of spectra of pure compounds in benzene solution to solutions of compound in benzene saturated with iodine. The weak iodine complex formed caused a decrease in the free phosphoryl absorption with concurrent appearance of a broader absorption about 40 cm^{-1} lower in energy.

Variable-temperature IR spectra were obtained with a Beckman IR-8 spectrometer with a sample cell whose temperature could be controlled with water circulating through a surrounding jacket. Reported temperatures are probably no more accurate than ±3 °C at the extremes.

Dipole Moment Measurements. The instrumentation and data treatment have been described in detail elsewhere.[24] Four solutions of each compound ranging in concentration from about 1 to 10×10^{-3} mole fraction in benzene solution prepared under nitrogen were employed.

LIS Experiments. These were carried out on $CDCl_3$ solutions 0.2 M in solute and 0.1 M in tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione)europium(III) [Eu(fod)$_3$] using a Varian Associates HA-100 NMR spectrometer.

Other Instrumentation. Routine ^1H NMR spectra were obtained on either a Varian Associates A-60 NMR spectrometer or an Hitachi Perkin-Elmer R20-B spectrometer operating at 60 MHz. Mass spectra of all the compounds used in this study displayed parent ion peaks at 19 or 70 eV on an Atlas CH-4 single focusing mass spectrometer. Liquid compounds were mixed with powdered molecular sieve before spectra were run.

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Registry No.—**3a**, 61558-34-7; **3b**, 61616-95-3; **4a**, 39762-82-8; **4b**, 39762-83-9; **5a**, 41158-22-9; **5b**, 41158-23-0; **6a**, 41158-15-0; **6b**, 41158-16-1; **7a**, 52265-58-4; **7b**, 52265-59-5; **8a**, 26339-67-3; **8b**, 26339-68-4; **9a**, 33996-03-1; **9b**, 33996-04-2; **10a**, 41158-21-8; **10b**, 41158-20-7; **14**, 13407-03-9; **15**, 16352-21-9; **16**, 33554-05-1; **17**, 61558-35-8; equatorial methyl phosphite, 7735-82-2; axial methyl phosphate, 7735-86-6; 2-methyl-1,3,2-dioxaphosphorinane, 61558-36-9; methyl iodide, 74-88-4.

Supplementary Material Available. A listing of the dielectric, refractive index, and orientation polarization data (1 page). Ordering information is given on any current masthead page.

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Δ^2-1,2,4-Oxadiazolines. 1. Molecular Orbital Calculations, Absorption, and Fluorescence Spectra

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Molecular orbital calculations of five Δ^2-1,2,4-oxadiazolines and one oxadiazole have been carried out using a CNDO/2 method. The results are in accordance with the experimentally observed values. The calculations strongly support a planar cyclic structure. Striking differences have been observed between the fluorescence spectra of the oxadiazolines and the oxadiazole. An explanation of this behavior is advanced. A facile aromatization of 5-ethyl-3-phenyl-Δ^2-1,2,4-oxadiazoline to 5-ethyl-3-phenyl-1,2,4-oxadiazole is described.

Substituted 1,2,4-oxadiazoles have been found to exhibit various types of biological activity including analgetic, sedative,[2] fungicidal and insecticidal.[3] Some of them are also anthelmintic when tested against *Nematospiroides dubius*.[4] Δ^2-1,2,4-Oxadiazolines are partially saturated oxadiazoles and comparatively less work has been done on the former. McCowen et al.[4] have tested a few of them for anthelmintic activity although the results were negative. To our knowledge, the molecular orbital calculations and the fluorescence spectra of oxadiazolines have not yet been reported in the literature. We plan to study the following: (a) absorption and fluorescence spectra, (b) the chemistry of the ring, (c) biological activity, and (d) mass spectra. This article deals principally with item a.

We have already prepared six compounds in small quantities. Activity testing will be undertaken as soon as larger quantities are available. This paper deals with the molecular orbital calculations and the absorption and fluorescence spectra of five oxadiazolines, i.e., 5-ethyl-3-phenyl-Δ^2-1,2,4-oxadiazoline (Ia), 5-ethyl-3-(*p*-tolyl)-Δ^2-1,2,4-oxadiazoline (Ib), 3-(*p*-anisyl)-5-ethyl-Δ^2-1,2,4-oxadiazoline (Ic), 3-(*p*-chlorophenyl)-5-ethyl-Δ^2-1,2,4-oxadiazoline (Id), and 5,5-pentamethylene-3-phenyl-Δ^2-1,2,4-oxadiazoline (III), and one oxadiazole, 5-ethyl-3-phenyl-1,2,4-oxadiazole (II). (See Figure 1.) In addition, an easy formation of II from Ia is discussed.

Experimental Section

The solvents used for spectroscopy were chloroform (Merck, Uvasol) and 2-propanol (Aldrich, spectrograde). Neither had detectable fluorescence upon excitation at the wavelengths used.

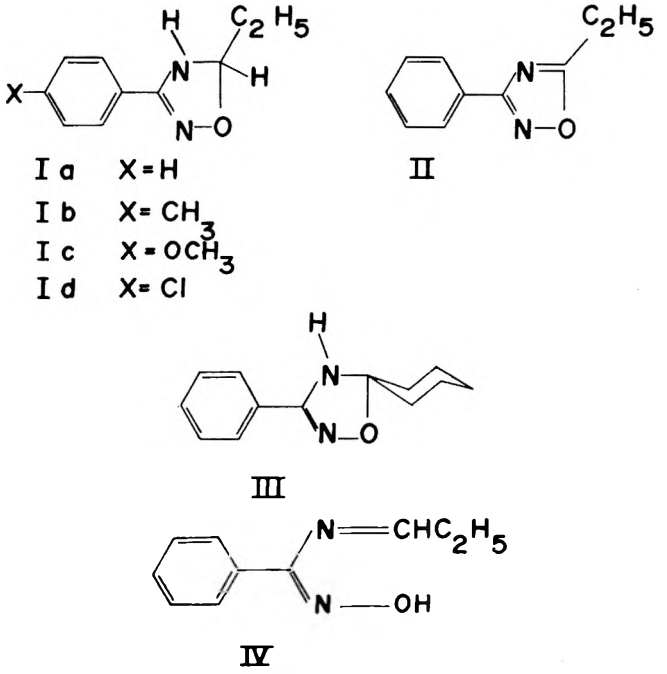

Figure 1. Structures of the molecules treated in this study. (I) 5-ethyl-3-(*p*-X-phenyl)-Δ^2-1,2,4-oxadiazoline, (II) 5-ethyl-3-phenyl-1,2,4-oxadiazole, (III) 5,5-pentamethylene-3-phenyl-Δ^2-1,2,4-oxadiazoline, and (IV) *N*-ethylidenebenzamidoxime (possible open structure of $C_{10}H_{12}N_2O$).

Infrared spectra were obtained on a Perkin-Elmer Model 337 spectrometer. A Varian A-60 and a Varian XL-100 spectrometer have been employed for the nuclear magnetic resonance spectra. Tetramethylsilane was used as internal reference. The fluorescence spectra were taken on an Aminco-Bowman spectrophotofluorimeter (employing a 1P21 photomultiplier) attached to a Hewlett-Packard 7005 B X-Y recorder. All fluorescence spectra were corrected by the method[5] of Chen. The absorption spectra were measured on a Jena Specord spectrophotometer.

Melting points are uncorrected. For thin layer chromatography, silica gel G (Type 60, Merck) has been employed. Benzene–chloroform (1:1) or chloroform was used as developer and iodine vapor for the detection of the spots.

Amidoximes. The amidoximes were prepared as described[6] previously.

5-Ethyl-3-phenyl-Δ^2-1,2,4-oxadiazoline (Ia). This was prepared by the known method.[7] The material obtained was chromatographed over silica gel to remove the starting amidoxime.

The 100-MHz NMR spectrum showed signals at δ 1.00 (3 H, t, CH_3), 1.6–1.96 (2 H, m, CH_2), 5.38 (1 H, b, NH), 5.64 (1 H, q, $J \approx 5$ and 4 Hz), and 7.20–7.76 (5 H, m, Ar).

5-Ethyl-3-(*p*-tolyl)-Δ^2-1,2,4-oxadiazoline (Ib). *p*-Tolylamidoxime (3.64 g, 0.024 mol) dissolved in 800 mL of ethanol–water (1:7) was added to freshly distilled propionaldehyde (1.55 g, 0.027 mol) and allowed to stand at room temperature in a stoppered flask for 16 days. The reaction was followed by thin layer chromatography. Some starting material remained unreacted. At this point the solution was transferred to a separatory funnel, extracted with ether (3 × 75 mL), dried over sodium sulfate, and filtered and the solvent was removed.

The total material, after chromatography over 30 g of silica gel using benzene–chloroform (1:1) as eluent, afforded various fractions containing pure oxadiazoline. Removal of the solvent gave 4 g of crystalline solid, mp 90 °C. Recrystallization from ethanol yielded 3.65 g (79%) of pure crystals, which melted at 95 °C.

The compound was dried at 60 °C for 4 h under vacuum.

Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.47; H, 7.42; N, 14.72. Found: C, 69.40; H, 7.41; N, 14.70.

The NMR spectrum (CCl_4) consisted of signals at δ 2.35 (3 H, s) 5.5 (1 H, q, CH), 5.20 (1 H, b, NH), and 7.27 (4 H, AB q, $J \approx 8.0$ Hz, Ar).

3-(*p*-Anisyl)-5-ethyl-Δ^2-1,2,4-oxadiazoline (Ic). *p*-Anisylamidoxime (1 g, 0.006 mol) was dissolved in 350 mL of water and propionaldehyde (0.38 g, 0.007 mol) was added. The solution was then kept at room temperature for 25 days. Workup followed by chromatography as described for Ib afforded the pure material. Recrystallization from chloroform–hexane provided 0.8 g (64.5%) of crystals, mp 102–103 °C.

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.06; H, 6.83; N, 13.55.

The NMR spectrum ($CDCl_3$) had peaks at δ 3.85 (3 H, s, OCH_3), 5.05 (1 H, b, NH), 5.70 (1 H, q), and 7.32 (4 H, AB pattern, $J \approx 9$ Hz, Ar). When the spectrum was run in a mixture of CCl_4 and CH_3OD a triplet appeared for the C_5 proton at δ 5.70.

3-(*p*-Chlorophenyl)-5-ethyl-Δ^2-1,2,4-oxadiazoline (Id). Id was prepared as described above and after purification 48% of the crystalline compound with mp 105 °C was obtained.

Anal. Calcd for $C_{10}H_{11}N_2OCl$: C, 57.03; H, 5.23; N, 13.30. Found: C, 57.02; H, 5.25; N, 13.30.

The NMR spectrum ($CDCl_3$) showed signals at δ 4.97 (1 H, b, NH), 5.62 (1 H, q, CH), and 7.4 (4 H, AB q, $J \approx 9.0$ Hz, Ar).

5-Ethyl-3-phenyl-1,2,4-oxadiazole (II). To Ia (0.4 g, 0.002 mol) in 50 mL of benzene was added *N*-bromosuccinimide (0.4 g, 0.002 mol) and a few crystals of azobisisobutyronitrile. The mixture was refluxed for 30 min and cooled. Washing of the benzene layer with 5% aqueous sodium carbonate solution, drying over sodium sulfate, filtration, and solvent removal gave a liquid weighing 0.35 g. Distillation provided a colorless liquid. Owing to the limited quantity obtained, the boiling point could not be determined.

The infrared spectrum was consistent with the structure assignment. The NMR spectrum ($CDCl_3$) showed signals at δ 1.42 (3 H, t, CH_3), 2.97 (2 H, q, $-CH_2-$), 8.22 (2 H, aromatic, ortho), and 7.55 (3 H, aromatic, meta and para).

5,5-Pentamethylene-3-phenyl-Δ^2-1,2,4-oxadiazoline (III). By modification of the previously published method[4] the yield was improved from 25% to 46%. Benzamidoxime (2 g, 0.015 mol), cyclohexanone (1.48 g, 0.015 mol), and 30 mL of glacial acetic acid were heated at 70–90 °C for 5 h. Removal of acetic acid under vacuum, dissolution of the residue in ether, washing the solvent layer with a saturated solution of sodium bicarbonate (aqueous), drying over sodium sulfate, and solvent removal left a solid. On a thin layer chromatogram it showed the presence of starting material and some other impurities. Chromatography over 15 g of silica gel followed by elution with chloroform gave 1.45 g (46%) of chromatographically pure and crystalline substance, which upon recrystallization from ethanol provided the compound which melted at 160 °C (reported[4] 160–161 °C).

The NMR spectrum ($CDCl_3$) showed signals at δ 1.33–2.30 (10 H, m, CH_2), 4.66 (1 H, b), and 7.3–8.08 (5 H, m, Ar).

Table I. Molecular Orbital Calculation Results

	μ_{Gd}, D	μ_{S^*}, D	E_{S^*}, eV	*f*
Ia[a]	4.90	8.98	7.36	0.26
Ib[a]	5.09	8.46	7.33	0.31
Ic[a]	4.97	9.02	7.32	0.32
Id[a]	4.33	9.47	7.26	0.33
II[a]	1.55	2.32	7.35	0.00
III[b]	4.88	8.87	7.44	0.27
IV[c]	1.02	10.37	2.13	0.00
V[d]	3.69	9.41	4.23	0.00

[a] A methyl group is substituted in the 5 position in place of the ethyl group. [b] Two methyl groups are substituted for the pentamethylene group. [c] Corresponding open-chain; *N*-ethylidenebenzamidoxime. [d] Nonplanar heterocyclic structure with oxygen out of plane.

Methods

Description of the Molecular Orbital Calculations. The calculations are a modified CNDO/2 type with the excited singlet states being calculated by taking the solution of the ground state as the basis set, constructing 64 singly excited configurations, being all of the possibilities N − 7, . . . , N → N + 1, . . . , N − 8 (N being the HOMO), and diagonalizing the configuration interaction matrix.[8]

The modifications in the original CNDO/2 formulation are the following: (1) Instead of using the Slater orbital exponents (ξ) a set of "best" exponents was used which was obtained from the reported[9] results on a series of small molecules by

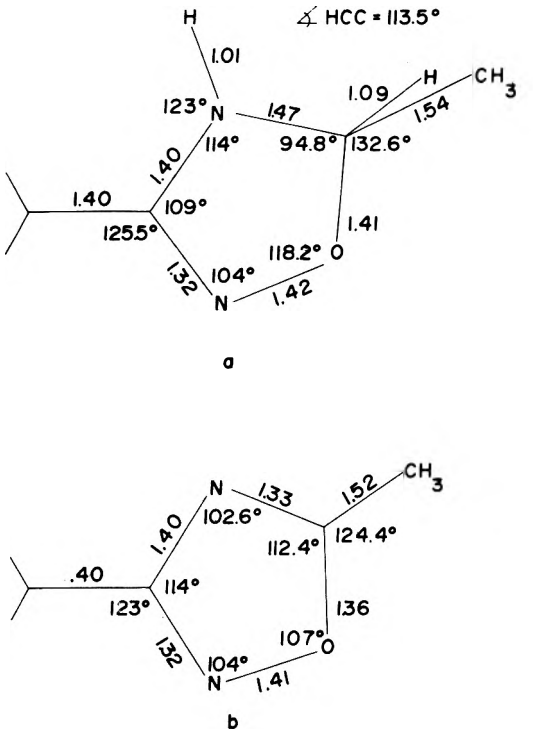

Figure 2. Assumed geometries of the heterocyclic ring in the molecular orbital treatment of (a) the Δ^2-1,2,4-oxadiazolines (angles shown at position 5 between ring atoms and the hydrogen and methyl substituents are with respect to the latters' projection in the plane of the ring; the C–CH_3 and C–H bonds at position 5 make the same angle with the plane of the ring) and (b) 1,2,4-oxadiazole.

means of INDO.[10] (2) Cl was taken to be a pseudo-second-row atom, following the suggestion of Kollman et al.,[11a] and their value of ξ was retained. The α and β values used were from Deb and Coulson.[11b] (3) The overlap integrals were calculated using the summations of Silver and Ruedenberg.[12] (4) The criterion for convergence was taken by comparison of the differences in the bond order matrix[13] between consecutive diagonalizations. Convergence was considered to obtain when (a) not a single element within the bond order matrix changed as much as 0.01, and (b) the sum of the absolute differences was not greater than $0.001J$ (J being the number of orbitals).

Standard geometry[14] was assumed, with the exceptions of the oxadiazole and oxadiazoline rings. These, because of angle strain in 5-membered rings, could only be constructed to satisfy the Pople–Gordon geometry if the ring was taken as nonplanar. Calculations on oxadiazoline showed a totally planar ring to be more stable than one with the oxygen out of the plane (structure V, Table I) by some 4 eV. (In addition, the latter is predicted to have an extremely weak first transition, contrary to what is observed experimentally.) Therefore, a planar structure was chosen. (See Figure 2.) An open structure for oxadiazoline was also considered. (See Discussion.) The calculations were made substituting a methyl group for the ethyl group and two methyl groups for the pentamethylene substituent. This involved a saving in computation time and memory space. Preliminary calculations showed the wave function to be basically unchanged. II was also taken as totally planar. The geometry assumed is shown in Figure 2.

Results

Synthesis. Condensation of benzonitrile or substituted benzonitrile with hydroxylamine hydrochloride in alcoholic solution containing sodium carbonate provided the corresponding amidoximes in 32–70% yield. The amidoximes, when allowed to react with propionaldehyde, provided the desired oxadiazolines, Ia–d. Three of these, Ib–d, have not been reported previously. Compound Ia, when allowed to react with *N*-bromosuccinimide in the presence of a catalytic amount of azobisisobutyronitrile, readily afforded II.

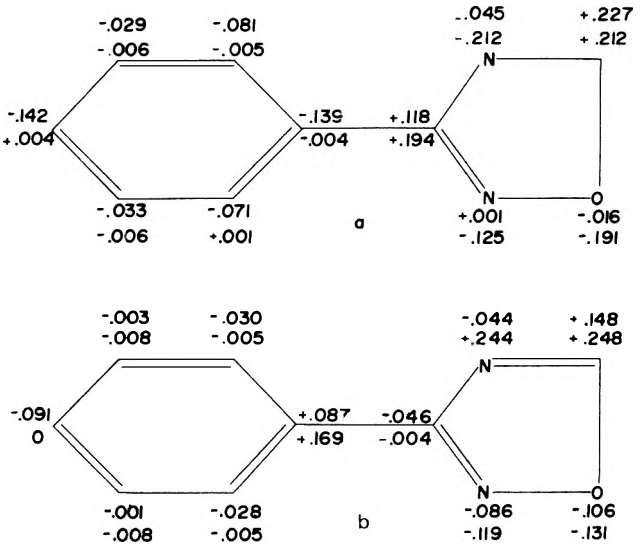

Figure 3. Calculated charges on ring atoms (electronic units). First excited singlet shown above ground state: (a) 5-methyl-3-phenyl-Δ^2-1,2,4-oxadiazoline, and (b) 5-methyl-3-phenyl-1,2,4-oxadiazole.

Table II. Experimental Spectroscopic Results

	Chloroform (ϵ 4.8)		2-Propanol (ϵ 18.3)		
	λ_{abs}, nm	λ_{Fl}, nm	λ_{abs}, nm	λ_{Fl}, nm	f_{CHCl_3}
Ia	285	415	292	439	0.18
Ib	283	407	289	433	0.25
Ic	283	427	285	437	0.46
Id	291	436	301	449	0.37
II	284	310	284	304	0.00
III	291	410	297	414	0.13

Molecular Orbital Calculations. Perhaps the most striking feature of the calculated results (Table I) is the large dipole moment (approximately 5 D) of all of the oxadiazolines in the ground state, whereas the oxadiazole dipole moment (1.6 D) is considerably smaller. Supporting experimental evidence is found in the qualitative observation that Ia–d are not perceptibly soluble in *n*-hexane, whereas II is. We also note that the excited singlet dipole moments for Ia–d increase dramatically (to approximately 9 D) whereas the increase in the dipole moment of II upon excitation is considerably smaller. (See Figure 3.) In considering the calculated energies of excitation we note that they are basically constant for all I and II. The calculated oscillator strengths are reasonably close to the experimental ones, correctly predicting the first excited singlet of II to be an n–π^* state.

Absorption and Fluorescence Spectra. The experimental spectroscopic results are shown in Table II. We point out five salient factors in these results. The first is that the absorption peak for the first excited state is basically the same for Ia and II, whereas the fluorescence peak of Ia is far to the red of that of II. Because the Ia fluorescence peak is also far to the red of what might be expected from a double ring planar system (in comparison, diphenyl in solution shows[15] a doublet fluorescence band which centers at approximately 310 nm), excimer formation appeared to be a very real possibility. However, no concentration dependence was found in the fluorescence spectra. In addition, the wavelength of the maximum at liquid air temperature is not radically different

from that at room temperature. Excimer formation was thus ruled out.

The second point is that although the p-Cl substituent causes a shift to longer wavelength, both p-CH_3 and p-CH_3O shift the absorption and fluorescence to shorter wavelength. This is in apparent contradiction to the general rule that any substituent (by increasing the size of the molecule) will cause a red shift according to the free electron theory. Thirdly, we point out that an electron-donating substituent on the phenyl ring (CH_3O and CH_3) has the opposite effect on absorption as that of an electron-donating substituent on the oxadiazoline ring, pentamethylene. Fourth, pentamethylene red shifts absorption but blue shifts fluorescence. Finally, we indicate that the shifts due to increasing the polarity of the solvent are to the red for the oxadiazolines, but blue for the oxadiazole.

Discussion

Synthesis and Structure. Δ^2-1,2,4-Oxadiazolines have been known for a long time. Previous workers simply assumed a cyclic structure without explanation, although there exists the possibility of an open structure (Figure 1). A recent infrared study found[16] that the NH stretching frequency generally occurred around 3400 cm^{-1}, supporting the cyclic structure. Our molecular orbital calculations on both 5-methyl-3-phenyl-Δ^2-1,2,4-oxadiazoline and N-ethylidenebenzamidoxime indicate the former to be more stable by some 10 eV. In addition, the calculations predict the first excited singlet state for the open structure to be due to an n–π^* transition, plainly in conflict with experiment. (See Table I.) The mass spectra results[17] also support this structure.

In the 100-MHz NMR spectrum the methine proton (H-5) appeared at δ 5.64 as a quartet. When the methyl protons were irradiated, there was no change on H-5, indicating the absence of any long-range coupling. Irradiation of the methylene protons at δ 1.76 collapsed the H-5 signal to a doublet with $J \approx 4.0$ Hz. In this double resonance spectrum the 5.0-Hz coupling was lost. This J value between H-5 and methylene protons was verified by deuterium exchange, wherein CH appeared as a triplet with $J \approx 5.0$ Hz. The double resonance experiment confirms the existence of a cyclic structure and rules out the open-chain form, IV.

Regarding the mechanism of the formation of II, presumably 4-bromo-5-ethyl-3-phenyl-Δ^2-1,2,4-oxadiazoline was an intermediate followed by the quick elimination of hydrogen bromide to give II. The possibility of another intermediate, 5-bromo-5-ethyl-3-phenyl-Δ^2-1,2,4-oxadiazoline, cannot be eliminated. It was not possible to isolate any of these intermediates under the experimental conditions because HBr elimination was quite fast. In any event, either of the intermediates would lose HBr to provide oxadiazole. Compound II has previously been prepared[18] by another method.

Absorption and Fluorescence Spectra. The experimental spectroscopic results can be explained on the basis of the following model: (1) the oxadiazoline ring is planar and in the same plane as the phenyl ring; (2) the ground state of Ia–d has a high dipole moment, the phenyl ring donating electrons to the heterocyclic ring; (3) II is also totally planar, however the ground state dipole moment is much lower; (4) the dipole moment of the first excited state of Ia–d is considerably larger than in the ground state, but with the heterocyclic ring donating electrons to the phenyl ring; (5) the first excited singlet state of II is only slightly more polar than its ground state, and the oxadiazole ring is negative in both cases.

Therefore we attribute the general blue shift of electron-donating groups (CH_3 and CH_3O) on the phenyl ring to stabilization of the ground state and destabilization of the excited state. The large fluorescence red shifting of Ia–d with respect to II we attribute to solvent stabilization of the former owing to the much larger excited state dipole moment of the former [$\Delta G_{solv} = \Delta G(\mu^2)$]. The effect of the pentamethylene substituent is to red shift absorption by means of stabilization of the excited state and destabilization of the ground state. However, the blue shifted fluorescence we explain on the basis of less solvation stabilization in the excited state owing to a smaller excited state dipole moment in III than Ia. All of these explanations are consistent with the results presented in Table I; however, the last does exaggerate the calculated differences.

Concluding Remarks. Oxadiazoles and oxadiazolines apparently have very similar structures and were expected to have similar electron distributions. We have calculated strikingly different wave functions in the two cases both in the ground and the first excited singlet state. These calculations are supported by spectroscopic results. We suggest that the biochemical behavior of oxadiazolines will be found to be very different from that of the corresponding oxadiazoles.

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Registry No.—Ia, 37467-27-9; Ib, 61477-41-6; Ic, 61477-42-7; Id, 61477-43-8; II, 10364-68-8; III, 16013-20-0; propionaldehyde, 123-38-6; p-tolylamidoxime, 19227-13-5; p-anisylamidoxime, 5373-87-5; p-chlorophenylamidoxime, 5033-28-3; benzene, 71-43-2; benzamidoxime, 613-92-3; cyclohexanone, 108-94-1.

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Fluorination with Xenon Difluoride. Stereochemistry of Fluorine Addition to Phenyl-Substituted Olefins

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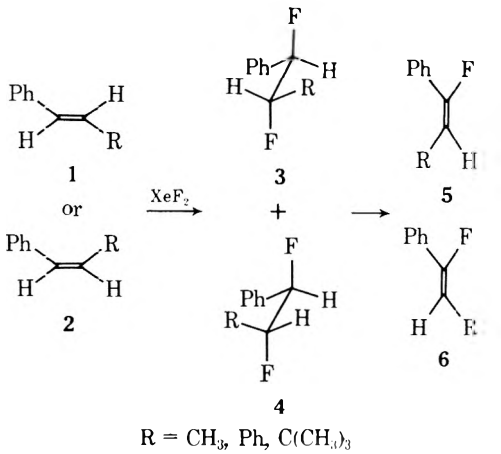
Acid-catalyzed liquid-phase fluorine addition with xenon difluoride to phenyl-substituted olefins, e.g., *cis*- and *trans*-1-phenylpropene, *cis*- and *trans*-stilbene, and *cis*- and *trans*-1-phenyl-2-*tert*-butylethene, results in the formation of vicinal difluorides in high yield. The reaction is nonstereospecific. Reaction with indene results in the formation of 70% trans and 30% cis adduct. The formation of β-fluorocarbonium ions is suggested.

The preparation of fluoroalkanes presents a different problem from that of the other haloalkanes, and necessitates a specific method of fluorination.[1] Recently, we observed that xenon difluoride readily adds fluorine to phenyl-substituted olefins[2,3] and acetylenes[4] in the presence of hydrogen fluoride as catalyst to give the corresponding 1,2-difluoro- or 1,1-2,2-tetrafluorophenylethanes in high yields and under mild conditions. When the same reactions were catalyzed by trifluoroacetic acid, the competitive fluoro trifluoroacetates also accompanied the difluorides.[3] In the course of our efforts to elucidate the stereochemistry and the reaction mechanism of fluorine addition to olefinic double bonds with xenon difluoride, and to compare it to molecular fluorine addition, or in general to other halogen additions, we found it instructive to fluorinate some trans (1) and cis (2) isomers of phenyl-substituted olefins. We chose these olefins because the stereochemistry of their halogenations is well known,[5] and so there was a possibility of drawing conclusions from the stereochemical results about the reaction pathway.

Results and Discussion

First we shall consider the identification of the products formed in the HF-catalyzed reactions of isomeric olefins (1, 2) with XeF_2 in various less polar solvents (methylene chloride, chloroform, carbon tetrachloride). Under these conditions *dl*-erythro (3) and *dl*-threo (4) difluorides were formed. They were separated by preparative GLC or TLC and their mass and ^{19}F and ^{1}H NMR spectra were recorded. The structures of the products were assigned from the products formed when the difluorides (3 or 4) were treated with base under conditions suitable for trans elimination. The products (*cis*-fluoro 5 and *trans*-fluoro 6 alkenes) were identified on the basis of differences in their NMR spectra: $J_{FH\text{-}trans} > J_{FH\text{-}cis}$ (Scheme I). The product distribution in the HF-catalyzed addition of fluorine with xenon difluoride to each of the six olefins is presented in Table I. The results from all olefins show that fluorine addition is clearly a nonstereospecific process. The nonstereospecific addition could be the result of an open or partly bridged cation as the product-determining intermediate, or the result of radical processes, and finally the result of the isomerization of the olefins or difluorides under the reaction conditions. We found that the lack of stereospecificity cannot be ascribed to the prior isomerization of the olefins (in the cis series we observed isomerization of the order of 10% for stilbene) or to secondary isomerization of the difluorides, since all have been shown to be stable under the reaction and isolation conditions. The absence of a free-radical inhibition effect (molecular oxygen) on the product distributions ruled out free-radical processes. It is clear that the stereochemical results must be explained within the framework of an electrophilic mechanism. The fact that these reactions are very strongly catalyzed by hydrogen fluoride and the nature of the products obtained in the fluorination of norbornene[6] confirm this view.

Scheme I

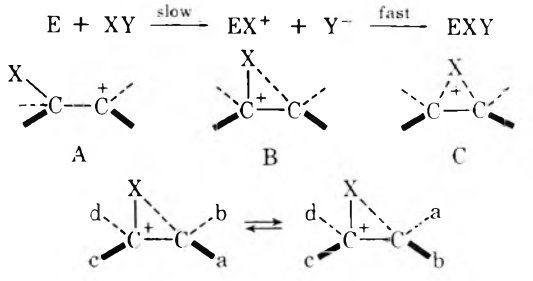


R = CH_3, Ph, $C(CH_3)_3$

The mechanisms of electrophilic addition of halogens to alkenes has been extensively investigated, from both kinetic and stereochemical points of view.[5,7] The most important mechanism for a electrophilic addition in the liquid phase is a stepwise addition via a carbonium ion intermediate (AdE2). It is now known that the nature of the intermediates (Scheme II) depends on the halogen X, on the structure of the substrate, and on the reaction medium, ranging from a strongly bridged ion of type C to a weakly bridged species of type B, or an open-chain ion like A. If the cation has an open (A) or partly bridged (B) structure, a mixture of syn and anti adducts is generally expected.

Scheme II

Ad_E2 mechanism



Turning to the results obtained with cis and trans olefins, we see that the ratios of *dl*-erythro (3) and *dl*-threo (4) difluorides (Table I) are nearly independent of the starting olefin, and that in the trans series of olefins, anti addition of fluorine predominates (3/4—1.50–1.70). On the basis of our experimental results obtained in HF-catalyzed fluorine addition to phenyl-substituted olefins with xenon difluoride, the following mechanism could be suggested. The mechanism of the fluorination must involve catalysis by hydrogen fluoride, since the reaction proved to be very slow without it. It might be expected that in the presence of hydrogen fluoride xenon difluoride behaves as an electrophile. Previously this has been

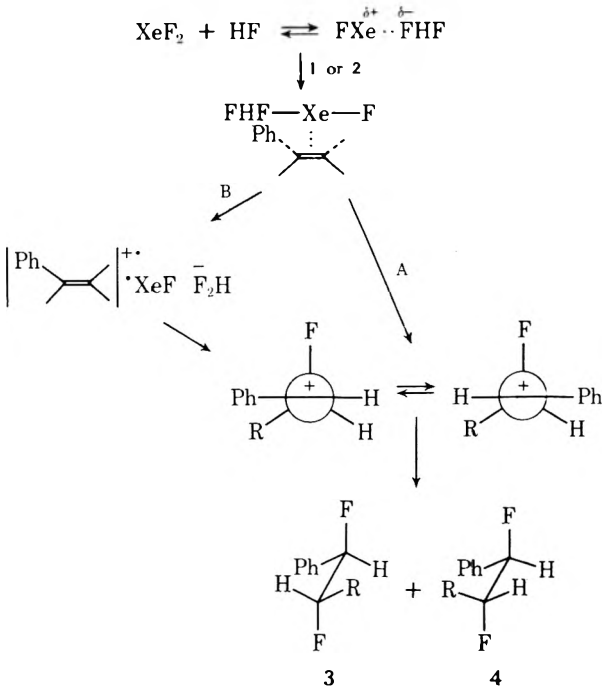
Table I. Product Distribution in Fluorination of Substituted 1-Phenylethylenes (1 and 2) with Xenon Difluoride in Methylene Chloride at 25 °C

Registry no.	Olefin	R	Rel yields, %[a] *dl*-erythro (3)	Ratio 3/4
873-66-5		CH_3	60	1.50
103-30-0	Trans (1)	Ph	62	1.67
3846-66-0		$C(CH_3)_3$	63	1.70
766-90-5		CH_3	64	1.78
645-49-8	Cis (2)	Ph	53	1.13
3740-05-4		$C(CH_3)_3$	64	1.78

[a] Determined by ^{19}F NMR spectroscopy.

suggested by Filler et al.[8] for the fluorination of aromatic compounds. In the next step, a π complex is probably formed between this electrophilic species and olefin 1 or 2, which could be transformed by a heterolytic Xe–F bond cleavage (Scheme III, path A) into an open β-fluorocarbonium ion intermediate.

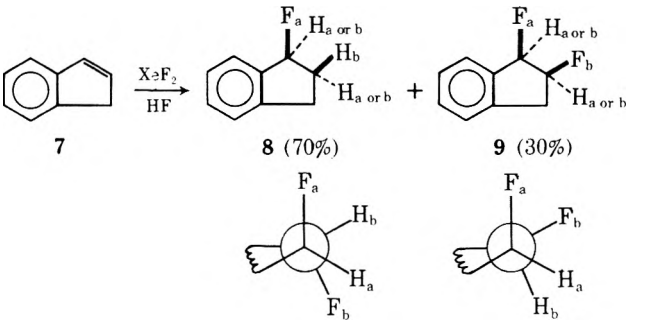
Scheme III



The intermediate from a trans olefin collapses preferentially to an anti adduct; on the other hand, the cis olefin intermediate can freely rotate about the newly formed single bond, thus assuming a sterically more favorable conformation, identical with that of the trans olefin intermediate. It is therefore clear why the product ratios are independent of the starting olefin. The proposed mechanism is also supported by the well-known fact that fluorine is a very poor neighboring group, preventing any bridging phenomena in the above mentioned β-fluorocarbonium ion intermediate. Furthermore, another possibility (path B) is the formation of an ion radical, which has already been observed in the fluorination of benzene and its derivates,[8] in the next step transforming by XeF· or XeF_2 into an open carbonium ion. The lower oxidation potentials of olefins (in comparsion to those of benzo derivates) make the suggested path (B) quite reasonable.[9]

We extended our studies on fluorine addition to cycloolefin so as to eliminate a complexity which exists in acyclic systems, in which there is the possibility of rotation about the carbon–carbon single bond in the β-fluorocarbonium ion, depending on its lifetime and on the energy barrier resisting free rotation about the newly formed single bond. Indene (7), which we might assume to be a "cyclic analogue" of *cis*-1-phenylpropene, adds fluorine preferentially anti (70%) but not syn, as was observed in fluorination of *cis*-1-phenylpropene. This fact also supports the idea of an open β-fluorocarbonium ion intermediate which cannot rotate in the case of a cyclic olefin such as indene (Scheme IV).

Scheme IV



NMR data	Trans adduct	Cis adduct
δ_{Fa}, ppm	−195.5	−211.5
δ_{Fb}, ppm	−207.5	−223.0
δ_{Ha}, ppm	5.8	5.5
δ_{Hb}, ppm	5.2	5.0
$J_{F_aF_b}$, Hz	9	4.5
$J_{F_aH_b}$, Hz	17	15
$J_{F_bH_a}$, Hz	16	5
$J_{H_aH_b}$, Hz	3	5

It is of interest to mention that in the fluorination of indene with molecular fluorine studied by Merrit,[10] a fluorine adduct was obtained which was interpreted as a trans product on the basis of its NMR spectra. By comparing our data for both cis (9) and trans (8) products to those of Merritt we deduced the cis structure for Merrit's product. We can see that there is little difference in H_aH_b coupling constants (Scheme IV), but there are differences in coupling constants F_bH_a between the two isomers. Following the Karplus rule,[11] the higher constant in the trans adduct is in full agreement with this assignment.

One of the reasons for undertaking the present study was to obtain data on the stereochemistry of fluorine addition to phenyl-substituted olefins with xenon difluoride which could be compared with the results of other halogen additions to this type of olefin. Stereochemical results for addition of various halogens to *cis*- and *trans*-1-phenylpropene are summarized in Table II. One can see that the stereochemistry of addition depends on the nature of the reagent. The reasons for these changes are known. Since fluorine and chlorine are poor neighboring atoms, electrophilic additions proceed via open carbonium ions and are nonstereospecific. The tendency toward syn addition observed with these reagents is the logical consequence of ion-pairing phenomena in nonpolar solvents. Bromine, which is a better bridging atom than chlorine, but poorer than iodine, represents an intermediate case. The addition of bromine is preferentially anti, and might be interpreted by an initially formed carbonium ion intermediate with a partly bridged structure. On the other hand, data on the electrophilic addition of iodine are not available. If we now compare the stereochemical results of fluorine addition with xenon difluoride to other halogen additions, we see that our results are very similar to the results of chlorine addition in methylene chloride, but differ from molecular fluorine addition, where ion-pairing phenomena are more dominant than in xenon difluoride fluorination.

The final conclusion of this study would be that xenon difluoride appears to be a mild, selective, electrophilic reagent for fluorine addition to olefins with some advantages in comparison to known fluorinating agents such as molecular

Table II. Stereochemistry of Halogen Addition to 1-Phenylpropene-1

Registry no.	Halogen	Solvent	Trans olefin		Cis olefin		Ref
			dl-erythro	*dl*-threo	*dl*-erythro	*dl*-threo	
7782-41-4	F_2	CCl_3F	31	69	78	22	12
7782-50-5	Cl_2	CCl_4	38	46	62	29	13
		CH_2Cl_2	55	28	62	22	13
7726-95-6	Br_2	CCl_4	88	12	17	83	14
13709-36-9	XeF_2	CH_2Cl_2	60	40	64	36	

fluorine, metal fluorides, etc. Some of them might be mentioned: (1) the good solubility of XeF_2 in organic solvents and no hazards in handling it; (2) no necessity for low temperature experiments, since reactions proceed smoothly at room temperature; (3) the only side product is xenon gas, which could be nearly quantitatively recycled to xenon difluoride.

Experimental Section

IR spectra were recorded using a Perkin-Elmer 257 spectrometer, ^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: *cis*-1-phenylpropene,[15] *trans*-1-phenylpropene,[16] *cis*-1-phenyl-2-*tert*-butylethylene,[17] *trans*-1-phenyl-2-*tert*-butylethylene.[17] Other olefins were commercially available and purified before use. Hydrogen fluoride of Fluka Purum quality was used without further purification. Methylene chloride, chloroform, and carbon tetrachloride were purified and stored over molecular sieves.[18] Xenon difluoride was prepared by a photosynthetic method[19] and its purity was better than 99.5%.

Addition and Isolation Procedures. To a solution of 1 mmol of olefin in methylene chloride (6 ml) in a Kel-F vessel, 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 slowly evolved. After 30 min gas evolution ceased and the reaction appeared to be complete. The reaction mixture was diluted with methylene chloride (5 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 reactions mixtures were separated by preparative GLC or TLC.

***dl-erythro-* and *dl-threo*-1,2-Difluoro-1-phenylpropane (3 and 4).** Products were separated by preparative GLC (DDP, Chromosorb Regular 80/100, 170 °C). *dl*-erythro (45%) and *dl*-threo (30%) isomers were isolated, both as colorless, liquid compounds. NMR for *dl*-erythro (**3**): δF_1 −202, δF_2 −216, δH_1 5.35, δH_2 4.67, δCH_3 1.28 ppm, $J_{F_1F_2}$ = 16.5, $J_{F_1H_1}$ = 48, $J_{F_2H_2}$ = 46.5, $J_{F_1H_2}$ = 16.5, $J_{F_2H_1}$ = 18, $J_{H_1H_2}$ = 3.75, $J_{F_2CH_3}$ = 22.5, $J_{H_2CH_3}$ = 6, $J_{F_1CH_3}$ = 1.5 Hz. *dl*-threo (**4**): δF_1 −204, δF_2 −208.5 ppm, δH_1 5.25, δH_2 4.71, δCH_3 1.17, $J_{F_1F_2}$ = 16.5, $J_{F_1H_1}$ = 48, $J_{F_2H_2}$ = 46.5, $J_{F_1H_2}$ = 16.5, $J_{F_2H_1}$ = 17, $J_{H_1H_2}$ = 5.25, $J_{F_2CH_3}$ = 22.5, $J_{H_2CH_3}$ = 6, $J_{F_1CH_3}$ = 0.5 Hz.

NMR data are in agreement with those in the literature.[12] The structures of the products were also established by elimination of hydrogen fluoride under basic conditions, thus converting them to *cis*-1-fluoro-1-phenylpropene (NMR J_{FH} = 22, J_{FCH_3} = 3, J_{HCH_3} = 7.2 Hz, δF −113.2 ppm) and *trans*-1-fluoro-1-phenylpropene (NMR J_{FH} = 36, J_{FCH_3} = 2, J_{HCH_3} = 6.75 Hz, δF −133.7 ppm).

***dl-erythro-* and *dl-threo*-1,2-Difluoro-1-phenyl-2-*tert*-butylethane (3 and 4).** Products were separated by preparative GLC (DDP-Chromosorb Regular 80/100, 170 °C). *dl*-erythro (40%) and *dl*-threo (32%) isomers were isolated, both as colorless, liquid compounds. NMR for *dl*-erythro (**3**): δF_1 −198, δF_2 −212 ppm, δH_1 5.33, δH_2 4.18, $\delta C(CH_3)_3$ 1.00, $J_{F_1F_2}$ = 18, $J_{F_1H_1}$ = 45, $J_{F_2H_2}$ = 43, $J_{F_1H_2}$ = 7.5, $J_{F_2H_1}$ = 7.5, $J_{H_1H_2}$ = 7.5 Hz. *dl*-threo (**4**): δF_1 −211, δF_2 −224 ppm, δH_1 5.51, δH_2 4.07, $\delta C(CH_3)$ 1.05, $J_{F_1F_2}$ = 7.5, $J_{F_1H_1}$ = 46.5, $J_{F_2H_2}$ = 43.5, $J_{F_1H_2}$ = 24, $J_{F_2H_1}$ = 27, $J_{H_1H_2}$ = 2.5 Hz. Mass spectrum: calcd for $C_{12}H_{16}F_2$ *m/e* 198.1220, found 198.1217, *m/e* 198 (M^+, 40), 109 (100), 91 (30), 89 (26).

***meso-* and *dl*-1,2-Difluoro-1,2-diphenylethane (3 and 4).** The crude reaction mixture was purified by preparative TLC and isolated in 78% yield. (The products were not separated.) The structures of the products were determined by elimination under basic conditions. One millimole of the reaction mixture of the difluorides (meso:*dl* products 2.5) was dissolved in 3 ml of *tert*-butyl alcohol and 1.5 mmol of potassium-*tert*-butoxide was added. The reaction mixture was stirred at room temperature for 20 h and 5 h at 50 °C, then cooled, mixed with water, and extracted with methylene chloride. The extract was washed with dilute acid and water, dried ($MgSO_4$), filtered, and evaporated and the residue was analyzed by GLC and NMR spectroscopy. The product was a 2.2:1 mixture of *cis*- and *trans*-fluorostilbene. The two compounds were separated by preparative GLC (Carbowax 20M, Varaport 30 70/80 at 180 °C). The spectroscopic data of fluorostilbenes are in agreement with the literature ones.[12]

To test the stability of the difluorides in the reaction mixture, a sample (0.2 g), containing pure difluorides **3** or **4** or the mixture of **3** and **4**, was dissolved in 2 ml of methylene chloride, 20 mg of xenon difluoride, and a catalytic amount of hydrogen fluoride, and the mixture was stirred at 25 °C for 30 min. After workup, the NMR spectra showed no significant differences. By using a mixture of **3** and **4** of known composition, it was demonstrated that no significant product fractionation occurred during the isolation.

Fluorination in the Presence of Oxygen. Trans olefin **1** (1 mmol) was dissolved in 6 ml of methylene chloride, 1 mmol of xenon difluoride was added at 25 °C, and under stirring a mixture of anhydrous hydrogen fluoride and oxygen was introduced into the reaction mixture for 30 min. The reaction mixture was diluted with methylene chloride, washed with 10 ml of 5% $NaHCO_3$ and water, dried ($MgSO_4$), filtered, and evaporated and the residue was analyzed by NMR spectroscopy. The product distribution was 61% of meso and 39% of *dl* difluorides in the case of *trans*-stilbene, and 60% of *dl*-erythro and 40% of *dl*-threo difluorides in the case of *trans*-phenylpropene. It can be seen that the free-radical inhibitor had no effect on the product distribution (Table I).

Isomerization of the Olefins under the Reaction Conditions. A. The olefin **1** or **2** (1 mmol), dissolved in methylene chloride, was stirred at room temperature in the presence of anhydrous hydrogen fluoride for 1 h. After adding water, washing with aqueous $NaHCO_3$ and water, drying over $MgSO_4$, and evaporation, the reaction mixture was analyzed by GLC. No significant isomerization of the olefin was observed.

B. In experiments made under the same reaction conditions as those for fluorination, in which a smaller amount (0.4, 0.5, or 0.6 mmol) of xenon difluoride and 1 mmol of olefin were used, the unchanged olefins were analyzed by GLC. No significant isomerization of trans olefins was observed, while the isomerization of cis olefins took place in the range of 5–7%.

Effect of Solvent Polarity on the Fluorination of *cis*- and *trans*-Stilbene. *trans*- or *cis*-stilbene (1 mmol) was dissolved in 6 ml of solvent (CCl_4, $CHCl_3$, or CH_2Cl_2), 1 mmol of xenon difluoride was added at 25 °C, and under stirring anhydrous hydrogen fluoride was introduced into the reaction mixture. After isolation in the usual manner, the NMR spectra were taken on the crude reaction mixture. The product distribution was as follows.

	Trans olefin		Cis olefin	
	Meso (3)	*dl* (4)	Meso (3)	*dl* (4)
CCl_4	56	44	53	47
$CHCl_3$	60	40	53	47
CH_2Cl_2	62	38	53	47

Studies of the effect of solvent polarity are limited to the above-mentioned solvents, because the reaction did not take place under similar conditions in other solvents (aliphatic alcohols, acetonitrile). The reaction is faster in methylene chloride than in chloroform or carbon tetrachloride.

Fluorination of Indene. To a solution of 1 mmol of indene in methylene chloride (6 ml), 1 mmol of xenon difluoride was added at

25 °C. After 20 min the reaction mixture was diluted with methylene chloride, washed with 10 ml of 5% $NaHCO_3$, and dried over anhydrous $MgSO_4$. The solvent was evaporated at room temperature. The reaction mixture was analyzed by NMR and showed 70% of trans and 30% of cis adduct. The reaction was repeated several times, and the reproducibility was better than 99%. The product were separated by preparative GLC (SE-30, Chromosorb A/AW 45/60, 10% at 160 °C). Trans difluoride (56%) and cis difluoride (16%), both colorless, liquid compounds, were isolated. The cis difluoride was found to be very unstable. Mass spectrum: calcd for $C_9H_8F_2$ *m/e* 154.0603, found *m/e* 154.0595. *m/e* 154 (M^+, 100), 153 (61), 134 (34), 133 (59), 127 (11), 115 (11), 107 (11). NMR data are stated in Scheme IV.

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Registry No.—3 (R = CH_3), 61047-36-7; 3 (R = $C(CH_3)_3$), 61047-39-0; 4 (R = CH_3), 61076-20-8; 4 (R = $C(CH_3)_3$), 61047-40-3.

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Fluorination with Xenon Difluoride. Fluorination of Bicyclic Olefins

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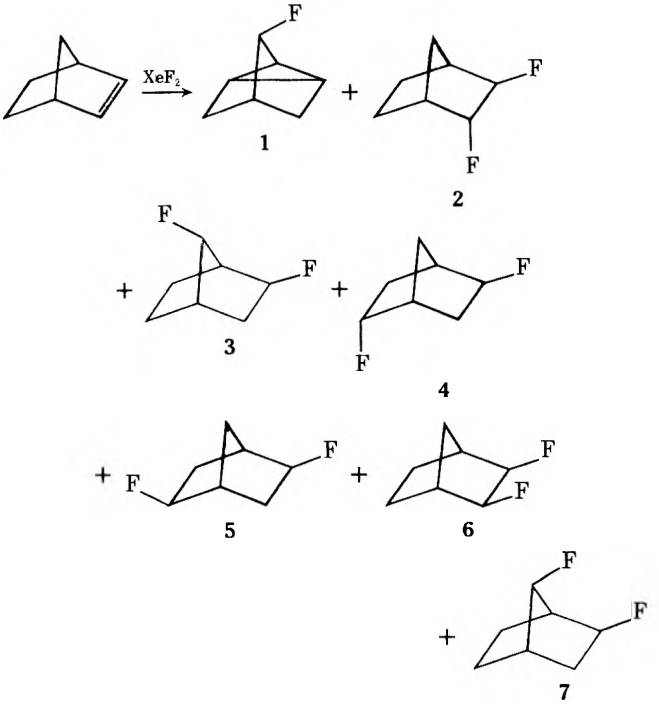
The reaction of norbornene has been used as a mechanistic probe to elucidate the reaction mechanism and the stereochemistry of the acid-catalyzed, liquid-phase fluorination with xenon difluoride, which resulted in the formation of seven products: fluoronortricyclane (1). 2-*endo*,3-*exo*-difluoronorbornane (2), 2-*exo*,7-*anti*-difluoronorbornane (3), 2-*endo*,5-*exo*-difluoronorbornane (4), 2-*exo*,5-*exo*-difluoronorbornane (5), 2-*exo*,3-*exo*-difluoronorbornane (6), and 2-*exo*,7-*syn*-difluoronorbornane (7). The fluorination of benzonorbornadiene resulted in the formation of 2-*exo*,7-*syn*-difluorobenzonorbornane (8), while the fluorination of norbornadiene resulted in the formation of 3-*endo*,5-*exo*-difluoronortricyclane (9), 3-*exo*,5-*exo*-difluoronortricyclane (10), and 2-*exo*,7-*syn*-difluoronorbornene-5 (11). A heterolytic Xe–F bond cleavage is suggested, resulting in an open β-fluorocarbonium ion intermediate or in a nonclassical ion, which undergoes the Wagner–Meerwein rearrangements and hydride shifts, thus forming fluorinated products. For the formation of the products 2 and 6 a free-radical intermediate is suggested.

With our continuing interest in acid-catalyzed liquid-phase fluorination of olefinic compounds[1] with xenon difluoride, we found it instructive to fluorinate some bicyclic alkenes, i.e., norbornene, benzonorbornadiene, and norbornadiene, in order to establish the reaction mechanism. The reactions of the bicyclic olefins norbornene and benzonorbornadiene have been used as a mechanistic probe to elucidate the mechanism of various reactions.[2] On the other hand, halogenations of norbornadiene have been studied much less intensively. Winstein[3] has studied bromination of norbornadiene and has pointed out the possibly dangerous properties of the products. We now report evidence for the formation of ionic intermediates in acid-catalyzed liquid-phase fluorination with xenon difluoride.

Scheme I



Results and Discussion

Fluorination of Norbornene. A 1-h reaction of norbornene with xenon difluoride in methylene chloride at room temperature and in the presence of a catalytic amount of hydrogen fluoride resulted in the formation of seven products. Analysis of the reaction mixture by GLC gave the relative yields which are listed in Table I. The products of the reaction were collected by preparative GLC. The structures of the compounds were determined on the basis of their mass, ^{19}F, and ^1H NMR spectra. The products formed in the reaction were fluoronortricyclane (1), 2-*endo*,3-*exo*-difluoronorbor-

Table I. Variation in Composition of Products from Addition of Xenon Difluoride to Norbornene at 25 °C[a]

Concn of norbornene, mg/ml	Solvent	Reaction times, min	1	2	3	4	5	6	7
200	CCl_4[b]	120	38	2.5	16	17.5	12	1.5	8
200	$CHCl_3$[b]	60	46	14	13	10.5	5	6.5	4
200	CH_2Cl_2	60	41.5	10.5	16.5	13.5	6	5.5	5
75	CH_2Cl_2	60	37.5	6	18	19	10	4	5.5
75	CH_2Cl_2	3	44	6	17	15.5	9	4	4.5
75	CH_2Cl_2/O_2	60	37.5	3.5	20	20	10	2	6
37.5	CH_2Cl_2	60	38	3.5	19.5	20	11	2	6
25	CH_2Cl_2	60	37	1.5	20	23	12	0.5	6

[a] Each experiment was repeated several times, average data being presented, and relative yields determined by GLC; maximum error is ±1.5% (Chromosorb Regular 100, 10% DDP with temperature program 45–120 °C). [b] Difference between 100% is one unidentified trifluoro product.

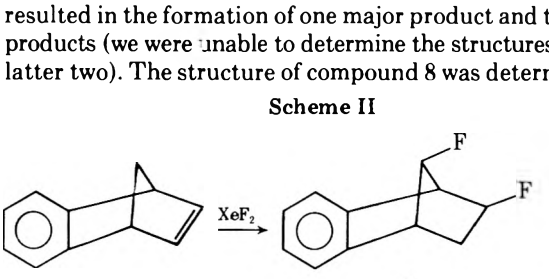
nane (**2**), 2-*exo*,7-*anti*-difluoronorbornane (**3**), 2-*endo*,5-*exo*-difluoronorbornane (**4**), 2-*exo*,5-*exo*-difluoronorbornane (**5**), 2-*exo*,3-*exo*-difluoronorbornane (**6**), and 2-*exo*,7-*syn*-difluoronorbornane (**7**) (the numbering of the products is in the order of increasing retention times). One can see that the retention times of the products **1**, **2**, **3**, **4**, **5**, and **7** are in the same order as those observed for dibromides by bromination of norbornene.[4] Products **1**, **3**, and **7** are known,[5] while products **4** and **5** have very similar mass spectra [*m/e* 132 (M^+), 86 ($M^+ - C_2H_3F$), 85 ($M^+ - C_2H_4F$)], which is also the case with **2** and **6** [*m/e* 132 (M^+), 68 ($M^+ - C_2H_2F_2$), 67 ($M^+ - C_2H_3F_2$)], with very little differences in the intensities of peaks. The similarity in fragmentation led us to the conclusion that **4** and **5** and **2** and **6** are isomeric compounds. Product **2** shows two signals in its ^{19}F NMR spectra, the first at δ −189.6 ppm (ddm) and the second at δ −219.0 ppm (ddt), and in its ^1H spectrum two signals at a lower field: δ 5.21 (ddd) and 4.72 ppm (ddd). Since endo-bonded hydrogen and fluorine atoms appear in the NMR spectrum at a higher field[6] than the exo-bonded ones, we have established the structure of the product **2** as 2-*exo*,3-*endo*-difluoronorbornane. Product **6** shows in its ^{19}F NMR spectrum one signal at δ −218 ppm (dm), and in its ^1H spectrum one signal at a lower field at δ 4.86 ppm (dm) corresponding to the two protons. The chemical shift of the two protons is characteristic of endo-bonded protons. On the other hand, the chemical shift for the fluorine atom is too high for an exo-bonded fluorine. However, a similar upfield effect on the chemical shift of two fluorine atoms in the nearly eclipsed position was also observed in the case of cis adducts formed in the fluorination of indene.[7] On the basis of mass spectral and NMR data, we have established the structure of the product **6** as 2-*exo*,3-*exo*-difluoronorbornane.

Compound **5** shows in its ^{19}F NMR spectrum a multiplet at δ −181.5 ppm and in its ^1H spectrum a doublet of multiplet signal at a lower field at δ 4.88 ppm, corresponding to two protons. The chemical shift for the fluorine atom corresponds to exo-bonded fluorine, and the chemical shift for lower field protons to the two endo-bonded protons. On the other hand, in the ^{19}F NMR spectrum of compound **4** we observed two signals, the first at δ −175.1 ppm (dm) and the second at δ −207.8 ppm (dddt), and in ^1H spectrum we observed two signals at a lower field, the first at δ 5.16 ppm (dd) and the second at δ 4.89 ppm (d). The fluorine atom at the lower field is exo and the one at higher field is endo bonded. The proton at the lower field corresponds to an exo- and that at a higher field to an endo-bonded proton. On the basis of the NMR and mass spectral data we have assigned the structure of the product **5** as 2-*exo*,5-*exo*-difluoronorbornane and the structure of the product **4** as 2-*endo*,5-*exo*-difluoronorbornane.

Product distribution as a function of solvent polarity, concentration of norbornene, and the presence of oxygen as an inhibitor of carbon radicals is given in Table I. The formation of the products **2** and **6**, depending significantly upon the conditions mentioned above, decreases in the presence of oxygen to one-half. Studying product stability under the reaction conditions, we observed no appreciable changes (3.5% decrease of product **4** and 6.5% increase of product **1**) in the distribution of the products **2**–**7** by shortening the reaction time to 3 min. However, significant isomerization took place when higher amounts of hydrogen fluoride in methylene chloride (at 25 °C) were used. Product **1** reacted with hydrogen fluoride, thus forming **2**, **3**, **4**, **5**, and **7**, product **3** isomerized into **2**, **4**, **5**, and **7**, while **7** isomerized into compounds **3**, **4**, **5**, and **6**, and product **4** was converted into **5** and **5** into **4**. On the other hand, under the above-mentioned conditions only **2** and **6** remained unchanged. The observed transformations of the products could be explained by the fact that hydrolysis of fluorinated compounds is acid catalyzed.[8]

Fluorination of Benzonorbornadiene. A 1-h reaction resulted in the formation of one major product and two trace products (we were unable to determine the structures of these latter two). The structure of compound **8** was determined on

Scheme II



8

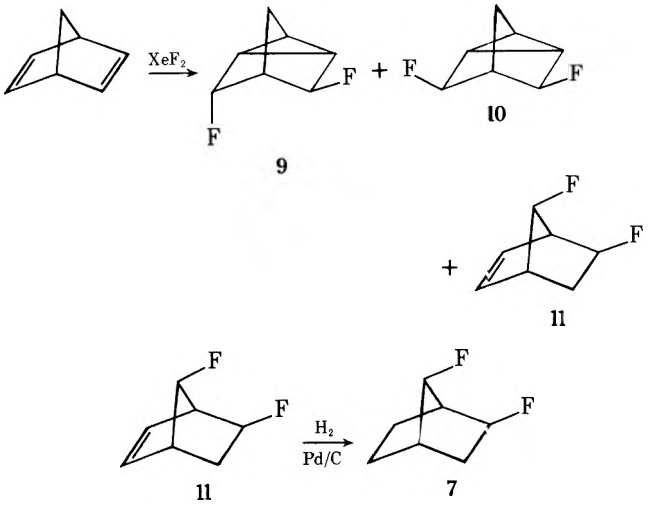
+ 2 unidentified minor products

the basis of its mass, ^1H, and ^{19}F NMR spectra. The major product shows in its ^{19}F NMR spectrum two signals, the first one as a multiplet at δ −182.25 ppm and the second one as a doublet of doublet at δ −183 ppm, and in its ^1H NMR spectrum two protons at lower field, the first at δ 4.75 ppm as a doublet of a multiplet and the second at δ 4.7 ppm as a doublet signal. Product **8** shows a fragmentation in its mass spectrum similar to those of 2-*exo*,7-*syn*- (**7**), 2-*exo*,7-*anti*-difluoronorbornane (**3**), and 2-*exo*,7-*syn*-difluoronorbornene-5 (**11**). The major peaks are *m/e* 147 ($M^+ - CH_2F$), 134 ($M^+ - C_2H_3F$), 133 ($M^+ - C_2H_4F$), and 129 ($M^+ - CHF_2$). The likeness in fragmentation led us to the conclusion that the structure of product **8** is very similar to those of **3**, **7**, and **11**. The signal in the ^{19}F NMR spectra, corresponding to a fluorine atom bonded at C-7, is shifted by about 50 ppm toward lower field than that of product **3** or **7**. However, if we compare the NMR data to those of product **11** formed in the fluorination of norbornadiene, whose structure was determined by hydrogenation, we observe very similar values for chemical shifts for fluorine atoms and signals for hydrogen atoms at a lower field. On the basis of its ^1H and ^{19}F NMR spectra, we have

established the structure of product 8 as 2-*exo*,7-*syn*-difluorobenzonorbornane.

Fluorination of Norbornadiene. Acid-catalyzed liquid-phase fluorination with xenon difluoride resulted in the formation of three products in relative yields of 50% of **9**, 40% of **10**, and 10% of **11** (determined by GLC or NMR spectroscopy),

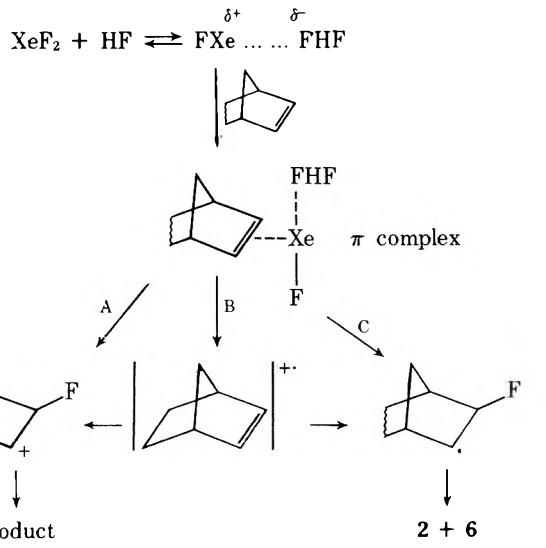
Scheme III



which could be separated by preparative GLC and whose structures were determined on the basis of their mass, ^{19}F, and ^{1}H NMR spectra and chemical transformations. product **9** shows in its ^{19}F NMR spectra two doublets, the first one at δ −201.8 ppm, corresponding to an exo-bonded fluorine atom, and the second one at δ −213 ppm, corresponding to an endo-bonded fluorine atom, with coupling constants of 60 Hz, and in its ^{1}H NMR two doublets at lower field, the first one at δ 5.22 ppm and the second one at δ 4.74 ppm, corresponding to exo- and endo-bonded protons, respectively. The molecular peak for product **9** was *m/e* 130. On the basis of the above-mentioned data we have established the structure of product **9** as 3-*endo*,5-*exo*-difluoronortricyclane. Product **10** shows in its ^{19}F NMR spectrum one doublet signal at δ −201.4 ppm with a coupling constant of 60 Hz, corresponding to the exo-bonded fluorine atom, and in its ^{1}H NMR a doublet signal at lower field at δ 4.53 ppm, corresponding to the two endo-bonded protons. The molecular peak was also *m/e* 130. By means of the above-mentioned data, the structure was found to be 3-*exo*,5-*exo*-difluoronortricyclane. The minor product formed (**11**) shows in its ^{19}F NMR spectrum one doublet of doublet signal at δ −180 ppm and one multiplet signal at δ −187.5 ppm, and in its ^{1}H NMR three signals at lower field. These were a multiplet signal at δ 6 ppm corresponding to two vinyl protons, a doublet of triplet signal at δ 4.74 ppm with coupling constants of 57 and 3 Hz, and a doublet signal at δ 4.6 ppm with a coupling constant of 60 Hz. The molecular peak was *m/e* 130. From the data mentioned above we propose the structure as 2-*exo*-7-difluoronorbornene-5. However, from the data just described, we were unable to make a decision about the stereochemistry at C-7. In order to establish the stereochemistry we converted product **11** to previously synthesized 2-*exo*,7-*syn*-difluoronorbornane (**7**) by catalytic hydrogenation.

Mechanism of the Fluorination with Xenon Difluoride. On the basis of the experimental results, we suggest the mechanism presented in Scheme IV. The mechanism of fluorination must involve catalysis by hydrogen fluoride since the reaction proved to be very slow without it. It might be expected that in the presence of hydrogen fluoride, xenon difluoride behaves as an electrophile. Previously this has been suggested by Filler et al.[9] for the fluorination of aromatic

Scheme IV



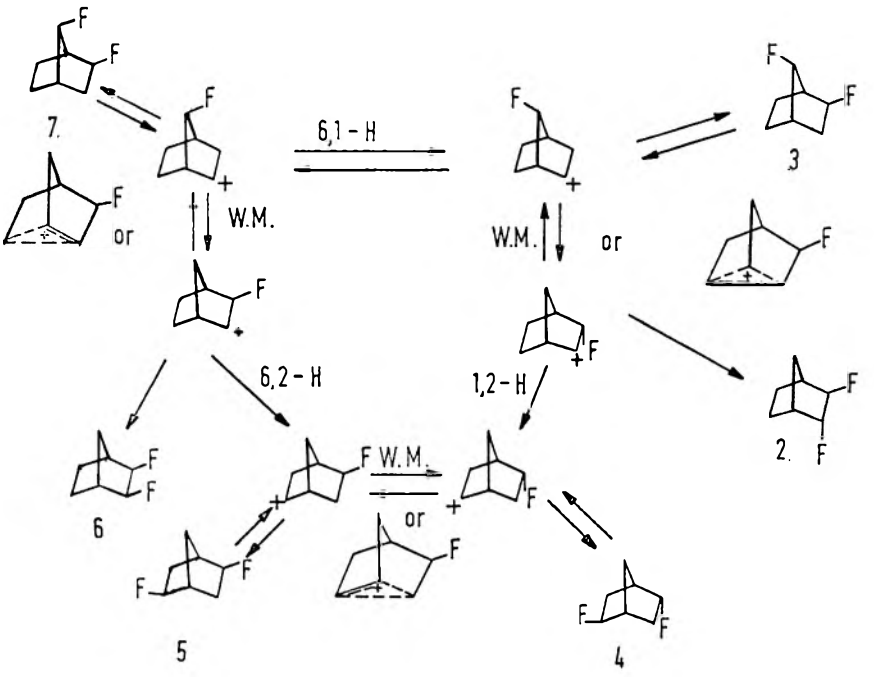
compounds. In the next step a π complex is probably formed between this electrophilic species and the bicyclic olefin, which could be transformed by the heterolytic Xe–F bond cleavage into an open β-fluorocarbonium ion intermediate (or into a nonclassical ion) (path A), which undergoes Wagner–Meerwein and hydride rearrangements, thus forming difluorides. Furthermore, another possible explanation for the formation of carbonium ion intermediates could be the formation of an ion radical (path B), which has already been observed in the fluorination of benzene and its derivates,[9] transforming in the next step by $XeF\cdot$ or XeF_2 to a carbonium ion or to a radical species. The lower oxidation potentials of olefins (in comparison to those of benzo derivates) make the above suggested path (B) quite reasonable.[16] For an explanation of the formation of the products **2** and **6**, whose differences in amount depend upon the concentration of norbornene and the presence of oxygen, we suggest another possible reaction path C, involving a free-radical species, formed by homolytic Xe–F bond cleavage or from an ion radical. We feel that the main intermediate formed in the acid-catalyzed liquid-phase fluorination with xenon difluoride is of carbonium ion nature, but also a free-radical intermediate is present.

An explanation of the formation of seven products in the reaction with norbornene is presented in Scheme V. The primarily formed β-fluorocarbonium ion intermediate (or nonclassical ion) undergoes hydride shifts and Wagner–Meerwein rearrangements,[10] thus forming difluorides **2**, **3**, **4**, **5**, **6**, and **7**.

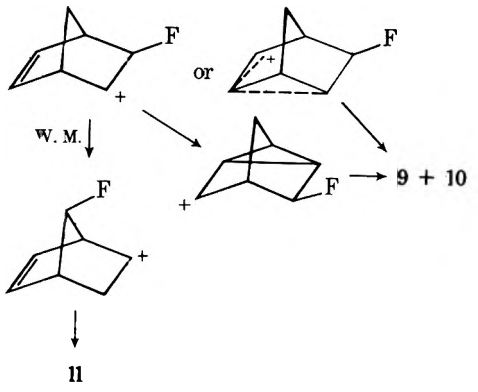
However, we suggest in the mechanism the irreversible hydride shifts 6,2-H and 1,2-H, based on the observation of the isomerization of the products in methylene chloride in the presence of hydrogen fluoride, where similar carbonium ions are formed. Explanation of the formation of three products in the reaction with norbornadiene is presented in Scheme VI. The primarily formed β-fluorocarbonium intermediate or delocalized ion undergoes Wagner–Meerwein rearrangement, thus forming difluoride **11**, while the formation of the products **9** and **10** could be explained by the attack of the fluorine anion on the fluoronortricyclyl cation or delocalized ion. The formation of 2-*exo*,7-*syn*-difluorobenzonorbornane (**8**) could be explained by Wagner–Meerwein rearrangement of the primarily formed β-fluorocarbonium ion.

Experimental Section

IR spectra were recorded using a Perkin-Elmer 257 spectrometer, and ^{1}H 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 spec-



Scheme VI



trometer. Gas–liquid partition chromatography was carried out on a Varian Aerograph Model 1800.

Materials. Benzonorbornadiene was prepared;[12] other olefins were commercially available and purified before use. Hydrogen fluoride of Fluka Purum quality was used without further purification. Methylene chloride, chloroform, and carbon tetrachloride were purified and stored over molecular sieves.[13] Xenon difluoride was prepared by a photosynthetic method[14] and its purity was better than 99.5%.

Addition and Isolation Procedures. To a solution of 1 mmol of olefin in methylene chloride (6 ml) in a Kel-F vessel, 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 slowly evolved. After 60 min 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 reaction mixtures were separated by preparative GLC.

Fluorination of Norbornene. Products were separated by preparative GLC (DDP-10%, Chromosorb Regular 100, 45–120 °C).

Fluoronortricyclane (1): yield 30%; mp 44–45 °C (lit.[15] 48–50 °C) (sealed capillary); NMR δF −218 ppm (dt), δCHF 5.05 ppm (dt) (J_{FH} = 69 Hz); the NMR spectrum is similar to that of the product synthesized from norbornadiene and HF.

2-*endo*,3-*exo*-Difluoronorbornane (2): yield 1.5% of volatile, waxy solid product; mp (sealed capillary) 96–97 °C; NMR (CCl_4) δF_{exo} −189.6 (ddm), δF_{endo} −219.0 (ddt), δCFH_{endo} 4.72 (ddd), δCFH_{exo} 5.21 ppm (ddd). $J_{FH\text{-}gem}$ = 60, $J_{F\text{-}exo\text{-}H\text{-}exo}$ = 31, $J_{P\text{-}endo\text{-}H\text{-}endo}$ = 18 Hz; mass spectrum calcd for $C_7H_{10}F_2$ *m/e* 132.0750, found 132.0759, *m/e* 132 (M^+, 8), 99 (24), 72 (38), 68 (96), 67 (100). Anal. Calcd for $C_7H_{10}F_2$: C, 63.60; H, 7.63. Found: C, 63.74; H, 7.30.

2-*exo*,7-*anti*-Difluoronorbornane (3): yield 13% of volatile, waxy solid product; mp (sealed capillary) 101–102 °C (lit.[5] 107–110 °C); NMR (CCl_4) δF2 −176.2 (dm), δF_7 −232.3 (dt), δH_2 4.28 (dm), δH_7 5.48 ppm (d), $J_{F_2H_2}$ = 60, J_{F_2H} = 30, 7.5 $J_{F_7H_7}$ = 65, J_{F_7H} = 3 Hz; mass spectrum calcd for $C_7H_{10}F_2$ *m/e* 132.0750, found *m/e* 132.0753, *m/e* 132 (M^+, 10), 99 (30), 86 (44), 85 (60), 81 (100), 72 (50). Anal. Calcd for $C_7H_{10}F_2$: C, 63.60; H, 7.63. Found: C, 63.44; H, 7.70.

2-*endo*,5-*exo*-Difluoronorbornane (4): yield 14% of volatile, waxy solid product; mp (sealed capillary) 82–84 °C; NMR (CCl_4) δF_2 −207.8 (dddt), δF_5 −175.1 (dm), δH_2 5.16 (dd), δH_5 4.89 ppm (d), $J_{F_2H_2}$ = 60, J_{F_2H} = 31.5, 15, 1.5, $J_{F_5H_5}$ = 60, J_{F_5H} = 40, 20, 7.5 Hz; mass spectrum calcd for $C_7H_{10}F_2$ *m/e* 132.0750, found *m/e* 132.0759, *m/e* 132 (M^+, 14), 99 (10), 86 (100), 85 (82). Anal. Calcd for $C_7H_{10}F_2$: C, 63.60; H, 7.63. Found: C, 63.44; H 7.70.

2-*exo*,5-*exo*-Difluoronorbornane (5): yield 8% of waxy solid product; mp (sealed capillary) 96–98 °C; NMR (CCl_4) δF −181.5 (m), δH_2H_5 4.88 ppm (dm), $J_{F_2H_2}$ = 60 Hz; mass spectrum calcd for $C_7H_{10}F_2$ *m/e* 132.0750, found *m/e* 132.0750, *m/e* 132 (M^+, 10), 99 (10), 86 (100), 85 (78). Anal. Calcd for $C_7H_{10}F_2$: C, 63.60; H, 7.63. Found: C, 63.63; H, 7.70.

2-*exo*,3-*exo*-Difluoronorbornane (6): yield 2.5% of waxy solid product; mp (sealed capillary) 121–122 °C; NMR (CCl_4) δF −218 (dm), δH_2H_3 4.86 ppm (dm), mass spectrum calcd for $C_7H_{10}F_2$ *m/e* 132.0750, found *m/e* 132.0750, *m/e* 132 (M^+, 6), 99 (30), 72 (46), 68 (100), 67 (76). Anal. Calcd for $C_7H_{10}F_2$: C, 63.60; H, 7.63. Found: C, 63.20; H, 7.66.

2-*exo*,7-*syn*-Difluoronorbornane (7): yield 4% of volatile, waxy solid product; mp (sealed capillary) 116–119 °C (lit.[5] 95–97 °C); NMR (CCl_4) δF_2 −179.5 (dm), δF_7 −223.5 (dm), δH_2 5.1 (dd), δH_7 5.2 ppm (d), $J_{F_2H_2}$ = 60, J_{F_2H} = 40, $J_{F_7H_7}$ = 63, J_{F_7H} = 12.6 Hz; mass spectrum calcd for $C_7H_{10}F_2$ *m/e* 132.0750, found *m/e* 132.0752. Anal. Calcd for $C_7H_{10}F_2$: C, 63.60; H, 7.63. Found: C, 63.32; H, 7.40.

Fluorination of Benzonorbornadiene. 2-*exo*,7-*syn*-Difluorobenzonorbornane (8) was purified by preparative GLC (SE-30, Chromosorb A/AW 45/60 10%, at 150 °C); yield 68% of waxy solid product; mp (sealed capillary) 40–43 °C; NMR (CCl_4) δF_2 −182.25 (m), δF_7 −183 (dd), δCFH_2 4.75 (dm), δCFH_7 4.7 (d), δH_1 3.7 (d), δH_4 3.45 ppm (s); mass spectrum calcd for $C_{11}H_{10}F_2$ *m/e* 180.0750, found *m/e* 180.0755, *m/e* 180 (M^+, 88), 159 (47), 147 (76), 146 (62), 134 (100), 133 (89), 129 (87), 116 (50), 115 (55).

Fluorination of Norbornadiene. Products were separated by preparative GLC (Carbowax 20M–25% Varaport 30 70/80, 160 °C).

3-*endo*,5-*exo*-Difluoronortricyclane (9): yield 35% of waxy solid product; mp (sealed capillary) 75–76 °C; NMR (CCl_4) δF_{exo} −201.8 ppm (d) J_{FH} = 60 Hz, δF_{endo} −213 ppm (d), J_{FH} = 60 Hz, δCFH_{exo} 5.22 (d), δCFH_{endo} 4.74 ppm (d); mass spectrum calcd for $C_7H_8F_2$ *m/e* 130.0594, found *m/e* 130.0597, *m/e* 130 (M^+, 58), 115 (53), 109 (30), 97 (100), 84 (35), 79 (65).

3-*exo*,5-*exo*-Difluoronortricyclane (10): yield 30% of waxy solid product; mp (sealed capillary) 76–77 °C; NMR (CCl_4) δF −201.4 (d),

δCFH 4.53 ppm (d), J_{FH} = 60 Hz; mass spectra calcd for $C_7H_8F_2$ *m/e* 130.0594, found *m/e* 130.0597, *m/e* 130 (M^+, 35), 115 (45), 109 (25), 97 (100), 84 (38), 79 (57).

2-*exo*,7-*syn*-Difluoronorbornene-5 (11): yield 6% of waxy solid product; mp (sealed capillary) 82–83 °C; NMR (CCl_4) δF_2 −187.5 (m), δF_7 −180 (dd), δCF**H**$_2$ 4.74 (dt), δCF**H**$_7$ 4.6 (d), δF**CH** 6.0 ppm (m, 2 H), $J_{F_7H_7}$ = 60, J_{F_7H} = 12, $J_{F_2H_2}$ = 57 Hz; mass spectrum calcd for $C_7H_8F_2$ *m/e* 130.0594, found *m/e* 130.0589, *m/e* 130 (M^+, 25), 109 (10), 97 (18), 84 (100), 79 (65).

Hydrogenation of 2-*exo*,7-*syn*-Difluoronorbornene-5 (11). 11 (0.5 mmol) was dissolved in 3 ml of methanol, and 0.3 g of 10% Pd on carbon was added, stirred at room temperature in a hydrogen atmosphere. After 0.3 mmol of hydrogen had reacted, the catalyst was filtered off and the reaction mixture was analyzed by GLC. The retention time of the product formed above was identical with that of 2-*exo*,7-*syn*-difluoronorbornane (7). The NMR spectra of the two compounds were the same.

Fluorination of Norbornene in the Presence of Oxygen. Norbornene (1 mmol) was dissolved in 2 ml of methylene chloride, 1 mmol of xenon difluoride was added at 25 °C, and under stirring a mixture of anhydrous hydrogen fluoride and oxygen was introduced into the reaction mixture for 60 min. The reaction mixture was diluted with methylene chloride, washed with 10 ml of 5% $NaHCO_3$ and water, dried ($MgSO_4$), and filtered, the solvent was evaporated in vacuo at room temperature, and the residue was analyzed by GLC. The product distribution is stated in Table I. It can be seen that the relative yields of products 2 and 6 are diminished to one-half.

The effects of solvent polarity and the concentration of norbornene on the product distribution are stated in Table I. The workup procedure was carried out in the usual way.

Isomerization of Norbornene Difluorides 2–7 and the Reaction of Fluoronortricyclane with Hydrogen Fluoride in Methylene Chloride. Pure difluorides or nortricyclane (0.3 mmol) was dissolved in methylene chloride (1 ml) at room temperature and under stirring 2 mmol of hydrogen fluoride was introduced into the reaction mixture. After 1 h the reaction mixture was washed with 1 ml of 5% $NaHCO_3$ and water and dried (Na_2SO_4). The composition of the mixture was determined by glc.

Fluoronortricyclane (1) gave a mixture of **2** (1%), **4** (37%), **5** (26%), **3** (26%), and **7** (10%).

2-*exo*,7-*anti*-Difluoronorbornane (3) gave a mixture of **2** (1%), **4** (34%), **5** (32%), **3** (29%), and **7** (4%).

2-*exo*,7-*syn*-Difluoronorbornane (7) gave a mixture of **6** (1%), **4** (20%), **5** (22%), **3** (9%), and **7** (48%).

2-*endo*,5-*exo*-Difluoronorbornane (4) gave a mixture of **4** (62%) and **5** (38%).

3-*exo*,5-*exo*-Difluoronorbornane (5) gave a mixture of **4** (24%) and **5** (76%).

Under the above-mentioned conditions only difluorides **2** and **6** remained unchanged.

Acknowledgments. We thank Professor J. Slivnik for xenon difluoride, Professor J. Marsel for providing facilities, and Professors N. Bartlett, F. H. Westheimer, and G. M. Whitesides for helpful discussion. The financial assistance of the Boris Kidrič Foundation is acknowledged.

Registry No.—**1**, 695-03-4; **2**, 61026-28-6; **3**, 36914-49-5; **4**, 61026-29-7; **5**, 61091-30-3; **6**, 61091-31-4; **7**, 36914-50-8; **8**, 61026-30-0; **9**, 61026-31-1; **10**, 61091-32-5; **11**, 61026-32-2; norbornene, 498-66-8; benzonorbornadiene, 4453-90-1; norbornadiene, 121-46-0; xenon difluoride, 13709-36-9; hydrogen fluoride, 7664-39-3.

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New Tetrapyrrolic Macrocycles. 18 and 20 π Electron Homoporphyrins

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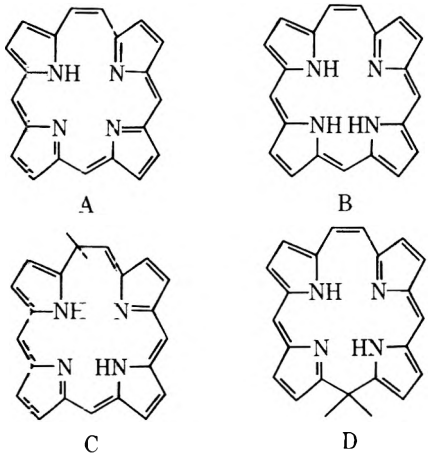
We describe the preparation and properties of a series of homoporphyrin derivatives, either as nickel(II) complex or as free bases. The π system may be fully unsaturated (18 or 20 π electrons) or interrupted by a sp^3 carbon at C_{21} or C_{10}. The nonplanar (helicoidal or rooflike) conformation of homoporphyrins is demonstrated.

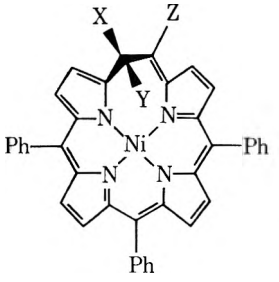
Homoporphyrin derivatives have only recently been characterized.[1,2] Typical representatives of this new class of unsaturated tetrapyrrolic macrocycles may be based on the ring systems A, B, C, and D (Scheme I). Fully conjugated systems

Scheme I



A and B are formally aza analogues of 18 π and 20 π annulenes, whereas conjugation is interrupted in the case of C and D.

In an earlier study,[1,2] we reported the preparation of a series of type C homoporphyrins, namely esters **1–4**, via nickel-catalyzed rearrangement of N-substituted porphyrins. We now describe the isolation of several derivatives of type A, B, and D systems.[3]

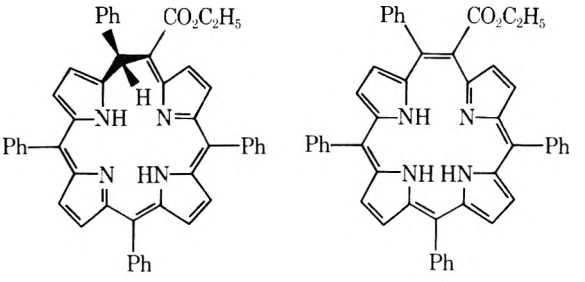


1, X = CO_2Et; Y = H; Z = Ph
2, X = H; Y = CO_2Et; Z = Ph
3, X = Ph; Y = H; Z = CO_2Et
4, X = H; Y = Ph; Z = CO_2Et

Results

Mild acid treatment of ester **2** (3×10^{-2} M CF_3COOH in CH_2Cl_2) yielded an equilibrium mixture of all four isomers **1, 2, 3,** and **4**. More drastic conditions (1 M CF_3COOH, or concentrated HCl) led to rapid demetalation and isolation of two isomeric bases **5** and **6** (20:80, prototropic equilibrium mixture).

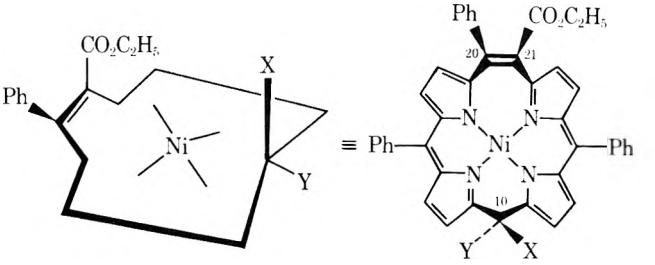
The structure of base **5** was confirmed by its spectral properties and its remetalation [$Ni(OAc)_2 \cdot 4H_2O$] to form the nickel complex **3**. The ^{13}C NMR spectrum of base **6** demonstrated the presence of the fully unsaturated system B. This was confirmed by its IR spectrum (conjugated ester). Moreover, its visible spectrum (λ_{max} 472 and 692 nm, ε 38 000 and 13 400) was quite different from that of esters **1–5**, and had no common feature with the spectrum of a porphyrin. Typical also was the occurrence of pyrrolic protons signals in the δ 6–7 ppm range. Base **6** was very unstable and decomposed slowly even at 0 °C in the solid state, yielding a multitude of polar products. This observation could fit the formal "antiaromaticity" of base **6** (this point and the possible conformation of **6** will be discussed further).



5 **6**

Metalation of **6**, under an inert atmosphere (purified N_2; $Ni(OAc)_2 \cdot 4H_2O$, AcOH, 25 °C), gave a 15% yield of ester **1**. The low yield of **1** is most likely due to the poor stability of **6** under the reaction conditions. The mixture of esters **1–4** (30%), which was obtained upon reaction at 60 °C, is undoubtedly the consequence of an acid-catalyzed equilibrium.

On the other hand, in the presence of oxygen, nucleophilic solvents, and base (CH_3OH or H_2O, K_2CO_3) metalation of **6** rapidly yielded type **7** compounds (X = OCH_3 or OH), which on heating in refluxing toluene gave quantitatively type **8** products (Y = OCH_3 or OH).

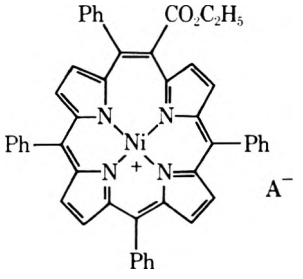


7a, X = OCH_3; Y = Ph
b, X = OH; Y = Ph
8a, X = Ph; Y = OCH_3
b, X = Ph; Y = OH

The structural determination by x-ray analysis of alcohol **8b** has been achieved.[4] It showed a large, rooflike folding of the macrocycle along the C_{10}–Ni axis, thus differentiating the two substituents on C_{10}. This deformation explained the formation of the kinetically favored **7** (X in axial configuration) and its transformation into the thermodynamically favored **8** (equatorial Y). Furthermore, the large C_{20}–C_{21} bridge and carbon C_{10} are placed in a "chimneylike" position, thus avoiding any conjugation with the neighboring pyrrole rings. Buchler et al.[5] observed a very similar deformation on studying a series of 5,15-dihydro-5,15-dimethylporphyrins,

in which the axial methyl substituents are located in the chimney position of the roof. The visible spectra of **7** and **8** (complex pattern between 400 and 500 nm, ϵ ca. 30 000) were of the dipyrromethene type, confirming the lack of conjugation through the C_{20}–C_{21} bridge. The low extinction coefficient agrees well with the structural data which indicate the presence of two nonplanar dipyrromethene units. The NMR data allow series **7** to be distinguished from series **8**. The pyrrolic protons of **8** (phenyl group axial) give rise to a 1:1:6 pattern (from high to low field), located between δ 6.0 and 7.0 ppm. The same protons in **7** exhibit a 3:4:1 pattern, thus illustrating the shielding of the neighboring protons due to the equatorial phenyl group of type **7** compounds. Although a ring inversion could explain the **7** → **8** isomerization, the expected stabilization of a cation at C_{10} suggests a different mechanism, one which proceeds via C–O heterolysis followed by equatorial addition of the resulting anion (CH_3O^- or HO^-). Kinetic measurements, which show a 77-fold increase in rate in going from benzene to CH_3CN, strongly support this hypothesis.

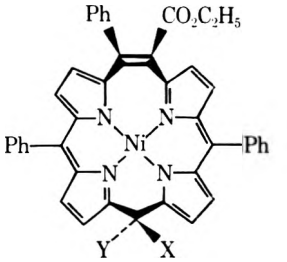
The intermediate cation **9** was isolated on acid treatment (CF_3COOH) of either **7** or **8**.



9

Acidic solutions of **9** were stable but pure crystals (A = ClO_4 or BPh_4) could not be obtained completely free of hydrolysis products. The spectral properties of cation **9** differed markedly from those of porphyrins. The pyrrolic protons resonance occurred at higher field (δ 7.3–8.1 ppm) as compared to *meso*-tetraphenylporphine (9 ppm). Its visible spectrum (λ_{max} 457, 594, and 796 nm; ϵ 55 000, 6800, and 10 600) was similar to those of systems where the cyclic conjugation has been interrupted. Methanolysis of **9** at room temperature gave exclusively **7** (X = OMe). Zinc–acetic acid reduction of **9** yielded, in addition to a small amount of esters **1** and **2**, an isomeric homoporphyrin **10**, belonging to the same series as **7** and **8**.

On refluxing in *o*-dichlorobenzene **10** gave isomer **11**. The structure of **10** and **11** was assigned from their NMR data: H_{10}

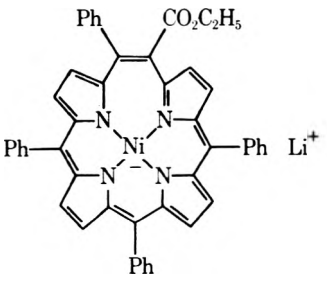


10, X = H; Y = C_6H_5
11, X = C_6H_5; Y = H

has an axial configuration in ester **10** and an equatorial configuration in ester **11**. This follows from the very similar pattern exhibited by the signals of the pyrrolic protons of **7** and **10**, and of **8** and **11**.

In the presence of a base (NEt_3), ester **10** isomerized within a few minutes to form ester **1** while, under the same conditions, **11** remained unchanged for more than a day. This observation allows us to postulate a thermal ring inversion for the **10** → **11** isomerization, thus ruling out the possibility of a base-catalyzed epimerization. Again we observed a large enhancement of the axial vs. equatorial reactivity, as in compounds **7** and **8**.

A study, which is still in progress, showed the formation of anion **12** from either **1** or **2** (*i*-Pr_2NLi, THF). Its protonation gave, depending on the conditions (H_2O or AcOH), a satisfactory yield of a mixture consisting of **1**, **2**, and **10**.



12

Discussion

The reactions described above allowed us to study a series of compounds possessing, in addition to the general homoporphyrin skeleton, the cyclic or interrupted π systems A (cation **9**), B (base **6**), C (esters **1–5**), and D (esters **7**, **8**, **10**, and **11**). Anion **12**, still under study, is another example of system B.

Only two of these reactions differ from simple metalation, demetalation, or prototropy, namely **6** → **7** and **9** → **10**. The former reaction required first metalation of **6** to yield anion **12** whose rapid oxidation in the presence of oxygen (solutions of **12** are highly oxygen sensitive and upon hydrolysis in the presence of air gave **7b** as the major identified product) gave cation **9**, which upon methanolysis or hydrolysis yielded **7** (X = OCH_3 or OH). Similar oxidation of metal complexes of tetrapyrrolic macrocycles have been described by Johnson.[6] On the other hand, the zinc reduction of cation **9** yielded anion **12** whose immediate protonation in acetic acid gave the same products, **1** + **2** + **10**, as did the quenching with acetic acid of a solution of **12** prepared from **1** or **2** and base.

The conformation of macrocycles **1–12** remains the major point to be discussed. Actually our observations indicate that, in the case of **6** and **9**, the overcrowding of the C_{20}–C_{21} bridge is determining, rather than the nature of the cyclic conjugated system (B or A). This point is well illustrated by the x-ray structural determination of **8** (Y = OH): when unsaturated, the large C_{20}–C_{21} bridge is unable to conjugate with the neighboring pyrrole rings, and its "expulsion" from the mean plane of the molecule introduces large deformations. The C_{20}–C_{21} olefinic bond is not conjugated and its length (1.43 Å) is close to that of an isolated double bond. This is also true for compounds **6–12**, whereas **1–5** exhibit a different conformation.[7] These facts explain the absence of aromatic character (e.g., NMR deshielding and porphinlike absorption spectra) of cation **9**, and the a priori unpredictable similarity of its visible spectrum with that of **6**. If the resulting U-shaped conjugated system is further interrupted at C_{10}, the molecule adopts a rooflike conformation leading to a dipyrromethene-like absorption (**7**, **8**, **10**, and **11**). Although possessing the same carbon skeleton, compounds **1–5** exhibit a helicoidal conformation and a Z-shaped C_{20}–C_{21} bridge. The better local planarity observed[7] compares well with the higher extinctions measured.[1,2]

The only known route to homoporphyrins requires the presence of bulky C_{20} and C_{21} substituents. It is obvious that homoporphyrins which are unsubstituted at these positions may adopt a more planar conformation. But it must be kept in mind that the effect of the metal itself, although difficult to measure, can lead to deformations by imposing given metal-N bond lengths.

Experimental Section[8]

Demetalation of Ester 1. To a solution of **1** (500 mg) in $CHCl_3$ (150 mL) was added concentrated HCl (2.5 mL). After stirring for 2 h at 25 °C, the mixture was neutralized (10% aqueous ammonium carbonate), washed with H_2O, dried (Na_2SO_4), and evaporated. Chromatography (alumina, 300 g) using toluene–cyclohexane (1:1) as eluent gave **5** (crystallized from CH_2Cl_2–MeOH, 84 mg, 18%). Further elution using toluene–EtOAc gave **6** (crystallized from CH_2Cl_2–hexane, 250 mg 54%). The same products were obtained when treating **2, 3,** or **4** under the same conditions. Treatment of either **5** or **6,** in $CHCl_3$ solution, with concentrated HCl gave the same 20:80 equilibrium mixture as demonstrated by visible spectrophotometry, after neutralization and rapid isolation of the products (TLC).

Base **5:** IR ν_{max} (KBr) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (t, 3, CH_3, J = 7 Hz), 1.92 (s, 1, H-20), 4.21 (q, 2, CH_2, J = 7 Hz), 6.97 (d, 1, pyrrole H, J = 5 Hz), 7.15 (s, 5, C-20 phenyl), 7.6 (m, 20, 15 phenyl + 5 pyrrole H), 7.90 (c, 1, pyrrole H, J = 4.5 Hz), 8.55 (d, 1, pyrrole H-2, J = 5.5 Hz); visible (C_6H_6) λ_{max} 668 nm (ε 10 000), 619 (11 400), 577 (7800), 532 (3000), 433 (75 000); no mass spectrum (decomposition). Anal. Calcd for $C_{48}H_{36}N_4O_2$: C, 82.27; H, 5.18; N, 7.99. Found: C, 82.42; H, 5.29; N, 8.11.

Base **6:** IR ν_{max} (KBr) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.71 (t, 3, CH_3, J = 7 Hz), 3.76 (q, 2, CH_2, J = 7 Hz), 4.0 (broad, 3, NH), 6.19 and 6.31 (2 d, 2, 2 pyrrole H, AB, J = 4 Hz), 6.59 and 6.73 (2 d, 2, 2 pyrrole H, AB, J = 4 Hz), 7.5 (m, 24, phenyl + 4 pyrrole H); ^{13}C NMR 12.3 (CH_3), 60.7 (CH_2), 110.5–159.2 (aromatic C), 167.1 (carbonyl); visible (C_6H_6) λ_{max} 692 nm (ε 13 400), 472 (38 000); no mass spectrum (decomposition). Anal. Calcd for $C_{48}H_{36}N_4O_2$: C, 82.27; H, 5.18; N, 7.99. Found: C, 79,96; H, 5.35; N, 6.53. The rapid decomposition of base **6** may explain the poor analytical result. All spectra were run on freshly crystallized samples.

Metalation of 5. A solution of base **5** (7 mg) and $Ni(OAc)_2 \cdot 4H_2O$ (20 mg) in CH_3OH (15 mL) was stirred for 2 h at 25 °C. Evaporation followed by alumina TLC gave ester **3** (5 mg, 67%, from CH_2Cl_2–MeOH).

Metalation of 6. 1. Under Nitrogen at 25 °C. Through a solution of $Ni(OAc)_2 \cdot 4H_2O$ (100 mg) in acetic acid (20 mL) was bubbled purified N_2 for 1 h. Solid **6** was then added and the solution was stirred for 36 h under N_2. After vacuum evaporation of the solvent and alumina chromatography ester **1** was isolated (6 mg, 15%) along with traces of **2, 3,** and **4.**

2. Under Nitrogen at 60 °C. The same procedure was used, except that the reaction mixture was heated at 60 °C for 0.5 h. The same workup led to the isolation of a mixture of esters **1, 2, 3,** and **4** (ratio 25:50:5:20; total yield 30%).

3. In the Presence of Air. A solution of $Ni(OAc)_2 \cdot 4H_2O$ (100 mg) in MeOH (2 mL) was added to base **6** (30 mg) in CH_2Cl_2 (5 mL), in the presence of K_2CO_3 (100 mg). The mixture was stirred at 25 °C for 1 h, then extracted (CH_2Cl_2), washed with water, dried (Na_2SO_4), and vacuum evaporated at 25 °C. Product **7a** was purified on TLC using benzene–cyclohexane (1:1) as eluent and crystallized from CH_2Cl_2–MeOH (8 mg, 24%). In the absence of K_2CO_3, in wet MeOH, a limited amount of alcohol **7b** was also obtained, although the yield was difficult to reproduce. A better procedure is the following: to a solution of **2** (170 mg) in tetrahydrofuran (35 mL) was added saturated aqueous Na_2CO_3 (5 mL). The mixture was stirred at 25 °C for 2.5 h and extracted ($CHCl_3$). Chromatography of the solution on alumina (100 g) using $CHCl_3$ as eluent gave **7b** (36 mg, 21%), contaminated with traces of **8b.**

Ether 8a from Isomer 7a. A solution of ether **7a** in toluene was boiled for 10 h. Evaporation of the solvent and crystallization from CH_2Cl_2–MeOH gave a quantitative yield of ether **8a.** Kinetic data were obtained from heating **7a** (2 mg) in benzene or acetonitrile (5 mL) at 80 °C. The products were separated on alumina TLC and the visible absorption measured in CH_2Cl_2 solution: $k_{C_6H_6} = (0.15 \pm 0.01) \times 10^{-4}$ s^{-1}; $k_{CH_3CN} = (11.6 \pm 1.0) \times 10^{-4}$ s^{-1}; ratio 1:77.

Ether 7a from Isomer 8a. To a solution of **8a** (32 mg) in $CHCl_3$ (10 mL) was added CF_3COOH (1 mL). The red-brown solution turned yellow green and was immediately evaporated. The residue was dissolved in CH_3OH (10 mL). On addition of solid K_2CO_3 the solution turned red brown. It was then evaporated and the residue filtered through a short column (alumina, CH_2Cl_2). The product was crystallized from CH_2Cl_2–MeOH to yield **7a** (28 mg, 88%).

Ether 7a: mp >290 °C; IR ν_{max} (KBr) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (t, 3, CH_3, J = 7 Hz), 3.37 (s, 3, OCH_3), 3.89 (q, 2, CH_2, J = 7 Hz), 6.2 (m, 3, pyrrole H), 6.8 (m, 4, pyrrole), 7.3–7.9 (m, 21, phenyl + 1 pyrrole H); visible (CH_2Cl_2) $\lambda_{shoulder}$ 605 nm (ε 4860), 500 (26 000), 465 (27 400), λ_{max} 425 (32 800); mass spectrum m/e (%) 756 (3), 700 (8), 684 (22), 670 (70), 607 (9), 594 (100).

Anal. Calcd for $C_{49}H_{36}N_4O_3Ni$: C, 74.72; H, 4.60; N, 7.12. Found: C, 74.30; H, 4.70; N, 7.39.

Alcohol 7b. This compound could not be obtained free of traces of isomer **8b.** It showed IR ν_{max} (KBr) 1715 cm^{-1}; ^1H NMR δ 0.82 (t, 3, CH_3, J = 7 Hz), 1.55 (s, 1, OH), 3.89 (q, 2, CH_2, J = 7 Hz), 6.2 (m, 3, pyrrole H), 6.8 (m, 4, pyrrole H), 7.5 (m, 1 pyrrole + 18 phenyl H), 8.0 (m, 2 phenyl H); visible (CH_2Cl_2) $\lambda_{shoulder}$ 610 nm (ε 4700), λ_{max} 480 (28 950), 420 (35 200).

Ether **8a:** mp >300 °C; IR ν_{max} (KBr) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, 3, CH_3, J = 7 Hz), 3.37 (s, 3, OCH_3), 3.83 (q, 2, CH_2, J = 7 Hz), 6.02 and 6.52 (2 d, 2, pyrrole H, AB, J = 4.5 Hz), 6.75–7.1 (m, 6, pyrrole H), 7.3–7.5 (m, 20, phenyl); visible (CH_2Cl_2) $\lambda_{shoulder}$ 610 nm (ε 3390), λ_{max} 498 (26 700), 422 (27 600); mass spectrum m/e (%) 728 (M^+·, 28), 756 (100), 683 (13), 581 (64).

Anal. Calcd for $C_{49}H_{36}N_4O_3Ni$: C, 74.73; H, 4.60; N, 7.12. Found: C, 74.58; H, 4.72; N, 7.72.

Alcohol **8b:** mp 294–297 °C; IR ν_{max} (KBr) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (t, 3, CH_3, J = 7 Hz), 2.87 (s, 1, OH), 3.86 (q, 2, CH_2, J = 7 Hz), 6.01 and 6.56 (2 d, 2, pyrrole H, AB, J = 4.7 Hz), 6.94–7.04 (m, 6, pyrrole H), 7.3–7.5 (m, 18, phenyl H), 7.9–8.05 (m, 2 phenyl H); visible (CH_2Cl_2) $\lambda_{shoulder}$ 605 nm (ε 3700), λ_{max} 499 (28 100), 424 (29 200); mass spectrum m/e (%) 772 (M^+·, 48), 756 (39), 683 (24), 667 (100), 621 (16), 593 (48), 582 (39).

Anal. Calcd for $C_{48}H_{34}N_4O_3Ni$: C, 74.53; H, 4.43; N, 7.25. Found: C, 74.59; H, 4.52; N, 7.95.

Cation 9. All spectra were run on acidified solutions of **8** (Y = OH). ^1H NMR ($CDCl_3$) δ 0.94 (t, 3, CH_3, J = 7 Hz), 4.12 (q, 2, CH_2, J = 7 Hz), 7.3–8.1 (m, 28, pyrrole + phenyl H); visible (CH_2Cl_2) λ_{max} 786 nm (ε 10 600), 594 (6800), 457 (55 000). Addition of aqueous $LiB(C_6H_5)_4$ to methanolic **9** precipited crystals but slow hydrolysis to **7** (X = OH) occurred leading to impure material.

Reduction of Cation 9. Alcohol **8** (2 mg) was dissolved in CH_2Cl_2 (3 mL) containing ca. 10% CF_3COOH. The solvent was evaporated, the residue dissolved in 1:1 benzene–acetic acid (1 mL), and zinc powder (50 mg) added. The mixture was stirred at 25 °C under argon for 2 h, diluted with water, extracted with CH_2Cl_2, dried (Na_2SO_4), and separated (alumina TLC). Visible spectrophotometry indicated a 6:12:82 ratio for isomers **1, 2,** and **10** (total yield 96%). Comparison of chromatographic data with samples of **1, 2,** and **10** confirmed the identity of the products.

Reaction of 1 (or 2) with Base. Solid **1** (100 mg) and i-Pr_2NLi (in THF, slight excess) were successively added to THF (10 mL, freshly distilled over $LiAlH_4$), kept at 0 °C under a flow of purified nitrogen. The initial green solution of **1** turned orange brown. After stirring for 0.2 h, acetic acid (0.1 mL) was slowly added. The solution was diluted with water, extracted with CH_2Cl_2, dried (Na_2SO_4), and evaporated. Chromatographic separation (silica gel, toluene–cyclohexane, 1:1) gave isomers **1** (35 mg, 35%) and **10** (25 mg, 25%, crystallized from CH_2Cl_2–CH_3OH). In a smaller scale experiment (20 mg of **1**) rapid quenching of the solution with a larger amount of acetic acid (3 mL) gave **1** + **2** + **10** (ratio 43:28:29, total yield 70% as determined spectrophotometrically). Opening of the reaction vessel before the addition of acid gave **7b** (50%), accompanied by a smaller amount of **1** and **2** (40%, 40:60 ratio).

Ester 10: mp 224–225 °C; IR ν_{max} (KBr) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, 3, CH_3, J = 7 Hz), 3.96 (q, 2, CH_2, J = 7 Hz), 5.39 (s, 1, H-10), 5.9–6.1 (m, 3, pyrrole H), 6.5–6.75 (m, 4, pyrrole H), 7.07 (d, 1, pyrrole H, J = 4.4 Hz), 7.4 (m, 10, phenyl H); visible (CH_2Cl_2) $\lambda_{shoulder}$ 610 nm (ε 4200), λ_{max} 462 (32 800), 420 (34 000); mass spectrum m/e (%) 756 (M^+·, 91), 683 (38), 679 (25), 670 (95), 582 (100), 545 (45).

Anal. Calcd for $C_{48}H_{34}N_4O_2Ni$: C, 76.10; H, 4.53; N, 7.40. Found: C, 76.05; H, 4.60; N, 7.20.

Ester 11 from Ester 10. Ester **10** (10 mg) was dissolved in o-dichlorobenzene (5 mL) and the solution refluxed for 4 h. The solvent was evaporated and the residue crystallized from CH_2Cl_2–MeOH (7 mg, 70%).

Ester 11: mp 216–218 °C; IR ν_{max} (KBr) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, 3, CH_3, J = 7 Hz), 3.94 (q, 2, CH_2, J = 7 Hz), 5.27 (s, 1, H-10), 6.01 (d, 1, pyrrole H, J = 4.5 Hz), 6.4–7.2 (m, 6, pyrrole H), 7.4–7.6 (2 m, 19, pyrrole H + 19 phenyl H), 8.55 (d, 1, phenyl H, J = 8 Hz); visible (CH_2Cl_2) $\lambda_{shoulder}$ 605 nm (3700), λ_{max} 495 (30 700), 422 (29 000); mass spectrum m/e (%) 756 (M^+·, 88), 683 (15), 679 (27), 670 (8), 605 (8), 582 (100).

Anal. Calcd for $C_{48}H_{34}N_4O_2Ni$: C, 76.10; H, 4.53; N, 7.40. Found: C, 75.70; H, 4.34; N, 7.23.

Treatment of 10 or 11 with Base. A solution of **10** (0.265 mg) in CH_2Cl_2 (10 mL) was transfered into a UV cell and flushed with argon. Triethylamine (0.04 mL) was added and the reaction followed at 675 nm. Transformation into **1** was complete within 12 min. Using the same conditions **11** remained unchanged over a day.

Registry No.—**1**, 55820-93-4; **2**, 55820-92-3; **5**, 57766-46-8; **6**, 57766-47-9; **7a**, 57811-82-2; **7b**, 57808-62-5; **8a**, 61664-37-7; **8b**, 58165-65-4; **9**, 61587-64-2; **10**, 61664-38-8; **11**, 57781-98-3.

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(8) All melting points are uncorrected. Infrared and visible spectra were recorded on a Perkin-Elmer 457 and a Cary 118 spectrophotometer, respectively. Proton magnetic resonance (^{1}H NMR) and ^{13}C NMR spectra were recorded on a Perkin-Elmer Model R-12 and a Varian Model XLS-100, respectively. The chemical shift values are expressed in δ values (ppm) relative to tetramethylsilane internal standard and the coupling constants in hertz (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet). Mass spectra (70 eV) were recorded on a LKB 9000 mass spectrometer equipped with a direct inlet system. Combustion analysis were performed by the Service Central de Microanalyses du C.N.R.S., Division de Strasbourg. Separation and purification of the products were obtained using Merck silica gel 60 (70–230 mesh) or Merck standardized alumina (II–III).

Photolysis of Allyl Iodide in Aromatic Solvents

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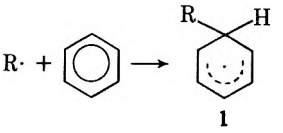
Photolysis of allyl iodide in aromatic solvents gives rise to allylated products. Isomer distribution and both total and partial rate factors determined for this reaction show a slightly electrophilic character of the substitution reaction. Total rate factors correlate well with the first ionization potentials of the aromatic substrates (slope −0.56, correlation coefficient 0.9966).

The first step in homolytic aromatic substitution in most of the cases investigated is a nonreversible exothermic addition of the attacking radical to the π system of the substrate, leading to a σ complex (1).



1

This reaction path is typical for highly reactive radicals like phenyl.[1] Positional selectivity and polar effects are normally low, if particular choice of highly polar solvents and substrates does not affect the original nonpolar character of the transition state.[2] The reaction may become reversible if the attacking species gives a relatively weak bond with the aromatic in the σ complex or if the stability of the attacking radical is increased; for instance, the homolytic aromatic thioarylation is very likely a reversible reaction, in which the aromatization step is of great importance in determining the products.[3,4] We wish now to report experiments in which a possible precursor of the stable π-delocalized allyl radical was decomposed in aromatic solvents.

Results

Photolysis of allyl iodide in aromatic substrates gives in almost every case investigated a good yield of isomeric allyl arenes (Scheme I); the presence of propene as a by-product was proved by mass spectrometry and no hydrogen iodide was observed in the reaction mixture. Low yields of high molecular weight iodinated by-products were detected in the reaction at very high reaction times; this does not seem, however, to affect isomer distribution of substitution products and relative reactivities between different substrates; reaction products are stable in the condition employed. In order to avoid any possible source of errors, in the quantitative experiments test analyses were carried out at different reaction times, but no variation of results was observed.

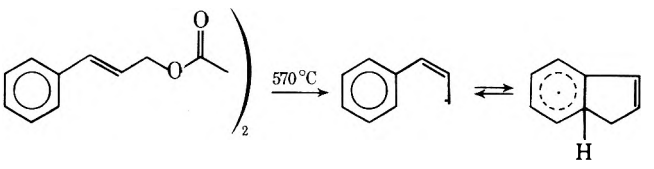
Scheme I

$$CH_2{=}CHCH_2I \xrightarrow[ArH]{h\nu} CH_2{=}CHCH_2Ar$$

$$+ I_2 + CH_2{=}CHCH_3 + (CH_2{=}CHCH_2)_2 \text{ (traces)}$$

No isotope effect on the products was found in the allylation of equimolecular benzene/benzene-d_6 mixtures. This result may be considered as indicative of the unimportance of the reverse reaction in the addition step at room temperature. Actually, a *reversible* intramolecular allylation reaction has been proposed by Trahanowsky and Ong[5] to explain an isotope effect k_H/k_D of 2.92 determined by analysis of the indene fraction obtained from pyrolysis of di-*trans*-o-deuteriocinnamyl oxalate at 570 °C (Scheme II).

Scheme II



Tables I and II report the reactivity data obtained from competitive experiments in which allyl iodide was photolyzed in a large excess of equimolecular solution of benzene and a substituted benzene or thiophene; total and partial rate factors were calculated in the usual way, assuming a reaction scheme in which products were formed by nonreversible parallel reactions of the same order, and the yield of conversion Ia → allyl arene not dependent on the particular isomer formed. This aromatization step is probably similar to that proposed by other workers[6] in the photolysis of CH_3HgI in aromatic solvents; iodine atoms are the oxidizing species, possibly through an addition–elimination process, and the so-formed hydrogen iodide then reduces the unreacted allyl iodide to propene. Product analysis is consistent with this mechanism.

Table I. Isomer Distribution of Allylation Products in the Photochemical Reaction between Arenes and Allyl Iodide

$$ArH + CH_2{=}CHCH_2I \xrightarrow{h\nu}$$

$$CH_2{=}CHCH_2ArH]\cdot + I\cdot \rightarrow CH_2{=}CHCH_2Ar$$
Ia

Arene	% ortho (or α)	% meta (or β)	% para
−OMe anisole	47.6 (69.4)	16.0 (18.1)	36.4 (12.5)
$-CH_3$ toluene	45.8 (66.5)	32.4 (19.3)	21.8 (14.2)
−Cl chlorobenzene	51.9 (50.1)	27.9 (31.6)	20.2 (18.3)
Methyl benzoate	(57.0)	52.4 (17.5)	47.6 (25.5)
Benzonitrile	46.0 (60.0)	25.9 (10.0)	28.1 (30.0)
Thiophene	63.8 (93.1)	36.2 (6.9)	

In parentheses are reported the corresponding data for the homolytic phenylation reaction.[7]

Analysis of the data reported in the tables reveals a generalized low reactivity of ortho positions in the aromatic substrates with respect to the data observed in homolytic substitution reactions, particularly pronounced when the substituent is bulky, and "electrophilic character" of the attacking species.

In addition, isomer distribution and partial rate factors indicate that electronic stabilizing factors on σ complexes (Ia) have a low effect in determining reactivity.

On the other hand, it is of particular interest to note that the logarithms of *total* rate factors (K_{tot}) correlate well with the first ionization potentials (I_1) of the aromatic reagent,[9] giving a straight line (correlation coefficient 0.9966; slope −0.56) (Figure 1). The only point that does not fall on the straight line is that for anisole. This correlation includes substituted benzenes, thiophene, and naphthalene. The same kind of correlation does not hold for the homolytic phenylation of the same substrates. In addition, no good σ–ρ relationship is obtainable from *partial* rate factors of the allylation reaction, although there exists a fairly good correlation between Hammett σ constants and *total* rate factors for this reaction (slope −0.55; correlation coefficient 0.988).

The linear relationship observed between first ionization potentials of the substrates and relative reactivities may be an indication of a mechanism in which the rate-determining step has a small but defined charge-transfer character.

A quantum yield study on the products of this photochemically initiated substitution may clarify details of the reaction mechanism.

Experimental Section

GLC analyses were carried out with Varian 1520 and 712 gas chromatographs, equipped with flame-ionization detectors, and with the gas chromatograph–mass spectrometer system JEOL JMS D100.

Reference Compounds. *o*-,[10] *m*-,[11] and *p*-[12] allylanisole, *o*-,[13] *m*-,[11] and *p*-[13] allyltoluene, *o*-,[14] *m*-,[11] and *p*-[11] allylchlorobenzene, *p*-allylmethyl benzoate,[15] 2-allylthiophene,[15] and α- and β-allylnaphthalene[16] were synthesized as reported in the literature.

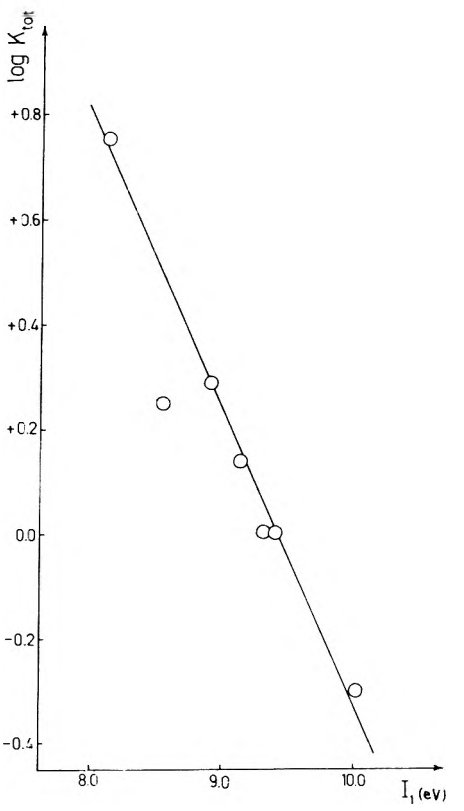


Figure 1. Plot of logarithms of total rate factors for the homolytic allylation reaction against the first ionization potentials of the aromatic reagents.

***o*-Allylbromobenzene.** To the solution of Grignard reagent obtained from o-iodobromobenzene (21.2 g) and magnesium turnings (2.1 g) in dry ether was slowly added under stirring 10.3 g of allyl bromide and the solution was refluxed for 1 h. Workup of the hydrolyzed reaction mixture gave the title product as an oil (11.5 g), bp 96–98 °C (18 mm).

Anal. Calcd for C_9H_9Br: C, 54.85; H, 4.60; Br, 40.55. Found: C, 54.70; H, 4.51; Br, 40.48.

***o*-Allylmethyl Benzoate.** To a solution of *n*-butyllithium [prepared from *n*-butyl bromide (11 mL) and lithium wires (1.4 g) in dry ether] was slowly added at 0 °C *o*-allylbromobenzene (18.0 g), and the solution was stirred for 3 h. The solution was then added to a mixture of solid CO_2 and dry ether and left overnight. The carboxylic acid obtained after workup was directly treated with diazomethane; 11 g of o-allylmethyl benzoate was obtained as an oil, bp 133–134 °C (18 mm).

Anal. Calcd for $C_{11}H_{12}O_2$: C, 75.01; H, 6.86. Found: C, 75.02; H, 6.96.

***m*-Allylmethyl Benzoate:** bp 136–137 °C (18 mm).

Anal. Calcd for $C_{11}H_{12}O_2$: C, 75.01; H, 6.86. Found: C, 74.86; H, 6.96.

***o*-Allylbenzonitrile** was prepared from *o*-allylbromobenzene (1.9 g) and cuprous cyanide (1.9 g) in boiling dimethylformamide, yield 1.1 g, bp 122–124 °C (18 mm).

Anal. Calcd for $C_{10}H_9N$: C, 83.87; H, 6.34; N, 9.78. Found: C, 83.92; H, 6.44; N, 9.85.

Table II. Total and Partial Rate Factors for the Photochemical Allylation of Some Aromatic Substrates

Substrate	K_{tot}	$f_{ortho\ (or\ \alpha)}$	$f_{meta\ (or\ \beta)}$	f_{para}
C_6H_6	1	1	1	1
$C_6H_5OCH_3$	1.77 (1.71)	2.52 (3.56)	0.85 (0.93)	3.86 (1.29)
$C_6H_5CH_3$	1.37 (1.23)	1.88 (2.50)	1.33 (0.71)	1.79 (1.00)
C_6H_5Cl	1.01 (1.06)	1.55 (1.60)	0.83 (1.00)	1.20 (1.20)
C_6H_5COOMe	0.69 (1.77)	(3.00)	1.08 (0.93)	1.99 (2.70)
C_6H_5CN	0.50 (3.70)	0.70 (6.50)	0.39 (1.1)	0.85 (6.50)
Thiophene	1.94 (2.6)[8]	3.75 (7.25)	2.12 (0.5)	
Naphthalene	5.71	Not determined		

Table III

Substrate	No. of expts	Standard deviation on % ortho (f_o)	% meta (f_m)	% para (f_p)	K_{tot}	Yield, %
$PhOCH_3$	3	0.70 (0.07)	1.01 (0.05)	0.52 (0.07)	0.03	46
$PhCH_3$	3	0.62 (0.05)	0.50 (0.05)	0.44 (0.04)	0.03	34
PhCl	3	0.85 (0.15)	0.46 (0.07)	1.13 (0.18)	0.1	
PhCOOMe	5		1.20 (0.09)	1.20 (0.11)	0.04	
PhCN	3	0.17 (0.03)	0.46 (0.01)	0.35 (0.04)	0.02	15
Thiophene	4	[α] 0.61 (0.08)	[β] 0.61 (0.07)		0.04	

***m*-Allylbenzonitrile,** bp 124–126 °C (18 mm) (Found: C, 83.72; H, 6.41; N, 10.03), and *p*-allylbenzonitrile, bp 128–129 °C (18 mm) (Found: C, 83.75; H, 6.42; N, 9.69), were prepared as described above for the ortho isomer from the corresponding bromo derivatives.[17]

3-Allylthiophene. To a solution of *n*-butyllithium prepared from *n*-butyl bromide (22.6 mL) and lithium wires (2.73 g) in dry ether was added 3-bromothiophene (32.6 g) at −70 °C, and the reaction mixture was stirred for 1 h. Allyl bromide was then added and the solution after 1 h at −70 °C was allowed to reach room temperature. After workup 12.0 g of the title product was obtained as an oil, bp 66–68 °C (18 mm).

Anal. Calcd for C_7H_8S: C, 67.70; H, 6.49; S, 25.82 Found: C, 67.58; H, 6.53; S, 26.04.

Photolysis of Allyl Iodide in Benzene. A solution of allyl iodide (0.1 mL) in benzene (4 mL) in a quartz vessel was carefully degassed in a vacuum line, then photolyzed for 12 h in a water bath at 25 °C using a Hanovia 100-W medium-pressure mercury lamp, about 5 cm away.

The vessel cooled at −20 °C was then directly connected to the gas inlet of a JEOL JMS D100 mass spectrometer. The presence of propene was detected by recording the spectrum.

The solution was then analyzed by GLC; unreacted allyl iodide was recovered (60% of the starting material) and the yield of allylbenzene was 26% (based on the reacted iodide). Small quantities of biallyl were also detected.

Isotope Effect in the Allylation of Benzene. The reaction was carried out as above on a solution of benzene (5 mL) and benzene-d_6 (Merck Uvasol 99.5% D, 5 mL). The molar ratio benzene:benzene-d_6 was determined by mass spectrometry, at a nominal ionizing voltage of 15 eV (relative intensities of $M^{\cdot+}$ and $M^{\cdot+}$ + 6). No substantial quantities of less deuterated benzenes were present in the solution.

After irradiation, the allylbenzene + allylbenzene-d_5 fraction was separated by preparative GLC [Varian 712 instrument; Bentone 34–didecyl phthalate (1:1), 15% on Chromosorb W AW-DMCS 45–60] and analyzed by mass spectrometry (15 eV). The ratio allylbenzene: allylbenzene-d_5 determined both by the relative intensities of ($M^{\cdot+}$):($M^{\cdot+}$ + 5) and ($M^{\cdot+}$ − 1):($M^{\cdot+}$ + 4) was identical with the initial ratio benzene:benzene-d_6.

Competitive Experiments. In a typical experiment, to an equimolecular mixture of benzene (1.7504 g) and toluene (2.0271 g) was added freshly distilled allyl iodide (0.816 mL) and the solution was irradiated in a sealed quartz vessel at 25 °C with a Hanovia 100-W medium-pressure mercury lamp. The reaction was directly analyzed first with a GC/MS system [5% Bentone 34:didecyl phthalate (1:1) on Varaport 30; 80–100 mesh; 3-m chromatographic column] in order to identify the reaction products, then isomer ratios and partial and total rate factors were determined by normal gas chromatography (flame ionization detector).

The results, reported in Tables I and II, are mean values of at least three determinations; Table III reports the number of independent experiments, standard deviations, and, when determined, total yield of allylated products.

Acknowledgment. We acknowledge support from the Consiglio Nazionale delle Ricerche, Rome.

Registry No.—*o*-Allylbromobenzene, 42918-20-7; o-iodobromobenzene, 583-55-1; allyl bromide, 106-95-6; *o*-allylmethyl benzoate, 61463-59-0; CC_2, 124-38-9; diazomethane, 334-88-3; *m*-allylmethyl benzoate, 61463-60-3; *o*-allylbenzonitrile, 61463-61-4; cuprous cyanide, 544-92-3; *m*-allylbenzonitrile, 61463-62-5; *p*-allylbenzonitrile, 51980-05-3; *m*-allylbromobenzene, 18257-89-1; *p*-allylbromobenzene, 2294-73-1; 3-allylthiophene, 33934-92-8; 3-bromothiophene, 872-31-1; allyl iodide, 556-56-9; benzene, 71-43-2; anisole, 100-66-3; toluene, 108-88-3; chlorobenzene, 108-90-7; methyl benzoate, 93-58-3; benzonitrile, 100-47-0; thiophene, 110-02-1.

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Influence of Substitution on the Photochemistry of Rigid Cyclopentenones[1]

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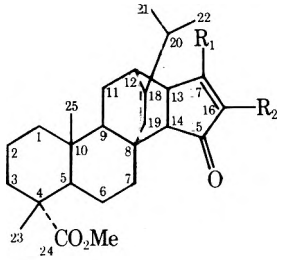
The rigid cyclopentenones **1c, 1d,** and **1e** were synthesized and photolyzed for comparison with the behavior of **1a,** which undergoes normal [2 + 2] photocyclization to **2a,** and **1b,** which undergoes intramolecular energy transfer from the cyclopentenone chromophore to the isolated double bond and a subsequent series of intramolecular hydrogen transfers. In solution, **1c** underwent competitive [2 + 2] photocyclization to **2c** and type I cleavage followed by steps eventuating in an oxycarbene rearrangement to **11. 1d** underwent photodimerization, whereas **1e** underwent [2 + 2] photocyclization to **2d.** The absence of products resulting from intramolecular hydrogen transfer is ascribed to the circumstance that **1c** and **1e,** like **1a** and unlike **1b,** have low-lying n–π^* enone triplets (77 K, phosphorescence). The difference in the results between **1c** and **1e** is explained in terms of the different values of the triplet energies (75 and 72 kcal/mol).

The photochemistry of the rigid cyclopentenones **1a** and **1b** exhibits surprising differences.[2-5] Whereas irradiation of **1a** yielded the expected [2 + 2] photocyclization to **2a,** irradiation of **1b** produced not only **2b** by a *reversible* photochemical reaction, but also *irreversibly* **3** by a then[2] unprecedented intramolecular energy transfer from cyclopentenone chromophore to the isolated double bond followed by hydrogen abstraction by C-19 from the C-10 methyl group.[2-4] In turn, **3** undergoes further photochemically induced hydrogen transfer to form **4a**[2-4] and **5.**[5] The photochemical mechanism of these unusual reactions has been investigated in some detail.[5] The difference between the photochemical behavior of **1a** and **1b** was attributed to the nature of the lowest lying triplet (^{3}n,π^*, in the case of **1a,** $^3\pi,\pi$ in the case of **1b**) and the possibility that more than one enone triplet may be involved in the formation of **2b** and **3** from **1b** and the formation of **4** and **5** from **3.**[5]

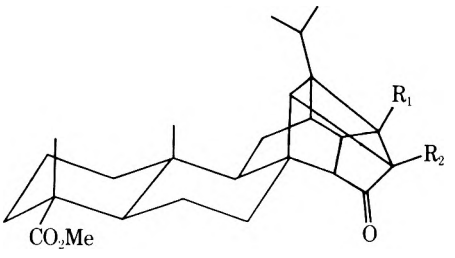
It seemed of interest to synthesize other derivatives of **1a** and to study their photochemical behavior. Details of such a study are reported herewith.

Syntheses of Starting Materials. In analogy with the initial step in the conversion of **1b** to **1a,**[3] reaction of **6** with lithium reagents was expected to furnish a series of 3-substituted cyclopentenones. Thus, addition of methyllithium to **6** at −70 °C in ether for 15 min and acid workup yielded **1c** quantitatively. The UV spectrum exhibited the characteristic absorption of a β-substituted α,β-unsaturated cyclopentenone and the NMR spectrum displayed the typical α-proton frequency at 5.7 ppm allylically coupled to the β-methyl signal at 1.85 ppm. Other signals corresponded to those previously observed.[3] In a similar fashion reaction of **6** with phenyllithium afforded a quantitative yield of **1d.** Again, UV and IR spectra exhibited the characteristic absorption of a β-substituted α,β-unsaturated cyclopentenone; in this instance, the H-16 singlet was sharp owing to absence of long-range coupling with the five protons of the phenyl group which appeared as a complex band in the 7.5-ppm region.[6]

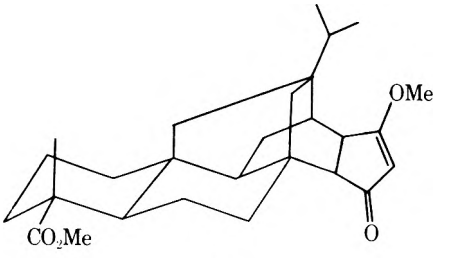
Introduction of substitution into the 16 position was a somewhat more complex matter and utilized the Favorskii rearrangement of epoxides of benzoquinone adducts which we developed earlier.[3,7] Reaction of methyl levopimarate with methyl *p*-benzoquinone yielded the two isomeric adducts **7a** and **7b,** mp 160 and 195 °C (5:6 ratio), which were separated easily by fractional crystallization from acetone and methanol.



1a, R_1, R_2 = H
b, R_1 = OMe; R_2 = H
c, R_1 = Me; R_2 = H
d, R_1 = Ph; R_2 = H
e, R_1 = H R_2 = Me
f, R_1, R_2 = Me



2a, R_1, R_2 = H
b, R_1 = OMe; R_2 = H
c, R_1 = Me; R_2 = H
d, R_1 = H; R_2 = Me



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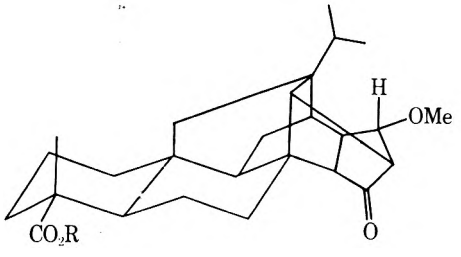
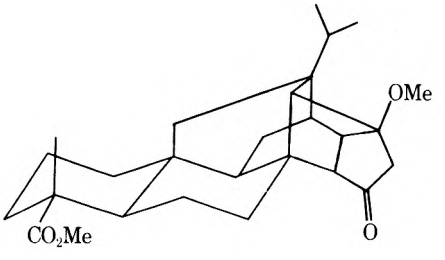


4a, R = Me
b, R = H



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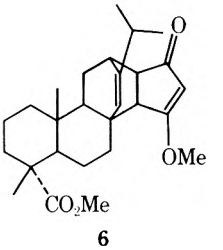

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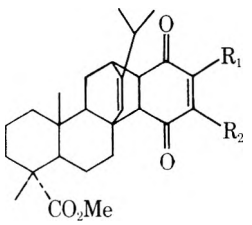
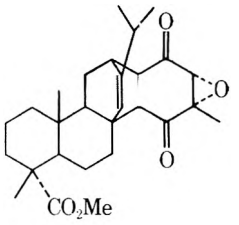


7a, R_1 = Me; R_2 = H
b, R_1 = H; R_2 = Me



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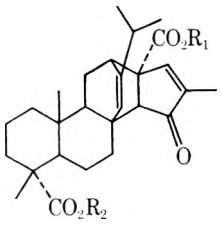
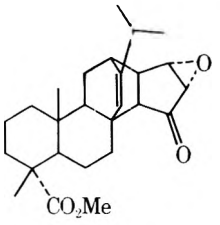


9a, R_1, R_2 = H
b, R_1, R_2 = Me
c, R_1 = H; R_2 = Me



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Structure assignment rested on subsequent transformations. The conventional method of epoxidation (H_2O_2–NaOH) of both isomers resulted only in recovery of starting material. However, oxidation of **7b** in dioxane–THF at room temperature by slow addition of H_2O_2 in the presence of aqueous $NaHCO_3$ gave an excellent yield of an epoxide subsequently shown to be 8.

Although it might have been expected that Favorskii rearrangement of 8 would produce a mixture, exposure of 8 to 10% aqueous NaOH in 95% ethanol resulted in isolation of only one rearranged γ-carboxy-α-methyl-α,β-unsaturated ketone (70% recrystallized yield) later shown to be **9c.** Apparently abstraction of H-14 by base encounters considerably more steric hindrance than abstraction of H-13. The NMR spectrum of the rearrangement product was compatible with an α,γ-disubstituted α,β-unsaturated ketone (β-vinyl proton at 7 ppm coupled allylically to a narrowly split vinyl methyl resonance). A singlet at 2.6 ppm could be attributed to H-14 and the presence of a carboxyl group was evident chemically and spectroscopically (IR spectrum; NMR resonance at 11.3 ppm exchangeable with D_2O).

Attempts to decarboxylate **9c** in the manner described for the lower homologue[3] gave only the diester **9b.** Hydrolysis of **9b** gave **9a.** However, decarboxylation of **9c** was efficiently carried out by heating it to the melting point in a nitrogen atmosphere. This furnished **1e** in quantitative yield. The ORD curve of **1e** exhibited a negative Cotton effect like that of the lower homologue **1a;** a Δ^{15}-17 ketone would have been expected to display a Cotton effect of opposite sign.[3] Consequently, the product was indeed **1e** and its precursors **7b,** 8 and **9c.**

Photolyses. Irradiation of **1e** in methanol (Pyrex filter) by the procedures previously employed for **1a** and **1b** gave the [2 + 2] photocyclization product **2d** exclusively. The structure of the product was evident from the IR spectrum, which exhibited carbonyl absorption at 1770 (strained ketone) and 1720 cm^{-1} (ester), in analogy with **2a** and **2b,** and the NMR spectrum, which was devoid of all low-field signals attributable to vinyl protons, but exhibited the required number of methyl resonances (methoxyl at 3.65 ppm, C-4 methyl and C-16 methyl superimposed at 1.15 ppm, unshielded C-10 methyl at 0.80 and isopropyl doublets centered at 0.92 ppm).

Irradiation of **1d** in methanol (Pyrex filter) for 24 h gave a complex mixture from which one pure substance was isolated in 30% yield. The NMR spectrum of this material indicated that the 18,19 double bond had been retained (broadened singlet at 5.20 ppm typical of H-19 and highly shielded methyl resonance at 0.5 ppm typical of C-10 methyl in normal Diels–Alder adducts). The remaining methyl groups (carbomethoxyl at 3.60, C-4 methyl singlet at 1.10, and isopropyl doublets at 0.8 and 0.6 ppm) were also in evidence. The absence of other low-field signals and the presence of a sharp singlet at 2.8 ppm characteristic of a proton α to a carbonyl group in a cyclobutane ring indicated that the product was one of the four possible dimers of **1d.** This conclusion was supported by the high-resolution mass spectrum, which was superimposable on the high-resolution mass spectrum of the precursor **1d,** thus indicating extremely facile fragmentation of the dimer under electron impact even at low voltage. Work on the structure of the dimer is in progress.

Table I. ^{13}C NMR Spectrum of 11[a]

C-1	38.5 t	C-15	104.9 d
C-2	17.2 t	C-16	59.6 d
C-3	36.9 t	C-17	27.4
C-4	47.3	C-18	89.7
C-5	49.9 d[a]	C-19	56.9 d
C-6	31.2 t	C-20	27.8 d
C-7	35.2 t	C-21	14.6 q[e]
C-8	31.4[b]	C-22	20.4 q[d]
C-9	47.9 d[a]	C-23	179.0
C-10	35.5[b]	C-24	17.2 q
C-11	20.2 t	C-25	16.5
C-12	32.9 d	C-26	51.6 q
C-13	24.3 d[c]	C-27	22.5 q[d]
C-14	23.3 d[c]	C-28	54.1 q

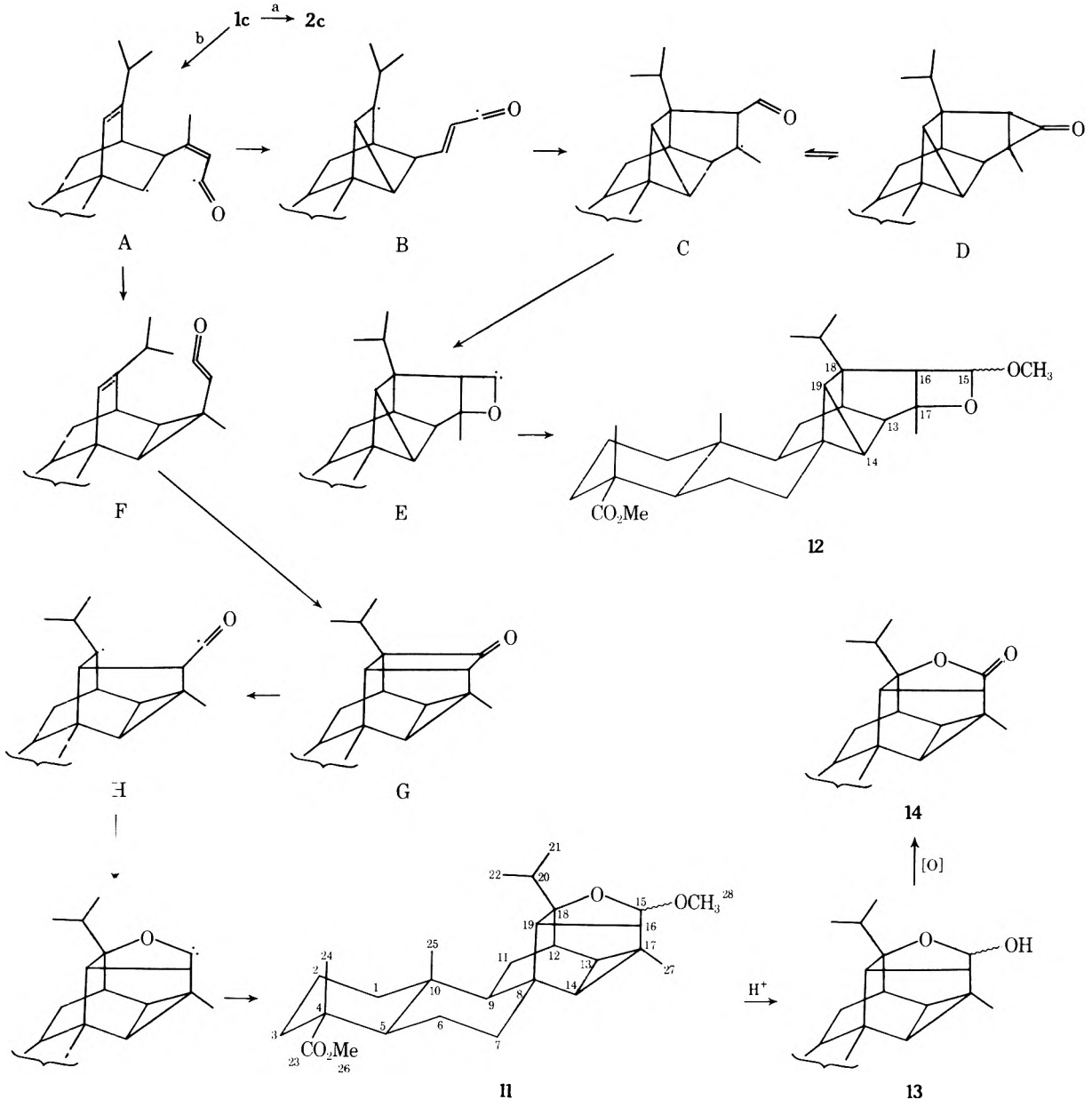
[a] Run in $CDCl_3$ at 67.905 MHz on Bruker HX-270 MHz instrument in a microcell, using Me_4Si as internal standard. [b,c,d] Assignments may be interchanged. [e] Assignment based on shielding of corresponding proton resonance.

Irradiation of **1c** in methanol (Pyrex filter) for 24 h gave equal amounts of two noncrystalline products (total yield quantitative) which were separated by preparative TLC. The less polar substance was the [2 + 2] photocyclization product **2c** whose structure was deduced by the same criteria previously employed for **2c** [IR bands at 1770 (strained ketone) and 1720 cm^{-1} (ester), NMR spectrum devoid of signals downfield from the methoxyl at 3.7 ppm]. The C-10 methyl signal occurred at a normal frequency of 0.8 ppm since it was no longer deshielded by a 17,18 double bond.

Analysis and high-resolution mass spectrum of the noncrystalline, more polar product demonstrated the empirical formula $C_{28}H_{42}O_4$, i.e., the inclusion of an extra molecule of methanol. Its spectral properties (ester band at 1720 cm^{-1}, absence of hydroxyl absorption or ketone bands, the latter confirmed by CD measurements which showed complete transparency in the 250–375-nm region, NMR signals at 4.82 singlet, 3.80 methoxyl of ester, 3.30 methoxyl of ether as the result of incorporation of a molecule of methanol, C-4 methyl and C-10 methyl signals at 1.18 and 0.80 ppm) indicated a structure entirely different from the previous photoproducts. Especially noteworthy was the remarkable great chemical shift difference between the methyl signals of the isopropyl group at 0.90 and 0.45 ppm and the conversion of the C-16 methyl group of **1c** to a singlet.

These data and the noise-decoupled ^{13}C NMR spectrum of the unknown photolysis product (see Table I), which exhibited the requisite 28 signals (six singlets, nine doublets, six triplets, and seven quartets), confirmed the absence of a ketone group, showed the absence of vinyl carbons, displayed a doublet at 104.8 ppm in the range of acetal or ketal carbons consonant with the proton singlet at 4.82 ppm and a singlet at 89.7 ppm attributable to the other terminus of the acetal which must be quaternary, as well as the quartet of a methoxyl group at 54.1 ppm, led to the conclusion that formation of the

Scheme I



second product must have initially involved a type I cleavage of **1c**, and, at some subsequent stage, reaction of an oxycarbene with methanol **9**. Of the two possible structures **11** and **12** (Scheme I), which satisfied the spectral data given so far,[10,13] **11** was shown to be correct as follows.

Serendipitously, it was discovered that the photoproduct underwent hydrolysis on silica during attempts at purification by TLC. Hydrolysis on a preparative scale ($CHCl_3$–HCl) resulted in irreversible formation of a hemiacetal (IR band at 3600 cm^{-1}) whose NMR spectrum was identical with that of the photoproduct except for the absence of the methoxyl resonance and a slight downfield shift (to 4.95 ppm) of H-15. This was more in keeping with structure **11** than with **12**, which because of the strain inherent in the four-membered ring of **12** would have been expected to form a hemiketal less spontaneously after hydrolysis. Lastly oxidation of the hemiketal with Jones reagent resulted in quantitative conversion to a γ-lactone **14** which exhibited IR bands at 1770 (γ-lactone) and 1720 cm^{-1} (ester) and no NMR signals downfield from the methoxyl resonance at 3.62 ppm. Thus the polar photolysis product of **1c** was **11**. The path from **1c** to **11** is outlined in Scheme I. Path b is the typical type I photochemical cleavage of cyclic ketones. Formation of B from A leading eventually to the discarded possibility **12** would involve participation of the 18,19 double bond analogous to reactions involved in somewhat simpler bicyclo[2.2.2]octene systems which in turn would result in another radical C. The latter could stabilize itself by forming a cyclopropane D, which, however, would be expected to react further with solvent methanol, or form oxocarbene E which would add methanol to give **12**.

Apparently, however, the preferred mode of reaction of A is intramolecular attack by C-14 on C-17 to form ketene F which adds to the 18,19 double bond to give cyclobutanone G.[14] Cyclobutanones have been shown to undergo photolytic rearrangement to ketals of type **11** by irradiation in hydroxylic solvents, presumably by way of type I cleavage to H and rearrangement to oxocarbenes.[8,9] However, although each step in the formation of **11** has precedent, the concatenation of steps as the result of the proximity of the 18,19 double bond is highly unusual.

That one of the isopropyl methyls resonates at unusually high field is in agreement with **11** since the formula requires that it be sterically compressed and shielded by the acetal oxygen. Such pronounced shielding of one of the isopropyl methyls has been observed previously in derivatives of Diels–Alder adducts where an oxygen is attached to C-18.[15] Moreover, the formation of the five-membered alicyclic ring of C by attack of the keto radical in B on C-18 would be highly

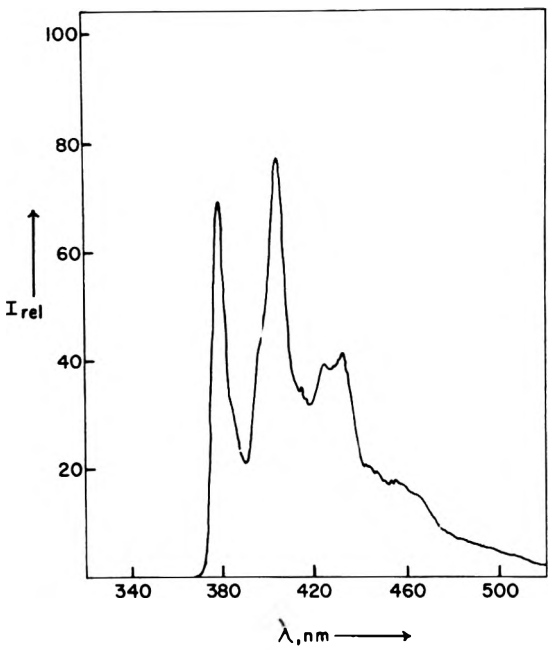


Figure 1. Phosphorescence spectrum of 1c at 77 K in EPA.

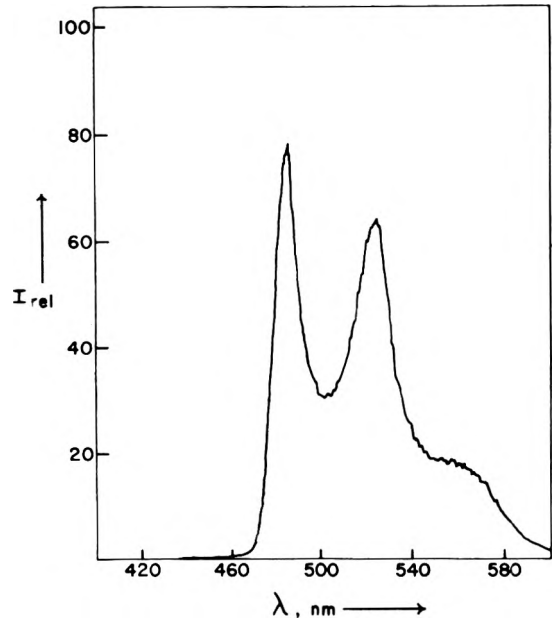


Figure 2. Phosphorescence spectrum of 1d at 77 K in EPA.

unusual, whereas cyclopropane formation by attack of the carbon β to the carbonyl in A on C-14 has been observed previously.[16]

Conclusions

Thus, although the products formed on photolysis of **1c, 1d,** and **1e** differed from compound to compound, the photolyses resembled that of **1a** and differed from that of **1b** in that no products resulting from intramolecular energy transfer to the isolated double bond were isolated. A possible explanation for this is provided by the phosphorescence emission spectra in EPA shown in Figures 1, 2, and 3.[17] These indicate that the lowest emitting triplets of **1c** and **1e,** like that of **1a** whose phosphorescence emission spectrum they resemble,[5] are n–π^*, as the vibrational spacing between the O-0 and the O-1 band corresponds to the stretching frequency of the ketone group. That they do not yield products resulting from intramolecular energy transfer like **1d** which has a low-lying π–π^* triplet is

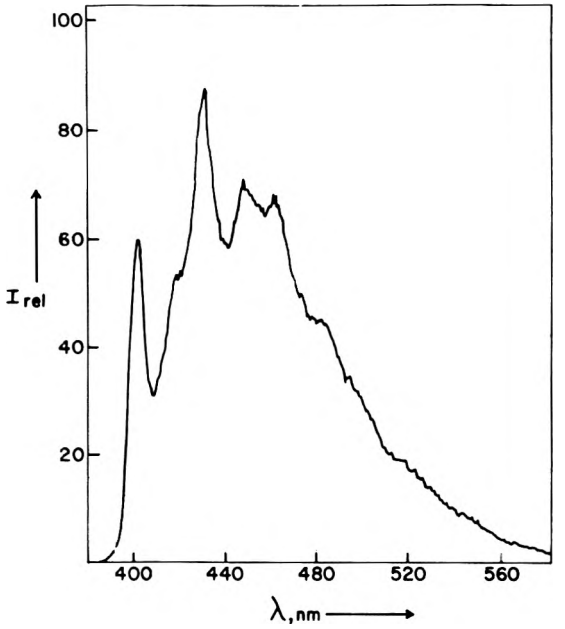


Figure 3. Phosphorescence spectrum of 1e at 77 K in EPA.

therefore understandable in the light of our earlier discussion.[5]

The energies of the triplets of **1a, 1c,** and **1e** are 72,[5] 75, and 72 kcal/mol, respectively. Since the triplet energy of **1e** is the same as that of **1a** it is not surprising that [2 + 2] photocyclization is the only photolytic reaction observed. As for **1c,** it is unusual for a β-alkyl α,β-unsaturated cyclopentenone to have a triplet energy as high as that of saturated ketones, which range from 75–80 kcal/mol and characteristically exhibit Norrish type I cleavage. Consequently, the high triplet energy of **1c** may be responsible for the type I cleavage which initiates the complex series of steps terminating in the oxycarbene rearrangement of Scheme I and competes with the normal [2 + 2] photocycloaddition characteristic of endo Diels–Alder adducts. Parenthetically we note that 2-methyl substitution has not had the effect of altering the characteristics of the phosphorescence spectrum to the extent observed in other rigid cyclopentenones;[18] in view of this, it would be interesting to study the phosphorescence emission spectrum and photochemical behavior of the yet unknown compound **1f.**

The situation with respect to **1d** is somewhat different. Although its phosphorescence spectrum is quite structured, its energy (59 kcal) indicates that it is a perturbed styrene and that the lowest triplet should be π–π^*. Localization of excitation in the styrene unit may be responsible for the circumstance that it undergoes dimerization rather than intramolecular cyclization.

Experimental Section[22]

Preparation of 1c. To a solution of 1 g of 6[3] in 20 mL of ether immersed in a dry ice–acetone bath (nitrogen atmosphere) was added with stirring 4 mL of a 0.2 M solution of methyllithium. After 15 min the reaction was quenched by addition of 20 mL of 5% H_2SO_4. The ether layer was separated, washed, dried, and evaporated to furnish **1c,** which crystallized on addition of hexane: yield 0.9 g; mp (after recrystallization from ethyl acetate–hexane) 170 °C; IR bands at 1720 (ester), 1680 and 1620 cm^{-1} (conjugated cyclopentenone); NMR signals at 5.2 br (H-19), 5.7 br (H-16), 3.51 (methoxyl), 1.85 (vinyl methyl), 1.00 (C-4 methyl), 0.80d J = 7 Hz (isopropyl methyls), and 0.50 ppm d (J = 7 Hz, C-10 methyl); UV λ_{max} (cyclohexane) 238, 323 nm (ϵ 12 100, 62); ORD curve $[\alpha]_{240}$ −2860.

Anal. Calcd for $C_{27}H_{38}O_3$: C, 78.98; H, 9.33; O, 11.69. Found: C, 78.72; H, 9.53; O, 11.70.

Preparation of 1d. The procedure was that employed in the previous section, using phenyllithium in place of methyllithium. The

yield of crude product was quantitative; after recrystallization from ethyl acetate–hexane it melted at 186 °C; IR bands at 1720, 1685, and 1625 cm^{-1}; NMR signals at 7.5 c (5 phenyl protons), 6.38 (H-16), 5.35 br (H-19), 3.8 (methoxyl), 1.18 (C-4 methyl), 0.70 d (J = 7 Hz, isopropyl methyls) and 0.6 ppm (C-10 methyl); UV (cyclohexane) λ_{max} 275, 340 nm (ϵ 19 400, 97).

Anal. Calcd for $C_{32}H_{40}O_3$: C, 81.32; H, 8.53; O, 10.15. Found: C, 81.34; H, 8.41; O, 10.06.

Reaction of Methyl Levopimarate with Methyl *p*-Benzoquinone. (This reaction was originally carried out by Dr. M. G. Nair.) A solution of 40 g of methyl levopimarate in 60 mL of benzene was allowed to stand at room temperature with 14 g of methyl *p*-benzoquinone in 30 mL of benzene for 24 h and evaporated. The resulting mixture was separated by fractional crystallization from acetone–methanol to yield 20 g of **7a**, mp 160 °C, and 24 g of **7b**, mp 195 °C. Both substances exhibited IR bands at 1720 (ester), 1690, and 1620 cm^{-1} (α,β-unsaturated cyclohexenone) and NMR signals at 6.4 br (α proton on α,β-unsaturated ketone), 5.35 br (vinyl proton of bridge), 3.6 (methoxyl), 1.9 d (J = 2 Hz, vinyl methyl), 1.18 (C-4 methyl), 1.00 d (J = 7 Hz, isopropyl methyls), and 0.60 ppm (C-10 methyl).

Anal. Calcd for $C_{28}H_{38}O_4$: C, 76.67; H, 8.73; O, 14.59. Found for **7a**: C, 76.61; H, 8.33; O, 15.02. Found for **7b**: C, 76.83; H, 8.61; O, 14.75.

Epoxidation of 7b. To a solution of 4 g of **7b** in 30 mL of dioxane–tetrahydrofuran was added slowly with stirring at room temperature 10 mL of 10% sodium carbonate solution and 20 mL of 30% H_2O_2. After the yellow color had disappeared, the reaction mixture was worked up in the usual fashion. The product 8 was recrystallized from methanol: yield 3 g; mp 138 °C; IR bands at 1720 cm^{-1} (broad, ester and ketones); NMR signals at 5.6 br (vinyl proton of bridge), 3.7 (methoxyl), 3.4 (H-17), 3.2 br (H-13 and H-14), 1.50 (C-16 methyl), 1.20 (C-4 methyl), 1.00 d (J = 7 Hz, isopropyl methyls), and 0.65 ppm (C-10 methyl).

Anal. Calcd for $C_{28}H_{38}O_8$: C, 73.98; H, 8.43; O, 17.60. Found: C, 74.23; H, 8.45; O, 17.47.

Under these conditions, the isomeric unsaturated ketone **7a** could not be epoxidized.

Favorskii Rearrangement of 8. To a solution of 1 g of 8 in 50 mL of ethanol was added with stirring 10 mL of aqueous 10% sodium hydroxide, the mixture being kept at 50 °C. After 1 h, the solvent was evaporated and the residue diluted with 20 mL of water. The aqueous portion was acidified and extracted with ether. The washed and dried ether extracts were evaporated. Trituration of the remaining gum with methanol–hexane resulted in crystallization of **9c** which was recrystallized from methanol: yield 0.7 g; mp 260 °C; IR bands at 3500 (–OH), 1720 (broad, ester and carboxyl), 1680 and 1620 cm^{-1} (cyclopentenone); NMR signals at 11.3 (carboxyl OH, exchangeable with D_2O), 7.00 br (β-H on cyclopentenone), 3.7 (methoxyl), 2.60 (H-14), 1.68 d (J = 2 Hz, vinyl methyl), 1.18 (C-4 methyl), 1.00 (J = 7 Hz, isopropyl methyls) 0.6 ppm (C-10 methyl).

Anal. Calcd for $C_{28}H_{38}O_5$: C, 73.98; H, 8.43; O, 17.60. Found: C, 73.99; H, 8.38; O, 17.62.

The dimethyl ester **9b** was obtained from **9c** by refluxing with methanol–sulfuric acid under the condition described for successful decarboxylation of the lower homologue.[3] Hydrolysis of the diester gave the dibasic acid **9a**.

Preparation of 1e. A two-neck flask containing 0.2 g of **9c** was swept with a stream of N_2, heated slowly by means of an electrically heated oil bath to 260 °C, and maintained at this temperature for 15 min. Decarboxylation proceeded smoothly at the melting point. After cooling, the product (**1e**) was recrystallized from hexane: yield 0.18 g; mp 148–149 °C; IR bands at 1720 (ester), 1690 and 1620 cm^{-1} (cyclopentenone); NMR signals similar to those of **9c** except for absence of the carboxyl –OH; uv λ_{max} (cyclohexane) 235, 324 nm (ϵ 11 800, 67); ORD curve $[\alpha]_{240}$ −2860.

Anal. Calcd for $C_{27}H_{38}O_3$: C, 78.98; H, 9.33; O, 11.69. Found: C, 79.11; H, 9.10; O, 11.93.

Photolysis of 1e. Irradiation of **1e** (0.01 M solution in methanol, Pyrex filter, 24 h) and evaporation of the solvent gave a gum which was chromatographed over alumina. The chloroform eluate furnished **2d** as a gum in 95% yield: IR bands at 1770 (strained cyclopentanone) and 1720 cm^{-1} (ester); NMR signals at 3.65 (methoxyl), 1.15 br (superimposed C-4 and C-16 methyl), 0.92d (J = 7 Hz, isopropyl methyls), and 0.80 ppm (C-10 methyl).

Anal. Calcd for $C_{27}H_{38}O_3$: mol wt, 410.2820. Found: mol wt (MS), 410.2819.

Photolysis of 1c. A 0.01 M solution of **1c** in methanol was irradiated for 24 h in a quartz immersion well (Pyrex filter) with the usual source (Hanovia 679-A-36 lamp). Evaporation of methanol furnished a gum (quantitative yield) which consisted of a 1:1 mixture of **2c** and **11**. The mixture was separated by preparative TLC; the less polar substance, a gum, being **2c**, IR bands at 1770 (strained cyclopentanone) and 1720 cm^{-1} (ester); NMR signals at 3.7 (methoxyl), 1.10 (superimposed C-4 methyl and methyl on cyclobutane ring), 1.00 ppm d (J = 7 Hz, two isopropyl methyls).

Anal. Calcd for $C_{27}H_{38}O_3$: C, 78.98; H, 9.33; O, 11.69. Found: C, 78.69; H, 9.15; O, 11.86.

The more polar product **11** was also a gum: IR band at 1720 cm^{-1} (ester); NMR signals at 4.82 (proton under methoxyl), 3.8 (ester methoxyl), 3.3 (ether methoxyl), 1.32 (methyl on cyclopropane), 1.18 (C-4 methyl), 0.9 d, 0.45 d (J = 7 Hz, isopropyl methyls), and 0.8 ppm (C-10 methyl). The ^{13}C NMR spectrum is given in Table I.

Anal. Calcd for $C_{28}H_{42}O_4$: C, 75.98; H, 9.56; O, 14.46; mol wt, 442.3082. Found: C, 75.69; H, 9.61; O, 14.20; mol wt (MS), 442.3074.

A solution of 0.1 g of **11** in 20 mL of $CHCl_3$ and a few drops of acetic acid was allowed to stand at room temperature overnight, washed with water, dried, and evaporated. The residue **13** crystallized on trituration with hexane and was recrystallized from ethyl acetate–hexane: mp 173 °C; IR bands at 3600 (–OH) and 1720 cm^{-1} (ester); NMR spectrum superimposable on that of **11** except for the absence of the methoxyl signal at 3.3 ppm which was replaced by a sharp one-proton singlet at 4.95 ppm.

To a solution of 50 mg of **13** in 10 mL of acetone was added dropwise with stirring Jones reagent until the solution became yellow. After 3 h the solution was worked up in the usual fashion; trituration of the product with hexane afforded **14** in quantitative yield. Recrystallization from methanol gave material of mp 183–185 °C; IR bands at 1770 (γ-lactone) and 1720 cm^{-1}; NMR spectrum identical with that of **11** except for the absence of the ether methoxyl singlet.

Anal. Calcd for $C_{27}H_{38}O_4$: mol wt, 426.2768. Found: mol wt (MS), 426.2758.

Photolysis of 1d. Irradiation of a 0.01 M solution of **1d** in methanol for 24 h (Pyrex filter) followed by evaporation of solvent and addition of ether resulted in formation of a crystalline dimer which was filtered and recrystallized from $CHCl_3$–ether: yield 30%; mp 195 °C; $[\alpha]^{CHCl_3}_D$ +142°; IR bands at 1720 cm^{-1} (esters and ketones); NMR signals at 7.0 c (phenyl protons), 5.2 br (vinyl proton of bridge), 3.6 (methoxyl), 2.80 (H-16), 1.1 (C-4 methyl), 0.70 d (J = 7 Hz, isopropyl methyls), and 0.5 ppm (C-10 methyl). The high-resolution mass spectrum was superimposable on that of **1d**.

Epoxidation of 1a. To a solution of a 0.5 g of **1a** in 20 mL of acetone was added with stirring 1 mL of 10% sodium hydroxide solution and 5 mL of 30% hydrogen peroxide. Stirring was continued for 30 min and the mixture worked up as usual. The product (**10**), obtained in quantitative yield, was recrystallized from heptane: mp 170 °C; IR bands at 1720 and 1710 cm^{-1} (ester and ketone); NMR signals at 5.35 br (H-19), 3.5 m (H-17), 3.6 (methoxyl), 3.1 d (J = 3 Hz, H-16), 1.15 (C-4 methyl), 1.05 d (J = 7 Hz, isopropyl methyls), and 0.55 ppm (C-10 methyl).

Anal. Calcd for $C_{25}H_{36}O_4$: C, 75.69; H, 8.81; O, 15.51. Found: C, 75.86; H, 8.81; O, 15.30.

Acknowledgment. The assistance of Mr. R. C. Rosanske with the ^{13}C NMR spectra is gratefully acknowledged. We also wish to thank Professor Jack Saltiel for aid and advice throughout.

Registry No.—**1a**, 21727-58-2; **1c**, 31570-46-5; **1d**, 61570-44-3; **1d** dimer, 61570-45-4; **1e**, 61570-47-6; **2c**, 61570-48-7; **2d**, 61570-49-8; **6**, 21727-52-6; **7a**, 61570-50-1; **7b**, 61570-51-2; **8**, 61570-52-3; **9c**, 61570-53-4; **10**, 61570-54-5; **11**, 61570-55-6; **13**, 61570-56-7; **14**, 61570-57-8; methyllithium, 917-54-4; phenyllithium, 591-51-5; methyl levopimarate, 3513-69-7; methyl *p*-benzoquinone, 553-97-9.

References and Notes

(1) Research supported in part by grants from the National Science Foundation (GP-12582) and from the donors of the Petroleum Research Fund, administered by the American Chemical Society.
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(5) W. Herz, V. S. Iyer, M. G. Nair, and J. Saltiel, *J. Am. Chem. Soc.*, in press.
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(14) Although ketenes readily react with methanol which is used as a solvent, thermally allowed intramolecular reaction of the strained double bond with properly aligned ketene might well take precedence over intermolecular solvent addition.
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(16) W. C. Agosta and A. B. Smith, *J. Am. Chem. Soc.*, **93**, 5513 (1971).
(17) The emission spectra were determined by Mr. Al Marinari in the manner described in ref 5.
(18) R. L. Cargill, W. A. Bundy, D. M. Pond, A. B. Sears, J. Saltiel, and J. Winterle, *Mol. Photochem.*, **3**, 000 (1971), and references cited therein. In the rigid 2-alkyl cyclopentenones discussed in this reference the lowest triplet is π-π^*, but it is apparently very close in energy to n-π^* with the result that vibronic mixing is favored. In such situations, caution is required in relating low temperature spectroscopic observations in rigid systems to room temperature solution photochemistry; moreover, in systems with closely lying lowest excited states the reactive state need not be the one possessing the lowest energy.[19-21]
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(22) Melting points are uncorrected. Analyses were carried out by Dr. F. Pascher, Bonn, Germany. NMR spectra were run on Varian HA-60 or Bruker HX-270 MHZ instruments in $CDCl_3$ and Me_4Si as internal standard, unless otherwise noted. Values for line positions are expressed in parts per million, coupling constants are expressed in hertz. Signals are characterized as d, doublet; t, triplet, q, quartet; br, broad singlet; m, multiplet; c, complex signal whose center is given. Unmarked signals are singlets. Infrared spectra were determined on a Perkin-Elmer Model 257 grating spectrometer in KBr pellets or as Nujol mulls. Ultraviolet spectra were recorded on a Carey Model 14 recording spectrophotometer in 95% ethanol, ORD or CD spectra on a Jasco Model ORD/UV-5 recording spectrophotometer. Silica gel $PF_{254+366}$ (Merck) was used for preparative TLC.

Asymmetric Reduction with Chiral Reagents from Lithium Aluminum Hydride and (*S*)-(−)-*N*-(*o*-Substituted benzyl)-α-phenylethylamines

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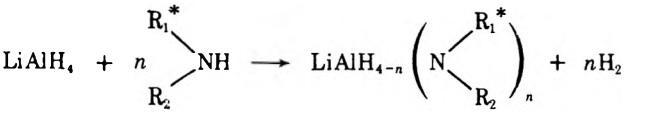
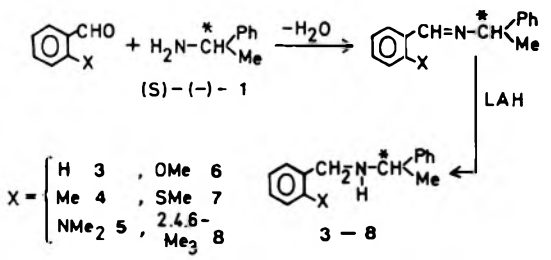
Asymmetric reduction of carbonyl compounds with chiral hydride reagents modified by (*S*)-(−)-*N*-(*o*-substituted benzyl)-α-phenylethylamines (**3**–**8**) in toluene was investigated in order to clarify the role of the functional group in the amine ligands on the stereoselectivity. Of all the functional groups in the chiral secondary amines tested, the NMe_2 group exerted a remarkable effect on the asymmetric reduction of ketones (toluene solvent) affording fairly good optical yields [$PhCH(OH)CH_3$, 43% ee; PhCH(OH)Et, 52% ee; and PhCH(OH)Bu-*t*, 47% ee]. The presence of additives such as 1,2-dimethoxyethane or *N,N,N′,N′*-tetramethylethylenediamine in the reaction mixture caused a dramatic decrease in the stereoselectivity, while that of 1,2-dimethylmercaptoethane did not. These observations strongly suggest that chelate ring formation in the chiral hydride reagent is one of the essential factors for the high observed stereoselectivities.

Reduction of an achiral carbonyl compound by a chiral reducing agent to give unequal amounts of the enantiomeric secondary carbinol has been the subject of much study. Most of such studies have been carried out by use of $LiAlH_4$ derivatives modified by the various chiral ligands.[1] One of the prerequisites for a useful chiral ligand is that it be readily available in optically pure form and that it can be easily recovered from the reaction mixture without any loss of optical purity. So far, various naturally occurring chiral carbinols and their derivatives, such as alkaloids,[2] monosaccharides,[3] terpene alcohols,[4] and tartaric acid derivatives,[5] have been so employed. Recently, synthetic chiral ligands such as (+)-(2*S*,3*R*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol,[6,7] oxazoline derivatives[8] and amino carbinols[9] have been used for the formation of $LiAlH_4$ complexes which provided substantial stereoselectivity.

These hydride reagents employed so far mostly have been limited to the chiral carbinol or amino carbinol complexes and little is known[10] concerning the stereoselectivity of carbonyl reductions with chiral amine–$LiAlH_4$ complexes. A systematic study of the effect of functional group substituents on the chiral amine ligands should afford a better understanding of the mechanism of these asymmetric reductions as well as the necessary information for the design of a more effective chiral amine–$LiAlH_4$ reagent. We have begun such a study using various chiral secondary amines (**3**–**8**) for the reaction with $LiAlH_4$ in various molar ratios. The effect of three achiral complexing additives also has been studied. The chiral reducing agent can be represented by the following scheme.



Ortho-substituted benzaldehydes were condensed with (*S*)-(−)-α-phenylethylamine (**1**) to give the corresponding Schiff bases which were in turn reduced with excess $LiAlH_4$ in boiling ether. The (*S*)-(−)-*N*-(o-substituted benzyl)-α-phenylethylamines (**3**–**8**) thus obtained were purified by



fractional distillation under reduced pressure. These chiral amines are tabulated in Table I.

It was shown conclusively that there was no racemization during the synthesis of amine **3**. The NMR spectrum of *dl* amine **2** in the presence of the chiral shift reagent $Eu(hfc)_3$, tris[3-(heptafluoropropylhydroxymethylene-*d*-campho-

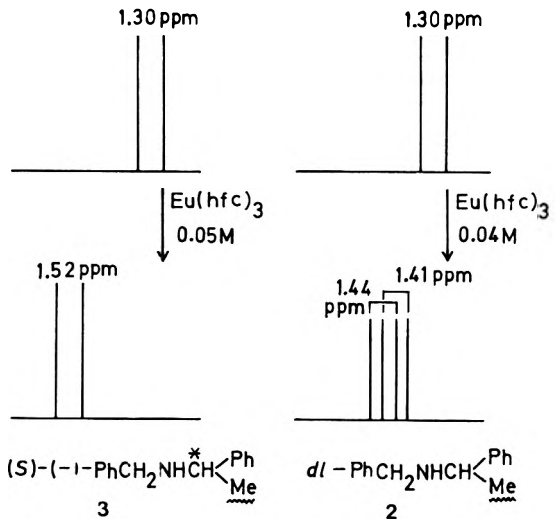


Figure 1. 90-MHz ^1H NMR spectra of Me group of racemic and (*S*)-(−)-*N*-benzyl-α-phenylethylamine (**3**) in the presence of Eu(hfc)$_3$, tris[3-(heptafluoropropylhydroxymethylene-*d*-camphorato]europium(III).

Table I. (*S*)-(−)-*N*-(*o*-Substituted benzyl)-α-phenylethylamines

Chiral amines[a]				
No.	Ortho substituent (X)	$[\alpha]^{25}D$	Bp, °C (Torr)	Yield, %
3	H	−49.2° (c 6.04)[b]	102 (0.03)	83
4	Me	−40.7° (c, 4.85)[b]	104–105 (0.002)	86
5	NMe_2	−53.5° (c 6.59)[b]	128–130 (0.001)	72
6	OMe	−73.7° (c 4.82)[b]	128–130 (0.01)	82
7	SMe	−58.7° (c 6.20)[b]	135–137 (0.005)	73
8	2,4,6-Me_3	−21.9° (c 4.57)[b]	126 (0.01)	80

[a] All compounds gave satisfactory N analysis. [b] Solvent: cyclopentane.

rato]europium(III), reveals the methyl signal as a pair of doublets, one set for each diastereomeric complex. Product **3** prepared from (*S*)-(−)-**1** showed only one set of doublets as seen in Figure 1. Therefore, **3** is enantiomerically pure within the limits of this NMR determination. Based on this it is assumed that **4**–**8** are also enantiomerically pure.

The asymmetric reductions of carbonyl compounds with chiral $LiAlH_4$ complexes have been generally conducted in ether solvents. In the present study, however, the reductions were carried out in toluene solvent in order to eliminate any influence due to coordination of the solvent. $LiAlH_4$ reacts with the excess chiral amines in toluene to give a complex evolving 1 mol of hydrogen at room temperature. At elevated temperature, however, successive reaction takes place evolving 2–3 mol of hydrogen according to the molar ratio of chiral amine employed. The complexes thus formed are soluble in toluene and do not separate even at −78 °C. The reduction of acetophenone with these complexes was carried out under various experimental conditions designed to explore the effect on the extent of asymmetric reduction exerted by (a) ortho substituents in the chiral amine ligands, (b) different molar ratios of the amines to $LiAlH_4$, (c) reaction temperature, and (d) the presence of added achiral complexing agents. The results are summarized in Table II.

Pertinent observations are as follows: (1) In some cases, the degree of asymmetric induction increased with increasing molar ratio of chiral amines to $LiAlH_4$. (2) All of the asymmetric reductions of acetophenone with these complexes (amine/$LiAlH_4$ 3/1) at 0 °C afforded corresponding (*R*)-(+)-carbinol except for the case in which the chiral amine carried the OMe group. (3) In many cases, the extent of preferential attack on the si face of acetophenone with various chiral hydride reagents decreased with decreasing reaction temperature. (4) The highest stereoselectivity was attained with reagent **5** (X = NMe_2, the ratio amine **5**/$LiAlH_4$ 3/1), at 0 °C. Contrary to the expectation, however, the stereoselectivity did not increase with decreasing temperature in this case. (5) As shown in Table III, fairly good optical yields were also obtained for the reduction of PhCOEt and PhCOBu-*t* with this reagent.

As to the roles of NMe_2 group in the chiral amine ligand for stereoselectivity, three possible functions—steric, electronic, and coordinating effects—can be expected. It has been suggested that the presence of coordinating groups such as NMe_2[2] or OMe[9] in the chiral ligand may be necessary for high stereoselectivity, but crucial experimental data about this suggestion have not been reported yet. In order to elucidate this problem, the asymmetric reduction of PhCOEt with $LiAlH_4$–amine **5** complex was carried out in the presence of additives. As shown in Table IV, addition of a two-molar ratio of *N,N,N′,N′*-tetramethylethylenediamine or 1,2-dime-

Table II. Asymmetric Reduction of Acetophenone with Chiral Reagents from $LiAlH_4$ and (*S*)-(−)-*N*-(*o*-Substituted benzyl)-α-phenylethylamines [$HN(R_1{}^*)R_2$]

$$PhCOCH_3 + LiAlH_{4-n}\left(N\begin{matrix}R_1{}^*\\R_2\end{matrix}\right)_n \longrightarrow \begin{matrix}Ph\\CH_3\end{matrix}\!\!>\!CHOH$$

Registry no.	Chiral amines: No.	Ortho substituent	Amine/$LiAlH_4$ mol ratio	Carbinol stereoselectivity: 0 °C % ee	−78 °C % ee
61491-37-0	3	H	2.0	(*R*) 6.8	
			3.0	(*R*) 10.7	(*S*) 5.4
61491-38-1	4	Me	2.0	(*R*) 14.0	
			3.0	(*R*) 8.4	(*R*) 6.1
61491-39-2	5	NMe_2	1.0	(*S*) 5.0	(*S*) 7.2
			2.0	(*R*) 27.0	(*R*) 18.4
			3.0	(*R*) 43.0	(*R*) 30.8
61506-24-9	6	OMe	2.0	(*R*) 5.0	
			3.0	(*S*) 1.2	(*S*) 15.3
61491-40-5	7	SMe	2.0	(*R*) 4.7	
			3.0	(*R*) 4.4	(*S*) 18.0
61522-03-0	8	2,4,6-Me_3	2.0	(*R*) 9.0	
			3.0	(*R*) 10.8	(*R*) 18.0

Table III. Asymmetric Reduction of Ketones with $LiAlH_4$–(Amine 5)$_3$ Complex

Registry no.	Ketone	Extent of redn, %	Carbinol: (Stereoselectivity) % ee	$[\alpha]^{20}D$
93-55-0	PhCOEt	90	(*R*) 52[a]	
938-16-9	PhCOBu-*t*	90	(*R*) 47	+11.3° (c 6.40, benzene)[b]
712-50-5	PhCO-C_6H_{11}	95	(*R*) 14	+ 2.8° (c 7.07, EtOH)[c]
1667-01-2	MeCO-mesityl	28	(*R*) 20	+10.3° (c 1.55, EtOH)[d]

[a] % ee was determined through its (*R*)-(+)-MTPA ester. [b] R. McLeod, F. J. Welch, and H. S. Mosher, *J. Am. Chem. Soc.*, **82**, 876 (1960). [c] M. P. Balfe, G. H. Beaven, and J. Kenyon, *J. Chem. Soc.*, 376 (1951). [d] V. Prelog, E. Philbin, E. Watanabe, and M. Wilhelm, *Helv. Chim. Acta*, **39**, 1086 (1956).

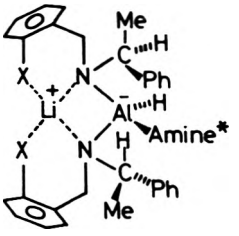
Table IV. Asymmetric Reduction of Propiophenone with $LiAlH_4$-(Amine 5)$_3$ in the Presence of Additives

Additives (XCH_2CH_2X) group X	Carbinol: Extent of redn, %	Carbinol: $[\alpha]^{20}_D$	Carbinol: (c in MeOH)	Carbinol: (Stereoselectivity) % ee
NMe_2	72	+1.1	(2.3)	(*R*)[a] 3.2
OMe	97.5	−0.5	(4.0)	(*S*) 1.4
SMe	99	+18.7	(4.2)	(*R*) 54
No additive added	98	+17.5	(4.3)	(*R*) 51

[a] R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).

thoxyethane to the reaction mixture caused a dramatic decrease in stereoselectivity, with or without inversion of the sign of induction, whereas the addition of 1,2-dimethylmercaptoethane did not. These results indicate that coordination of the ortho NMe_2 group of the reagent with Li cation undoubtedly plays an important role in the stereoselectivity.

The structure of these chiral amine–$LiAlH_4$ complexes in toluene is still obscure. However, it is reasonable to assume that the structures of these complexes resemble that proposed for sodium dihydrobis(2-ethoxymethoxy)aluminate.[11] It is



9 X = NMe_2, OMe, SMe

known[12] that the stabilities of crown ligand–alkaline metal complexes (cation K^+) decrease in the order of electronegativities of the heteroatoms (O > NR > S) in the macrocyclic ligand. The order of chelate ring stabilities of these $LiAlH_4$–amine complexes might be also the same as that of the crown ligand–alkaline metal complexes.

If the stability constant of the chelate ring formation were the sole controlling factor for the stereoselectivity, one might expect that the extent of asymmetric induction would decrease as X in the chiral ligand was changed from OMe to NMe_2 to SMe. This is contrary to observation (Table II). These results suggest that the ortho X substituent functions in more than one capacity, probably both as a coordinating substituent and as a substituent which exerts steric effects as well. In the case of $LiAlH_4$–amine **5** complex represented by formula **9**, two axially oriented N–Me groups are present in the chelate ring when X = NMe_2. These two axial N–Me groups could restrict the conformation of the chiral moiety around the C–N bond thus leading to higher asymmetric induction than observed when X = OMe or SMe. In these latter complexes the methyl groups can assume a nonhindering equatorial orientation.

It is worthwhile to note that the formation of the chelate ring is an important factor to enhance the stereoselectivity even though the chiral center of the ligand is not included in the chelate ring.

Further investigation to explore the more effective chiral amine hydride complex is now in progress.

Experimental Section

Instruments. NMR spectra were taken on a Hitachi R-22, 90-MHz spectrometer. Optical rotations were taken on a Perkin-Elmer 241 electronic polarimeter using 1-dm thermostated microcell. VPC analyses were made on a Shimazu GC-5A using PEG 20M or polydiethylene glycol succinate, 1.5 m × 3 mm column. Preparative VPC was carried out on a Varian Aerograph (Model 700) using the same stationary phase, 2–3 m × 4 mm column.

Solvent and Reagent. Toluene was distilled over NaH and stored over Linde molecular sieve 3A. A stock $LiAlH_4$ solution in ether was passed through a glass filter under nitrogen and stored in a flask closed with a rubber septum. It was analyzed by iodometry[13] immediately prior to use. Aliquots were removed by syringe as needed.

(*S*)-(−)-*N*-Benzyl-α-phenylethylamine (3). A solution of benzaldehyde (15 g) and (*S*)-(−)-phenylethylamine (1) [15 g, $[\alpha]^{20}_D$ −39° (neat)], in 60 mL of benzene was refluxed for 2 h with a Dean-Stark water separator. After the benzene had been removed by distillation, the remaining Schiff base was dissolved in 45 mL of ether, which was then added to a stirred ether solution (75 mL) containing excess $LiAlH_4$ during 30 min. Reflux was continued further for 4 h, after which excess $LiAlH_4$ was decomposed by dropwise addition of ethyl acetate. The reaction mixture was dissolved (dilute HCl) and extracted with ether; the water layer was made alkaline (NaOH) and the separated oil was extracted with ether. The ether extract was washed (H_2O, three times), dried ($MgSO_4$), and concentrated. Fractional distillation under reduced pressure afforded colorless oil, bp 102 °C (0.03 Torr), 21.6 g (83% from the starting 1). VPC analysis indicated that the amine 3 was almost pure (PEG 20M, 1.5 m × 3 mm, 180 °C, N_2 70 mL, retention time 10.9 min), $[\alpha]^{20}_D$ −49.2° (c 6.04, cyclopentane).

Anal. Calcd for $C_{15}H_{17}N$: N, 6.38. Found: N, 6.63.

By a similar procedure, the amines (*S*)-(−)-*N*-(*o*-methylbenzyl)- (4), (*S*)-(−)-*N*-(*o*-dimethylaminobenzyl)- (5), (*S*)-(−)-*N*-(*o*-methoxybenzyl)- (6), (*S*)-(−)-*N*-(*o*-methylmercaptobenzyl)- (7), (*S*)-(−)-*N*-(2,4,6-trimethylbenzyl)- (8) phenylethylamines were also prepared. Satisfactory analytical data (±0.3% for N) were reported for all of these new compounds. These amines were stored in a refrigerator under argon atmosphere.

Asymmetric Reduction of Ketone with $LiAlH_4$–Chiral Amine 5 Complex (Representative Example). Under nitrogen, 1.2 mmol of $LiAlH_4$ in ether was transferred to a 30-mL flask. The ether was removed under high vaccum around 60 °C and the remaining $LiAlH_4$ was allowed to react with 907 mg (3.6 mmol) of amine **5** in 4 mL of toluene. After hydrogen evolution had ceased, the flask was immersed in an oil bath (135 °C) for 10 min, then refluxed for 5 min in order to complete the complex formation. At this point, the solution turned to deep red and most of the $LiAlH_4$ went into solution leaving a small amount of solid that did not dissolve. When cooled, the solution faded to a pale yellow color. To the stirred, cooled toluene solution was added dropwise 120 mg (1.0 mmol) of $PhCOCH_3$ at 0 °C. After the reaction mixture was left for 12 h at 0 °C, excess hydride was decomposed by adding 1 drop of water (evolution of gas) and then excess dilute HCl to remove amine **5**. The ether extract was washed (H_2O, three times), dried ($MgSO_4$), and concentrated. The remaining crude carbinol was purified by preparative VPC to remove the unreacted $PhCOCH_3$ (ca. 10%). (*R*)-(+)-$PhCH(OH)CH_3$ thus obtained had a rotation of $[\alpha]^{20}_D$ +18.1° (c 7.3, cyclopentane). The enantiomeric purity of the carbinol was estimated to be 43% ee by reference to the calibration curve[14] developed by Mosher and Reich.

Asymmetric Reduction of Propiophenone with $LiAlH_4$–(Amine 5)$_3$ in the Presence of Additives. A chiral hydride complex solution made of 4.8 mmol of $LiAlH_4$ and 3.63 g (14.4 mmol) of amine **5** in 16 mL of toluene was divided into four portions (flask no. 1–4). To the above three flasks (no. 1–3) containing the hydride solution (1.2 mmol) were added 2.4 mmol of additives, 1,2-dimethoxyethane (216 mg, no. 1), *N,N,N',N'*-tetramethylethylenediamine (278 mg, no. 2), and 1,2-dimethylmercaptoethane (293 mg, no. 3). After these flasks were immersed in ice bath, 100 mg (0.75 mmol) of PhCOEt was added dropwise to each hydride solution. Processing as in the case of $PhCOCH_3$, to remove the unreacted ketone and additives, gave partially active PhCH(OH)Et. The enantiomeric purity of the carbinol, $[\alpha]^{20}_D$ +17.5° (c 4.3, MeOH), obtained in the control reaction, which had no additive, was confirmed to be 51% ee (*R*)-(+) by NMR method[7] through its (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester. These data are summarized in Table IV.

Acknowledgment. The authors wish to express their deep gratitude to Professor Harry S. Mosher, Stanford University, for his helpful suggestions throughout this work.

Registry No.—**1**, 2627-86-3; **3**, 17480-69-2; **4**, 61491-04-1; **5**, 61491-05-2; **6**, 61491-06-3; **7**, 61491-07-4; **8**, 61491-08-5; benzaldehyde, 100-52-7; acetophenone, 98-86-2.

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Preparation and Reactions of Diorganocuprate Reagents Derived from 2-Lithio-3,3-diethoxypropene. Functionalized Reagents for the Transfer of an α Acrolein Carbanion Equivalent

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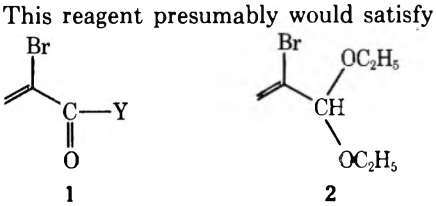
The preparation of several cuprate reagents from 2-lithio-3,3-diethoxypropene is described. The reactivity of these reagents is described with a variety of α,β unsaturated ketones to afford 1,4 adducts in moderate to excellent yields depending upon steric hindrance in the enone. Allylic halides couple but epoxides and saturated vinyl halides are unreactive. Enolate oxygenation experiments are described which allow introduction of an α oxygen via epoxidation of the derived enol trimethylsilyl ether. An interesting solvent effect is observed for this process. The use of ether affords α-benzoyloxy ketones and methylene chloride the α-trimethylsilyloxy ketone. Some model compound experiments suggest that this solvent effect might be general.

The application of organocopper chemistry to synthesis has seen an enormous amount of activity in the recent past. These organometallic reagents have found wide use for selective coupling and alkylation reactions,[2] conjugate addition to various α,β unsaturated carbonyl derivatives,[3,4] as well as acylation.[5] However, the majority of the activity has been directed toward the utilization of simple, readily available lithium reagents. Relatively little is known about the potential for successful formation and use of cuprate reagents containing highly functionalized ligands. Among the examples already documented is the work of the Syntex group on the transfer of the prostaglandin β side chain,[6] as well as the work of Eaton[7] and Heathcock,[8] and that from our laboratories.[9,10]

One class of carbanions which would be particularly valuable would be those derived from α-bromo acrylate derivatives (**1**). A number of potential applications including the synthesis of derivatives of the much sought after α-methylene-γ-butyrolactones[11] were apparent. Marino's elegant use of α-bromoacrylic ester[12] provides a valuable reagent in certain cases; however, this organometallic reagent seems to be of much lowered reactivity, and does not appear to undergo conjugate addition cleanly. Ficini[13] and later Depazay[14] prepared what appeared to be a more promising carbanion for complex formation by metalation of α-bromoacrolein diethyl acetal (**2**). This reagent presumably would satisfy the requirements of complex formation in a more straightforward way and is presumably convertible to all the required oxidation states. After our studies of the complexes derived from this carbanion were nearly completed, two preliminary reports[15,16] of the formation of cuprate reagents derived from **2** appeared. We now report the results of our studies of the utility of these reagents.



1

Y = H, R, OR

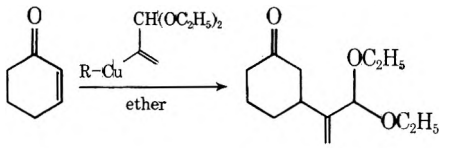
2

We found initially that the homogeneous diorganocuprate reagent derived from **2** and cuprous iodide in the usual fashion proved to be relatively difficult to handle, providing solutions which were not completely homogeneous. The reagent was indeed present as was demonstrated by its addition in moderate yield to 2-cyclohexen-1-one. We turned to the use of mixed reagents without further study in hopes of achieving the preparation of reagents soluble in the usual reaction media, ether and tetrahydrofuran (THF). Mixed diorganocuprate reagents were prepared utilizing *n*-pentynylcopper (**4**),[17] phenylthiocopper (**6**),[18] and *tert*-butylethynylcopper (**5**).[19] Only the latter reagent provided, reproducibly, a nicely soluble reagent. A similar conclusion was reached by Marino.[15]

All the reagents react with 2-cyclohexen-1-one to afford adduct **3** as shown in Table I. Ether appears to be a superior solvent to THF where applicable.

We then set out to determine the reactivity of the cuprate reagent (**5**) [R = $(CH_3)_3CC{\equiv}C$–] with various unsaturated ketones, halides, and epoxides. From the results in Table II, for enones, the reactivity seems comparable to most cuprate reagents. The branched ligand is sterically somewhat more demanding as can be seen by the reduction in yield as the substitution at the β carbon increases. This effect is generally observed, but it is significant that moderate yields are obtained from quite hindered enones such as **7** and **8**. Other

Table I



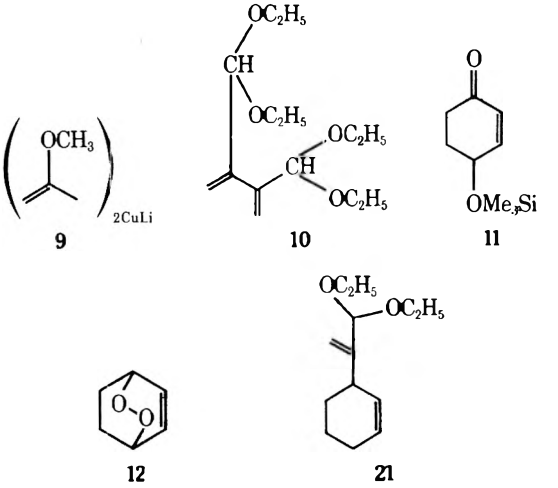
3

4, R = *n*-Pr-≡-	65%
5, R = $(CH_3)_3C$-≡-	92% (85)[a]
6, R = PhS-	50%

[a] Reaction conducted in anhydrous THF.

branched cuprate reagents such as **9** studied by ourselves[10] and Heathcock[8] fail to react appreciably when even a methyl is present at the β position. Typical reaction conditions involve treatment of the substrate with 1.5 equiv of the mixed cuprate reagent at −78 °C, warming to −20 °C for 12 h, and warming to 0 °C for 4 h followed by workup [ammonium chloride–ammonium hydroxide solution (pH 10)]. The cases such as 4 and 5 (Table II) presented some purification problems due to the presence of significant amounts of symmetrical dimer **10**. When the reagent fails to react, the dimer **10** is produced exclusively, presumably via thermal decomposition of the reagent.

4-Hydroxy-2-cyclohexen-1-one trimethylsilyl ether (**11**) reacts extremely readily, producing exclusively the compound derived from addition trans to the 4-trimethylsiloxy group

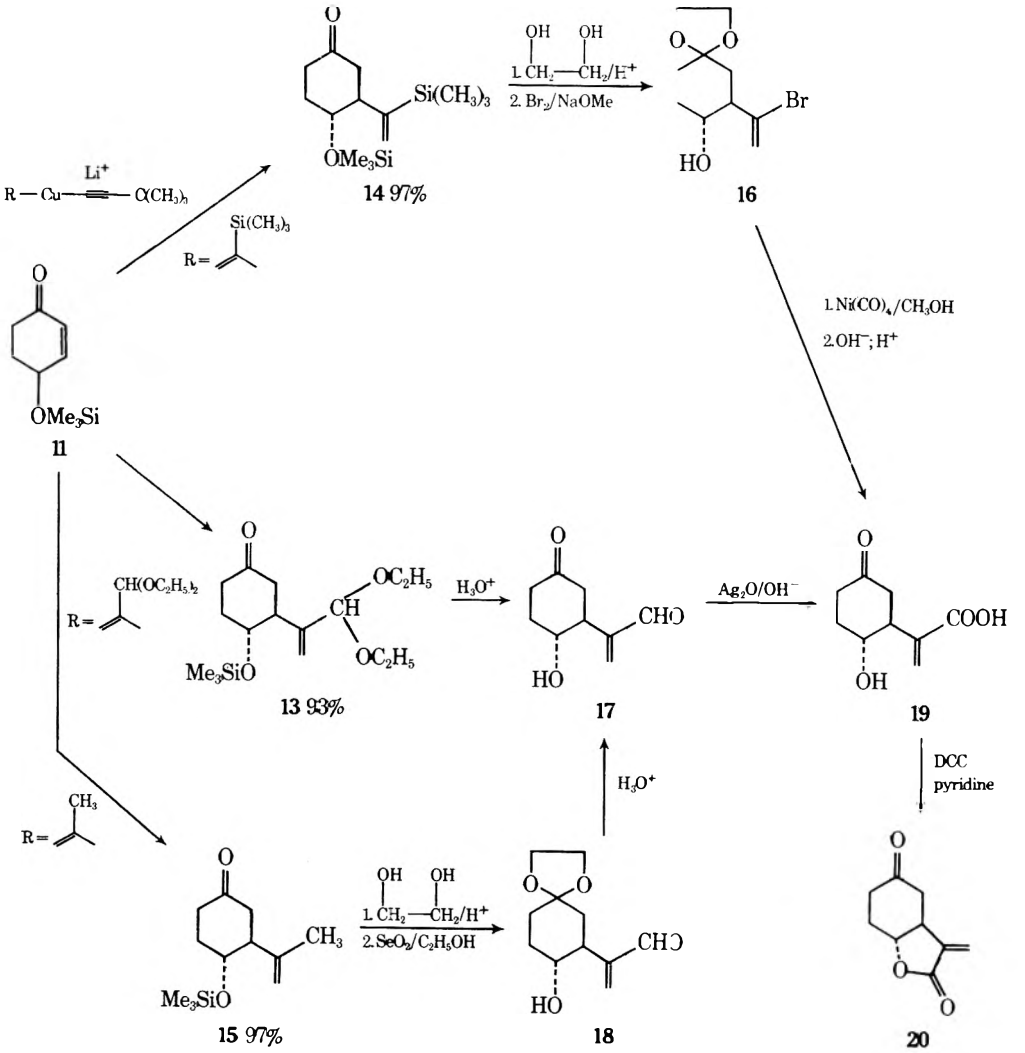


9 **10** **11**

12 **21**

(**13**). The substrate enone (**11**) is prepared conveniently by oxidation of 1,3-cyclohexadiene with singlet oxygen[20] followed by treatment of the endoperoxide (**12**) with pyridine containing a catalytic amount of triethylamine and trimethylchlorosilane. For example, ketone **13** was obtained in 93% yield upon treatment of **11** with 1.5 equiv of cuprate **5** in ether at −78 to 0 °C. Several other substituted cuprates also afforded exclusively trans addition products upon reaction with **11** (Scheme I). Since considerable interest has been generated in the production of trans α-methylene lactones, we proved the structure of the adducts and demonstrated the feasibility of each of these substituted vinyl groups as precursors of keto

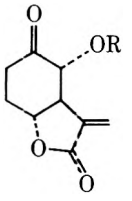
Scheme I



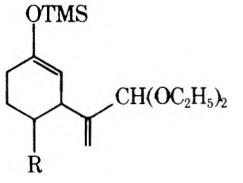
acid **19** and lactones such as **20**. The trans nature of each of the adducts is demonstrated by their conversion to **19** and the characteristic reluctance of this type of hydroxy acid to form the lactones. The corresponding cis lactones close spontaneously.[21]

The coupling reactions of cuprate **5** have also been investigated. Successful coupling with alkyl halides would lead to a variety of α-substituted acrolein derivatives. Of particular interest were the reactions with vinyl halides which would provide access to derivatives of 2-formylbutadiene. We have found that reaction of the cuprate in excess (5–6 equiv) with allylic halide provides 1,4-dienes such as **21** in high yield (98%). However, remarkably, cuprate **5** does not react with primary and secondary vinyl bromides and iodides or a variety of aliphatic primary bromides and iodides, affording only dimer **10** upon prolonged reaction. A variety of solvent and temperatures were investigated without success. A similar selectivity was observed in one case, benzyl bromide, by Grieco.[16] This troublesome lack of reactivity, while severely limiting the generality, should allow the potentially useful selective coupling of an allylic bromide in preference to any other halide or tosylate in a multifunctional molecule. All attempts to open a variety of substituted epoxides were also unsuccessful.

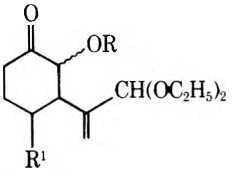
Finally, we have investigated the use of cuprate **5** for the production of dioxygenated lactones such as **22** and determined the potential for stereochemical control in these processes. Oxygenation patterns such as that present in **22** are



22



23, R = H
34, R = OMe_3Si

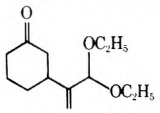
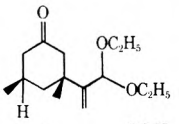
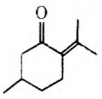
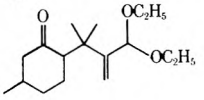
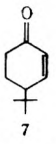
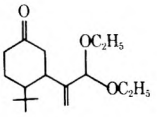
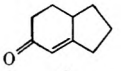
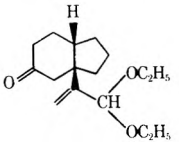


24, R = CC_6H_4Cl; R' = H
25, R = $Si(CH_3)_3$; R' = H
26, R = H; R' = H

35, R = CC_6H_4Cl; R' = OMe_3Si

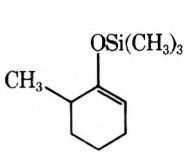
found in a number of naturally occurring terpenes.[22] Initially, our attempts focused upon the oxidation of the enolate formed from the conjugate addition of cuprate **5** to enones. Treatment of the intermediate enolate from the addition of cuprate **5** to 2-cyclohexen-1-one with oxygen,[23] lead tetraacetate,[24] or molybdenum peroxide,[25] all of which have been utilized to oxidize enolates to α-oxygenated systems, were uniformly unsuccessful. Consequently, we turned to the use of the derived enol trimethylsilyl ether **23** which could be isolated in 75% yield by addition of trimethylchlorosilane and triethylamine to the enolate solution.[26] It is well known that enol ethers, upon oxidation with peracids, afford the α-benzoyloxy ketone.[27] However, enol silyl ethers have been shown by Rubottom,[28] and more recently by Hassner,[29] to afford the α-trimethylsiloxy ketones on treatment with peracids in nonpolar media. We have observed a rather remarkable solvent effect for this process. Treatment of silyl ether **23** with *m*-chloroperbenzoic acid in ether at 0 °C to room temperature affords the α-*m*-chlorobenzoyloxy ketone (**24**) as a mixture

Table II

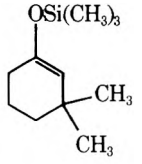
	Substrate	Adduct	Yield,[a] %
1			92
2			56
3			20
4	 7		25
5	 8		30

[a] Isolated yields of products purified by chromatography or distillation.

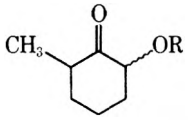
of cis and trans isomers (~1:1). Remarkably, upon treatment of **23** with the same peracid in methylene chloride only the trimethylsiloxy derivative (**25**) is obtained. Consequently it is possible to select either an acid-labile or non-acid-labile group by simply changing the solvent. Control experiments have demonstrated that the production of the benzoyloxy ketone does not proceed via the trimethylsiloxy compound. Exposure of **25** to ethereal *m*-chlorobenzoic acid results only in slow conversion of **25** to the hydroxy compound **26**. Furthermore, we have demonstrated that the products do not arise via the intermediacy of the ketone by conversion of enol silyl ethers **27** and **28** to the *m*-chlorobenzoates **29** and **30** in



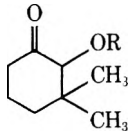
27



28



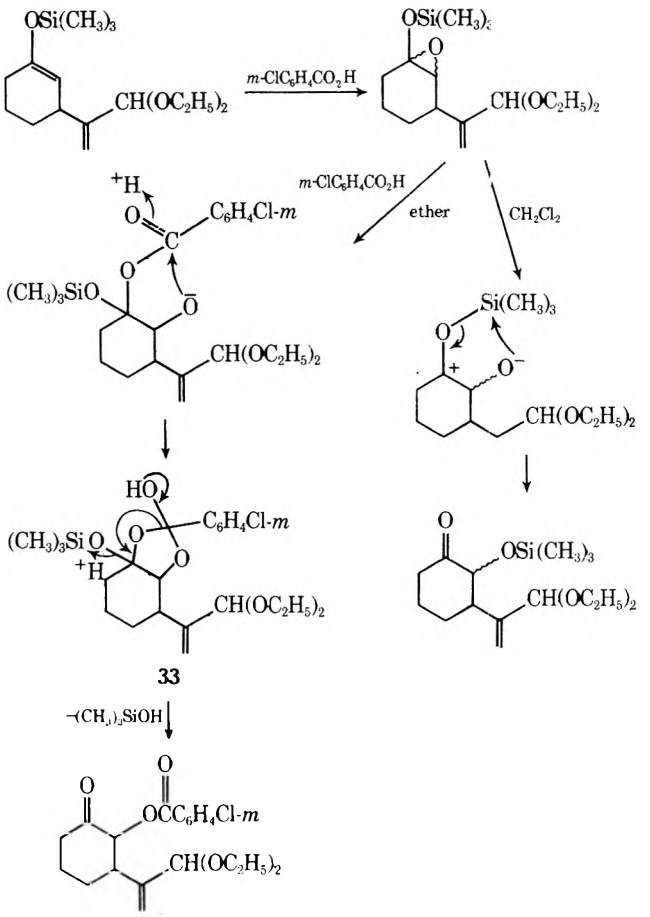
29, R = *m*-ClC_6H_4C
31, R = $Si(CH_3)_3$



30, R = *m*-ClC_6H_4C
32, R = $Si(CH_3)_3$

ether solvent and the silyl ethers **31** ad **32** in methylene chloride It seems that the most plausible explanation for this effect is the enhanced nucleophilicity of the benzoic acid in ether due to higher basicity of ether. This increases the rate of attack of the benzoic acid upon the epoxy ether leading via intermediate **33** to benzoate. In nonpolar media internal transfer of silicon as postulated by Rubottom and Hassner[28,29] is much more rapid (Scheme II). Further experiments to clarify this are in progress. Extension of this process to enone **11** afforded silyl enol ether **34** in 62% yield accompanied by 36% of the ketone **13**. However, treatment of (**34**) with *m*-chloroper-

Scheme II



benzoic acid did not produce the desired benzoate (**35**). We could obtain only the hydrolysis product, ketone **13.**

Summary

The preparation of mixed ligand cuprates from 2-lithio-1,1-diethoxy-2-propene is convenient with the *tert*-butylacetylene ligand preferred owing to enhanced solubilities. The cuprate reagent adds rapidly and in high yield to unhindered unsaturated ketones and sluggishly to more hindered enones. Considerable sensitivity of the reagent to steric congestion about the β carbon of the enone is observed, although additions proceed with some hindered cases but the yields are lower. High selectivity for reaction with allylic halides is shown and this selectivity nicely complements the reactivity of the lithium reagent itself with alkyl halides.[14] We have demonstrated that this cuprate serves as an efficient precursor of trans α-methylene lactones and that the addition of a single oxygen function is possible although presently not with high stereoselectivity or in the presence of a second oxygen function.

Experimental Section

Melting points were determined on a Fisher-Johns or Thomas-Hoover melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained on a Varian T-60 spectrometer and are reported in δ downfield from Me_4Si (internal standard). Infrared (IR) spectra were obtained on a Perkin-Elmer 137 infrared spectrophotometer and are reported in reciprocal centimeters. Mass spectra (high and low resolution) were determined on an AEI MS-9 spectrometer. Reaction solvents such as ether and tetrahydrofuran (THF) were freshly distilled from lithium aluminum hydride under argon to obtain them anhydrous. All reactions involving organometallics were performed in flame-dried, septum capped apparatus under an argon atmosphere. All transfers were via syringe. The copper iodide used was purified by reprecipitation from concentrated potassium iodide after Norit treatment and dried at 100 °C under high vacuum for 12 h. *tert*-Butyllithium was obtained from Alfa Inorganics as ~0.5 M in pentane and used as received. All other commercial materials were purified as appropriate before use.

Lithium (3,3-Dimethyl-1-butynyl)-1,1-diethoxy-2-propenylcuprate (5). A solution of lithio-3,3-dimethyl-1-butyne [prepared from 3,3-dimethyl-1-butyne (0.240 g, 3 mmol) and methyllithium (1.5 mL, 3 mmol, 2.3 M in ether) at 0 °C in ether (4 mL) under argon] was added to a suspension of purified copper iodide (0.570 g, 3 mmol) in ether (4 mL) under argon at 0 °C and stirred at 15–20 °C for 15 min (red color). To a cold (−78 °C) solution of 1,1-diethoxy-2-bromopropene (0.527 g, 3 mmol) in ether (4 mL) under argon, *tert*-butyllithium (5.1 mL, 6 mmol, 1.25 M in hexane) was added dropwise in ~20 min and then stirred for 1.5 h. This solution was transferred by means of a precooled syringe to the above cooled (−78 °C) solution of copper 3,3-dimethyl-1-butyne (3 mmol) and stirred for 2 h. The temperature was then raised to −40 °C and the solution stirred for 30 min. The complete formation of cuprate **5** was assumed when the red color of the copper acetylide disappeared and it was also assumed that this solution contained 3 mmol of **5.**

Lithium (3,3-Dimethyl-1-butynyl)-2-trimethylsilylvinylcuprate and lithium (3,3-dimethyl-1-butynyl)-2-propenylcuprate were prepared analogously. Similar procedures were used to prepare these cuprates in THF.

Preparation of 11 from Endoperoxide 12. Endoperoxide (11.2 g, 0.1 mol), pyridine (20 mL), and a catalytic amount of triethylamine were stirred at room temperature for 12 h. When the endoperoxide was completely consumed (TLC), trimethylsilyl chloride (40 mL) was added slowly through a rubber septum and then stirred for 12 h (followed by TLC). Excess pyridine and trimethylsilyl chloride were removed in vacuo and ether (200 mL) was added. The solution was filtered and the filtrate concentrated. The concentrate was dissolved in ether (50 mL) and then passed through a small column of silica gel and the column further eluted with ether. The combined ether solution was concentrated and distilled to afford **11:** 15.5 g (85%); bp 70 °C (0.4 mm); NMR ($CDCl_3$) δ 0.23 (s, 9 H), 2.4 (m, 4 H), 4.63 (m, 1 H), 6.01 (dd, 1H, J_2 = 10 Hz), 6.98 (q, 1 H, J = 1.2, 2, 10 Hz); IR (film) 1690, 1255, 1110 cm^{-1}; M^+ 184.

Anal. Calcd for $C_9H_{16}O_2Si$: C, 58.69; H, 8.69. Found: C, 60.04; H, 8.65.

***trans*-4-Trimethylsilyloxy-3-(1,1-diethoxy-2-propenyl)cyclohexanone (13).** To the cuprate **5** (3 mmol) in ether, a solution of enone **11** (0.368 g, 2 mmol) in ether (1 mL) was added dropwise at −78 °C, allowed to warm to −15 °C, and then kept at this temperature for 12 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL) and then stirred for 5–10 min. The entire reaction mixture was transferred to a separatory funnel and ether (100 mL) was added. This two-phase mixture was extracted with ammonium hydroxide (20%, 2 × 10 mL). The organic layer was separated, and the aqueous phase extracted twice with ether (20 mL). The combined organic layers were extracted once with saturated sodium chloride and then dried over anhydrous magnesium sulfate. After filtration, the solvent was removed on a rotary evaporator. The residue was distilled (bulb to bulb) to afford **13:** 0.584 g (93%); bp 98 °C (1.0 mm); NMR ($CDCl_3$) δ 0.22 (s, 9 H), 1.3 (t, 6 H), 2.40 (m, 7 H), 3.55 (m, 4 H), 4.20 (m, 1 H), 4.95 (s, 1 H), 5.08 (s, 1 H), 5.32 (s, 1 H); IR (film) 1715, 1250, 1110, 1060, 1010, 880, 840 cm^{-1}; M^+ 314.

Anal. Calcd. for $C_{16}H_{30}O_4Si$: C, 61.14; H, 9.55. Found: C, 60.85; H, 9.61.

3-(1,1-Diethoxy-2-propenyl)cyclohexanone. To the cuprate **5** (3 mmol) in ether, a solution of 2-cyclohexen-1-one (0.196 g, 2 mmol) in ether (1 mL) was added dropwise at −78 °C under argon. After 2 h stirring (−78 °C), the solution attained a red color. The temperature was gradually raised to −20 °C (1 h) and then the mixture was quenched with saturated ammonium chloride (10 mL). The crude product was isolated according to the procedure described for **13.** Distillation (bulb-bulb) afforded the ketone 0.442 g (98%): NMR ($CDCl_3$) δ 1.2 (t, 6 H), 2.4 (m, 9 H), 3.5 (m, 4 H), 4.75 (s, 1 H), 5.10 (s, 1 H), 5.35 (s, 1 H); IR (film) 1710, 1450, 1230, 1110 cm^{-1}; M^+ 226.

***trans*-4-*tert*-Butyl-3-(1,1-diethoxy-2-propenyl)cyclohexanone.** To the cuprate **5** (3 mmol in THF) under argon a solution of 4-*tert*-butyl-2-cyclohexen-1-one (0.152 g, 1 mmol) in THF (1 mL) was slowly added at −78 °C and stirred for 3 h. The reaction mixture was left at −15 °C overnight and at 0 °C for 4 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL) and worked up as described for compound **13** to afford a mixture of products. Preparative thick layer chromatography [silica gel, pentane–ether (1:1)] gave starting enone (0.025 g, 16.4%) and title compound: 0.060 g (25% based on recovered starting material; conversion 81%); NMR ($CDCl_3$) δ 1.00 (s, 9 H), 1.20 (t, 6 H), 2.32 (m, 8 H), 4.80 (s, 1 H), 5.12 (s, 1 H), 5.35 (s, 1 H); IR (film) 1710 cm^{-1}; M^+ 270.

5-(1,1-Diethoxy-2-propenyl)hydrindan-3-one. To the cuprate

5 (3 mmol) in THF, under argon, a solution of indenone (0.272 g, 2 mmol) was added at −78 °C, stirred for 2 h at −78 °C, and then kept at 0 °C for 36 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL) and worked up as described for compound **13** to afford a mixture of compounds. Preparative thick layer chromatography on silica gel (ether–pentane, 1:2) gave starting enone (0.053 g, 20%) and title compound: 0.140 g (29%, based on recovered starting enone, 80.5% conversion); NMR ($CDCl_3$) δ 1.33 (t, 6 H), 2.35 (m, 13 H), 3.65 (m, 4 H), 4.95 (s, 1 H), 5.3 (s, 1 H), 5.98 (s, 1 H); IR (film) 1710, 1110, 1060 cm^{-1}; M^+ 266.

3,5-Dimethyl-3-(1,1-diethoxy-2-propenyl)cyclohexanone. To the cuprate **5** (3 mmol) in THF, under argon, a solution of 3,5-dimethyl-2-cyclohexen-1-one (0.248 g, 2 mmol) in THF (1 mL) was added at −78 °C and stirred for 3 h. The temperature was gradually raised to 0 °C (2 h) and then kept at 0 °C for 24 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL) and then worked up as described for compound **13** to afford a mixture of products. This mixture was separated on preparative TLC (silica gel, ether–benzene, 1:3) to afford starting enone 0.090 g (36%) and the ketone (0.180 g, 55%); conversion 63%. NMR ($CDCl_3$) δ 1.3 (m, 12 H), 2.2 (m, 7 H), 4.90 (s, 1 H), 5.23 (s, 1 H), 5.6 (s, 1 H); IR (film) 1715, 1110, 1070 cm^{-1}; M^+ 254.

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.86; H, 10.23. Found: C, 70.76; H, 10.29.

1-Trimethylsilyloxy-3-(1,1-diethoxy-2-propenyl)-1-cyclohexene (23). The reaction mixture, obtained from cuprate **5** (3 mmol) and cyclohex-2-en-1-one (0.196 g, 2 mmol) as described above for the compound **3**, was quenched with purified trimethylsilyl chloride (3 mL) (added through a rubber septum with the help of a syringe), and then stirred for 2 h at room temperature. Dry pentane (30 mL) was added and the solution stirred for 5 min before filtering and washing with pentane (10 mL). The combined pentane solutions were concentrated on a rotary evaporator. A second portion of pentane (20 mL) was added and the mixture filtered and concentrated. This process was repeated until no more precipitate was formed on further addition of pentane. Column chromatography over silica gel, using benzene as eluent, afforded the silyl ether, 0.447 g (75%): bp 120 °C (0.5 mm) (bulb-to-bulb); NMR ($CDCl_3$) δ 0.2 (s, 9 H), 1.22 (d, 6 H), 2.0 (m, 7 H), 3.5 (m, 4 H), 4.8 (s, 2 H), 5.10 (d, 1 H, J = 1 Hz), 5.3 (d, 1 H, J = 1 Hz); IR (film) 1670, 1250, 1110, 1055, 910 cm^{-1}; M^+ 298.

***trans*-3-(1,1-Diethoxy-2-propenyl)-1,4-ditrimethylsilyloxy-1-cyclohexene (34).** The reaction mixture obtained from cuprate **5** (15 mmol) in THF and **11** (1.84 g, 10 mmol) according to the procedure described for the compound **34**, was quenched with purified trimethylsilyl chloride (15 mL) and stirred for 3–4 h at room temperature (reaction was followed by TLC). Dry pentane (100 mL) was added and stirred for 5–10 min. The precipitate was filtered off and the solids washed with pentane (50 mL). The combined filtrates and washings were concentrated on a rotavapor. To the gummy residue pentane (50 mL) was further added and the precipitate was again filtered off. The filtrate was concentrated. This process was repeated until no more precipitate was separated on further addition of pentane. Column chromatography over silica gel using benzene–ether mixture (20:1) afforded **13** (1.10 g, 30%) and the enol ether (2.4 g, 62%): bp 120 °C (0.5 mm) (bulb-bulb); NMR ($CDCl_3$) δ 0.15 (s, 9 H), 0.20 (s, 9 H), 1.3 (t, 6 H), 3.6 (m, 5 H), 3.2 (m, 1 H), 3.6 (m, 4 H), 4.65 (d, 1 H, J = 4 Hz) 4.88 (s, 1 H), 5.15 (d, 1 H, J = 1 Hz), 54 (d, 1 H, J = 1 Hz); IR (film) 1670, 1380, 1250, 1180, 1070, 910, 850 cm^{-1}; M^+ 386.

2-(*trans*-2-Hydroxy-5-oxocyclohexyl)propenoic Acid Lactone (20). A mixture of pyridine (2 mL), dicyclohexylcarbodiimide (0.640 g), and acid **19** (0.303 g, 1.65 mmol) was stirred for 24 h. (Reaction was followed by TLC.) Dry ether (15 mL) was added, the solution filtered, and the filtrate concentrated on a rotary evaporator. This process was repeated until no more precipitate was formed. Filtrate fractions were discarded and precipitate fractions were collected and extracted with chloroform (3 × 5 mL). The chloroform solution was filtered through a small silica gel column and washed with chloroform (10 mL). The chloroform was removed on a rotary evaporator to give a solid. Crystallization from chloroform–ether (1:10) afforded **20**: 0.150 g (55%); mp 149–150 °C; NMR ($CDCl_3$) δ 2.6 (m, 7 H), 4.22 (m, 1 H), 5.45 (d, 1 H, J = 2 Hz), 6.2 (d, 1 H, J = 2 Hz); IR (Nujol) 1750, 1715, 1425, 1260, 1150, 1130, 1015, 980 cm^{-1}; M^+ 166.

Anal. Calcd for $C_9H_{10}O_3$: C, 65.06; H, 6.02. Found: C, 65.33; H, 6.65.

1-(1,1-Diethoxy-2-propenyl)-2-cyclohexene (21). To the cuprate **5** (10 mmol in THF) under argon a solution of 1-bromo-2-cyclohexene (0.483 g, 3 mmol) in THF (2 mL) was added dropwise at −78 °C and then stirred for 2 h. The reaction mixture was kept at −15 °C for 12 h and then quenched with saturated ammonium chloride (10 mL). The product (**21**) was isolated according to the workup described for **13**, affording 0.617 g (98%): bp 130 °C (0.5 mm) (bulb to bulb); NMR ($CDCl_3$) δ 1.22 (t, 6 H), 2.0 (m, 6 H), 3.0 (m, 1 H), 3.6 (m, 4 H), 4.9 (s, 1 H), 5.18 (s, 1 H), 5.4 (s, 1 H), 5.8 (m, 2 H); IR (film) 1650, 1450, 1320, 1060, 920 cm^{-1}; M^+ 210.

2-(*trans*-2-Hydroxy-5-oxocyclohexyl)propenaldehyde (17). Ethanol (20 mL), water (10 mL), concentrated sulfuric acid (2 mL), and **13** (2.2 g, 9.7 mmol) were stirred at room temperature for 4 h. The alcohol was removed on a rotary evaporator and the solution neutralized with 5% sodium bicarbonate, then extracted with ether in a continuous extractor. The ether solution was dried over anhydrous magnesium sulfate and the solvent removed on a rotary evaporator. The residue was chromatographed over silica gel, first eluting with benzene (50 mL) which was discarded and then with ether (100 mL). Concentration of the ether fraction afforded pure aldehyde (1.15 g, 68%). Distillation caused polymerization. NMR ($CDCl_3$) δ 2.6 (m, 7 H), 4.17 (m, 1 H), 6.30 (s, 1 H), 6.48 (s, 1 H), 9.54 (s, 1 H); IR (film) 3400, 1715, 1705, 1430, 1240, 1075, 965 cm^{-1}; M^+ 168.

2-(*trans*-2-Hydroxy-5-oxocyclohexyl)propenoic Acid (19). To a mixture of ethanol (12 mL), water (12 mL), silver nitrate (0.890 g, 5.28 mmol), and the aldehyde **17** (0.82 g, 4.8 mmol), a solution of sodium hydroxide (1.1 g, 2.6 mmol, in 5 mL of water) was added dropwise at room temperature over 2 h and then stirred for 14 h. The mixture was filtered and acidified with 10% hydrochloric acid. The aqueous solution was extracted continuously with ether, and the ether solution dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a brown liquid which was passed through a small silica gel column in ether. The combined ether solutions were concentrated in vacuo to afford **19** (0.750 g, 85%) which was homogeneous by TLC. Distillation of **19** caused polymerization and it could not be crystallized. NMR (CD_3COCD_3-D_2O) δ 2.32 (m, 7 H), 4.3 (m, 1 H), 5.82 (s, 1 H), 6.5 (s, 1 H); IR (film) 3300, 3700 (broad), 1250 cm^{-1}; M^+ 184.

***trans*-4-Trimethylsiloxy-3-(1-trimethylsilylvinyl)cyclohexanone (14).** To the cuprate prepared from α-bromovinyltrimethylsilane as described for **5** above (3 mmol) in ether, at −78 °C, under argon, a solution of enone **11** (0.368 g, 2 mmol) in ether (1 mL) was added dropwise and stirred for 2 h. The temperature was gradually raised to −15 °C and kept for 12 h. The reaction mixture was then quenched with saturated ammonium chloride (10 mL) and worked up as described for compound **13** affording **14**: 0.520 g (97%); bp 95 °C (0.2 mm) (bulb-bulb); NMR ($CDCl_3$) δ 0.18 (s, 9 H), 0.22 (s, 9 H), 2.2 (m, 7 H), 4.2 (m, 1 H), 5.6 (d, 1 H, J = 0.8 Hz), 5.7 (d, 1 H, J = 0.8 Hz); IR (film) 1715 cm^{-1}; M^+ 268.

***trans*-8-Hydroxy-7-(1-trimethylsilylvinyl)-1,4-dioxaspiro[4.5]decane.** Ketone **14** (0.134 g, 0.5 mmol), ethylene glycol (0.031 g, 0.5 mmol), *p*-toluenesulfonic acid (a few crystals), and benzene were heated at reflux over a Dean-Stark apparatus for 12 h. The benzene solution was concentrated on a rotary evaporator and then ether (10 mL) was added. The ether solution was extracted with water and saturated sodium chloride solution, and then dried over anhydrous magnesium sulfate. After removal of the solvents on a rotary evaporator, the residue was distilled (bulb-bulb) to afford the ketal (0.100 g, 77%): bp 95 °C (0.2 mm); NMR ($CDCl_3$) δ 0.2 (s, 9 H), 1.8 (m, 7 H), 3.8 (m, 1 H), 4.0 (s, 4 H), 5.7 (d, 1 H, J = 1 Hz), 5.9 (d, 1 H, J = 1 Hz); IR (film) 3350, 1370, 1260, 1150, 1080, 920, 860 cm^{-1}; M^+ 256.

***trans*-8-Hydroxy-7-(1-bromovinyl)-1,4-dioxaspiro[4.5]decane (16).** To a solution of the above ketal (0.095 g, 0.42 mmol) in methylene chloride (2 mL), a solution of bromine (0.067 g) in methylene chloride (1 mL) was added at 0 °C in 3 min. Immediately, the solvent was removed on rotary evaporator and the residue was dissolved in methanol (2 mL). This methanolic solution was added to freshly prepared sodium methoxide (0.020 g of sodium in 2 mL of methanol) and stirred for 3 h. The methanol was removed on a rotary evaporator and the residue neutralized with 0.1 N hydrochloric acid. The aqueous solution was repeatedly extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and filtered and the solvent removed on a rotary evaporator to give 0.115 g of gummy material. Column chromatography (silica gel–chloroform) afforded the liquid ketal **16** (0.050 g, 45%): NMR ($CDCl_3$) δ 1.8–2.6 (m, 7 H), 4.1 (s, 4 H), 4.2 (m, 1 H), 5.7 (d, 1 H, J = 1 Hz), 5.9 (d, 1 H, J = 1 Hz); IR (film) 1630, 1460, 1350, 1160, 1070, 1025, 950 cm^{-1}; M^+ 201.

***trans*-8-Hydroxy-7-(1-carbomethoxyvinyl)-1,4-dioxaspiro[4.5]decane.** To a solution of sodium methoxide (0.15 g in 2 mL of dry methanol) and nickel carbonyl (0.26 mL), a solution of **16** (0.05 g, 0.2 mmol) in methanol (2 mL) was added under argon with stirring. The reaction mixture was heated to 55 °C for 5 h and then saturated with carbon monoxide for 15 min. The residue was acidified with 0.1 N hydrochloric acid and then extracted with ether (5 × 10 mL). The combined ether fractions were washed with saturated sodium chloride and then dried over anhydrous magnesium sulfate. After the solvent

was removed in vacuo the residue was chromatographed over silica gel (chloroform) to afford the ketal ester as a liquid (0.02 g, 41.6%): NMR ($CDCl_3$) δ 1.8 (m, 7 H), 3.8 (s, 3 H), 4.1 (s, 4 H), 4.35 (m, 1 H), 5.9 (s, 1 H), 6.45 (s, 1 H); IR (film) 3445, 1695, 1520, 1445, 860 cm^{-1}; M^+ 242.

***trans*-3-(2-Propenyl)-4-trimethylsiloxycyclohexanone (15).** To the ethereal solution of the isopropenyl cuprate prepared as for **5** (3 mmol), under argon at −78 °C, a solution of 4-trimethylsiloxy-2-cyclohexen-1-one (0.368 g, 2 mmol) in ether (1 mL) was added and stirred for 2 h, then kept at −15 °C for 12 h and quenched with saturated ammonium chloride (10 mL). The workup described for the compound **13** afforded **15** (0.440 g, 97%): bp 100–105 °C (2.5 mm) (bulb-bulb); NMR ($CDCl_3$) δ 0.20 (s, 9 H), 1.8 (s, 3 H), 2.5 (m, 7 H), 4.2 (m, 1 H), 4.80 (s, 1 H), 4.95 (s, 1 H); IR (film) 1700, 1200, 1100, 845 cm^{-1}; M^+ 138.

***trans*-7-(2-Propenyl)-8-hydroxy-1,4-dioxaspiro[4.5]decane.** Ketone **15** (0.226 g, 1 mmol), ethylene glycol (0.062 g, 1 mmol), and *p*-toluenesulfonic acid (a few crystals) in benzene were refluxed under a Dean-Stark apparatus for 12 h. The benzene was evaporated and water (2 mL) was added. The mixture was extracted with ether (3 × 8 mL) and the ether extracts were washed with saturated sodium chloride. After drying the organic layer over anhydrous magnesium sulfate, the solvent was removed and the residue was distilled to afford the ketal (0.130 g, 66.5%): bp 140 °C (2.5 mm) (bulb-bulb); NMR ($CDCl_3$) δ 1.8 (m, 7 H), 2.1 (s, 3 H), 3.6 (m, 1 H), 4.0 (s, 6 H), 4.95 (s, 2 H); IR (film) 3450, 1380, 1245, 840 cm^{-1}; M^+ 198.

Conversion of Ketal 15 to 2-(*trans*-2-Hydroxy-5-oxocyclohexyl)propenaldehyde. Selenium dioxide (0.120 g, freshly sublimed), ethanol (3 mL), water (0.25 mL), and the above ketal (0.120 g, 0.6 mmol) were refluxed for 3 h. The solvent was evaporated and the residue extracted with ether (twice). The ether solution was dried and the solvent removed to afford a brown liquid which on chromatography (silica gel–benzene) afforded the aldehyde (0.020 g, 20%). The spectral properties of this material were identical with the spectra of the material prepared from **13**.

2-(*m*-Chlorobenzoyloxy)cyclohexanone. To a solution of 1-(trimethylsiloxy)cyclohexanone (0.340 g, 2 mmol) in dry ether (4 mL), a cold solution of *m*-chloroperbenzoic acid (0.516 g, 3 mmol) in dry ether (3 mL) was added at 0 °C and stirred for 10 min. The reaction mixture was passed through a column (1 × 8 cm) of alumina (neutral, activity I, Woelm) in ether and then concentrated in vacuo to afford the ketone (0.410 g, 81%): mp 152–153 °C (pentane); NMR ($CDCl_3$) δ 1.8–2.8 (m, 8 H), 5.5 (m, 1 H), 7.5 (m, 2 H), 8.1 (m, 2 H); IR (Nujol) 1730, 1720, 1315, 1230, 1215, 1125, 875, 750 cm^{-1}; M^+ 254, 252.

Anal. Calcd for $C_{13}H_{13}ClO_3$: C, 61.50; H, 5.15. Found: C, 61.67; H, 5.13.

2-(*m*-Chlorobenzoyloxy)-6-methylcyclohexanone (29). To a cold solution of 1-(trimethylsiloxy)-6-methyl-1-cyclohexene (0.366 g, 2 mmol) dry ether (4 mL) was added at 0 °C and stirred for 10 min. The reaction mixture was then passed through a small column of alumina (neutral, activity I, Woelm) in ether (30 mL). The combined ether fractions were concentrated on a rotary evaporator to afford **29** (0.250 g, 50%) which could not be crystallized: NMR ($CDCl_3$) 1.1 (d, 3 H), 2.2 (m, 7 H), 4.3 (m, 1 H), 7.8 (m, 4 H); IR (film) 1720, 1450, 1250, 1120, 1000, 845 cm^{-1}; M^+ 268, 266.

2-(*m*-Chlorobenzoyloxy)-3,3-dimethylcyclohexanone (30). To a cold solution of 1-(trimethylsiloxy)-3,3-dimethyl-1-cyclohexene (0.396 g, 2 mmol) in dry ether (4 mL), a cold solution of *m*-chloroperbenzoic acid (0.516 g, 3 mmol) in dry ether (3 mL) was added at 0 °C and then stirred for 10 min. The reaction mixture was then passed through a small column of alumina (neutral, activity I, Woelm) in ether (30 mL). The combined ether fractions were concentrated on a rotary evaporator. The NMR spectrum showed the presence of the ketone resulting from the hydrolysis of the starting material. Chromatography on silica gel using a pentane–ether mixture afforded semisolid **30** (0.410 g, 73%). This material was homogeneous on TLC. NMR ($CDCl_3$) δ 1.1 (s, 3 H), 1.24 (s, 3 H), 2.1 (m, 6 H), 5.2 (s, 1 H), 2.6 (m, 2 H), 8.1 (m, 2 H); IR (film) 1720 (b), 1370, 1250, 1120 cm^{-1}; M^+ 282, 280.

Anal. Calcd for $C_{15}H_{17}O_3Cl$: C, 64.28; H, 6.07. Found: C, 64.15; H, 6.07.

2-Trimethylsilyloxy-3-(1,1-diethoxy-2-propenyl)cyclohexanone (25). Utilizing the procedure of Hassner,[29] silyl enol ether **23** (48 mg, 0.28 mmol) afforded ketone 25 (40 mg, 80%). TLC and VPC analysis showed a mixture of two epimeric substances (~1:1): NMR ($CDCl_3$) δ 0.2 (s, 9 H), 1.25 (d, 6 H) 2.0 [m (br), 7 H], 3.85 (m, 4 H), 4.5 [s (br), 1 H], 5.0 (s, 1 H), 5.28 (s, 1 H), 5.5 (s, 1 H); IR (film) 1720, 1250, 1105, 1050, 835 cm^{-1}, M^+ 314.

2-(*m*-Chlorobenzoyloxy)-3-(1,1-diethoxy-2-propenyl)cyclohexanone (24). To a cold solution (0 °C) of 1-trimethylsiloxy-3-(1,1-diethoxy-2-propenyl)-1-cyclohexene (0.149 g, 0.5 mmol) in dry ether (1 mL) was added a solution of *m*-chloroperbenzoic acid (0.130 g, 0.75 mmol) in ether (1 mL). The mixture was stirred for a total of 1.5 h during warming to room temperature. The total reaction mixture was applied to a small column of alumina and eluted with ether (20 mL). Removal of the solvent gave ketone **25** (95 mg, 50%) as a mixture of isomers (~1:2): NMR ($CDCl_3$) δ 1.25 (m, 6 H), 2.5 (m, 7 H), 3.8 (m, 4 H), 4.8 (m, 1 H), 5.2–5.6 (m, 3 H), 7.5–8.1 (m, 4 H); IR (film) 1720, 1275, 1250, 1110, 1050, 750 cm^{-1}; M^+ 382, 380.

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On the Mechanism of the Molybdenum and Vanadium Catalyzed Epoxidation of Olefins by Alkyl Hydroperoxides

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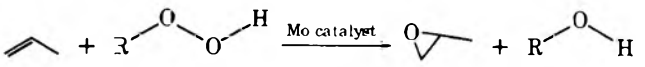
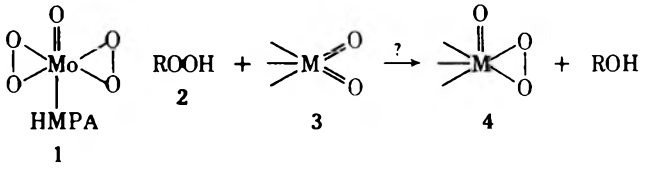
Epoxidations carried out in the presence of ^{18}O-enriched water provide evidence that the intact alkyl hydroperoxide is present in the activated complex responsible for oxygen transfer to the olefin. The literature mechanisms for these epoxidations are criticized, and a new mechanistic approach is presented.

On a worldwide basis almost a billion pounds of propylene oxide will be produced this year by the molybdenum catalyzed epoxidation of propylene with alkyl hydroperoxides (Halcon process[1]):



The by-product alcohol (ROH) is either converted to styrene (R = α-phenethyl) or used as an octane booster in gasoline (R = *tert*-butyl). In spite of the importance of this very efficient epoxidizing system some essential facts concerning the mechanism are missing.[2] For example, it is not known whether the alkyl hydroperoxide (or some coordinated version of it) is present in the activated complex which effects transfer of the oxygen atom to the olefin. A priori one cannot exclude initial reaction of the alkyl hydroperoxide with the metal producing the alcohol and a metal species which epoxidizes the olefin in a subsequent step. This latter possibility seemed especially worthy of consideration following the important discovery by Mimoun, de Roch, and Sajus that molybdenum(VI) peroxo compounds, such as **1**, stoichiometrically epoxidize olefins under anhydrous conditions in organic solvents.[3]

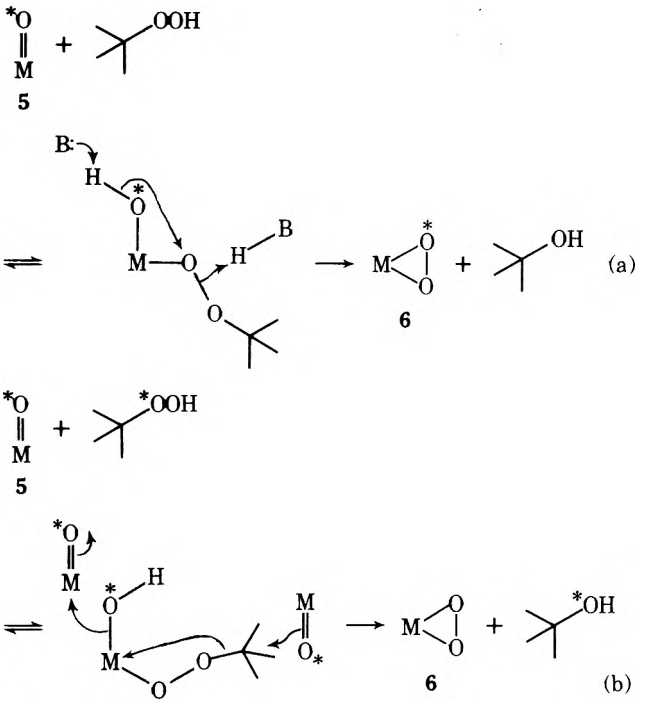


Thus these French workers[3] and several other groups[2,5] including ourselves[4] speculated that the active oxidants in the catalytic systems might also be peroxo species (**4**, analogous to **1**) generated in situ by reaction of the alkyl hydroperoxide (**2**) with a metal oxo compound (**3**). There are reports, albeit under fairly drastic conditions, that molybdenum compounds react with alkyl hydroperoxides to give peroxo complexes.[5] We made numerous unsuccessful attempts to isolate peroxo complex **1**, under the normal (*tert*-butyl hydroperoxide, PhH, reflux) $Mo(CO)_6$ catalyzed reaction conditions, by adding HMPA at different stages. Promising-looking yellow mixtures (**1** is yellow) were sometimes obtained, but all efforts at purification failed.[6]

The issue of whether or not the alkyl hydroperoxide is directly involved in the epoxidation step is an important one. No serious mechanistic considerations can begin until this question is answered. It seemed that an ^{18}O-labeling experiment might provide useful information. We had previously shown that the oxo oxygen of peroxo complex **1** exchanged rapidly with ^{18}O-enriched water, and that there was no scrambling of the oxo and peroxo oxygens.[4] It was this selectively labeled specimen of **1** which enabled us to demonstrate that only the peroxo oxygens of **1** were transferred during epoxidation of olefins.[4]

In order to speculate on how a peroxo–metal linkage might arise from interaction of an alkyl hydroperoxide and a metal species, one must know something about the nature of the metallic catalyst under the reaction conditions. Sheldon has made the important observation that the same *cis*-dioxomolybdenum(VI) diol complex is isolated from these epoxidations regardless of which molybdenum compound is initially added as catalyst.[7] For this and other reasons[8] it seems very likely that the active catalytic species bear oxometal groups. If peroxo species are formed from reaction of alkyl hydroperoxides with the oxometal groups on the catalyst, we feel that the two reaction paths shown in Scheme I are the most

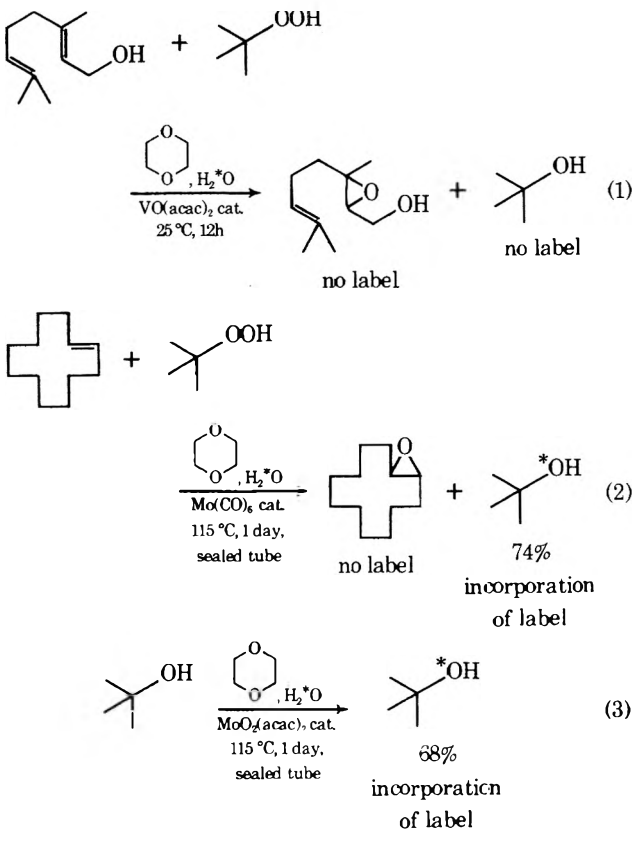
Scheme I. Peroxo Mechanisms



reasonable alternatives. Since these epoxidations proceed readily under anhydrous conditions, and since the alcohol is formed in essentially quantitative yield, path a appears more likely than path b. In path b the only oxygen nucleophile available, under the usual dry conditions, to capture the incipient tertiary cation would be a metal oxo group; it is not likely that this would be an efficient enough process to account for the high yields of *tert*-butyl alcohol observed.

The oxometal group **5** is shown as labeled in both pathways in Scheme I. It is apparent that if such labeling was possible, one could determine whether either of these peroxo paths were involved. Path a predicts ^{18}O incorporation into the epoxide (via the partially labeled peroxo species **6**) but none into the *tert*-butyl alcohol, and path b predicts label in the *tert*-butyl alcohol but none in the epoxide. Since oxo transition metal compounds are known to exchange readily with water,[9,4] we tested for the involvement of the peroxo paths in Scheme I by carrying out epoxidations in the presence of ^{18}O-enriched

Scheme II. $H_2{}^{18}O$ Incorporation Experiments

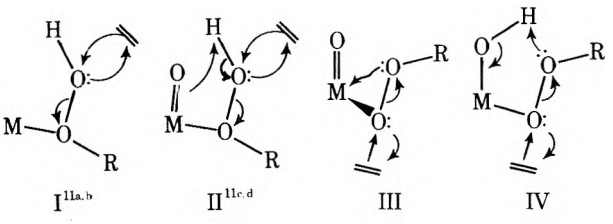


water. As shown in Scheme II, both the vanadium and the molybdenum systems were examined. The epoxidations were carried out in dioxane containing 10% by volume 66% ^{18}O-enriched water. Lucidol 90% *tert*-butyl hydroperoxide was dried by swirling with anhydrous magnesium sulfate prior to use. The reactions were performed using 1% of the metal catalyst, excess olefin (2 equiv), and 0.15 mmol of the hydroperoxide all in 0.5 mL of the dioxane–water (9:1) solvent. The reactions were continued until the *tert*-butyl hydroperoxide had been consumed. The ^{18}O content of the products was determined by mass spectrometry.

A crucial assumption underlying the interpretation of the experiments in Scheme II is that the rate of exchange of the oxometal groups (**5**, Scheme I) is faster than the rate of formation of the peroxo species (**6**, Scheme I). If, as seems likely,[4,9] this assumption is correct, then the results in Scheme II speak against the involvement of peroxo species (both paths a and b of Scheme I) in these oxidations. Although experiment 2 (Scheme II) reveals that the *tert*-butyl alcohol has exchanged extensively with the labeled water, the control experiment 3 indicates that, in the presence of a catalytic amount of a molybdenum(VI) compound, *tert*-butyl alcohol is itself extensively exchanged under these rather harsh conditions (115 °C, 1 day).[10] Note that in experiment 1 at room temperature the *tert*-butyl alcohol produced is unlabeled.

Thus it appears that the epoxidation of olefins by the molybdenum peroxo compound **1** is not directly related to the catalytic systems employing alkyl hydroperoxides. The catalytic epoxidations must proceed by a mechanism involving an intact alkyl hydroperoxide; actually all of the detailed mechanistic proposals in the literature fall into this category.[11] In Scheme III are shown the two published mechanisms (I and II) which are most often cited, along with the two new proposals (III and IV) which we feel are more consistent with the facts of these oxidations. Note that the new mechanisms III and IV are rather similar. In III the coordinated peroxide is polarized by a three-centered interaction with an empty

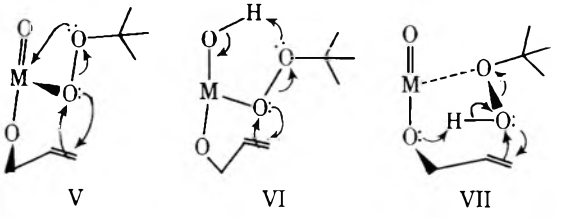
Scheme III. Mechanisms Involving Coordinated Alkyl Hydroperoxide



coordination site on the Lewis acidic metal; thus the transition state resembles that which we favor[12] for epoxidations by the peroxomolybdenum substance **1**. In IV the peroxidic bond is polarized by an acidic hydrogen through a five-membered interaction. In both mechanisms III and IV the epoxide is initially produced coordinated to the metal. It must be emphasized that all of our mechanistic considerations are based on the assumption, which we feel is highly reasonable, that the optimum direction of approach of the olefin to the oxygen will be from the back side and roughly along the axis of the oxygen–oxygen bond.[13]

The previous mechanisms (I and II) are in our opinion less attractive than these new proposals. For one thing they require coordination of the metal to the more hindered hydroperoxide oxygen, but a much more serious shortcoming is their failure to account for the exceptional reactivity of allylic alcohols[14] in these systems. It is geometrically impossible for the double bond of an allylic alcohol to approach the oxidant as indicated in mechanisms I and II, and at the same time coordinate to the metal through its hydroxyl group. By contrast the direction of approach required in mechanisms III and IV is ideal for an allylic alcohol which is simultaneously coordinated through its hydroxyl group to the same[15] metal center. Approximate transition states for the epoxidation of coordinated allylic alcohols via mechanisms III and IV are indicated in V and VI, respectively, of Scheme IV.

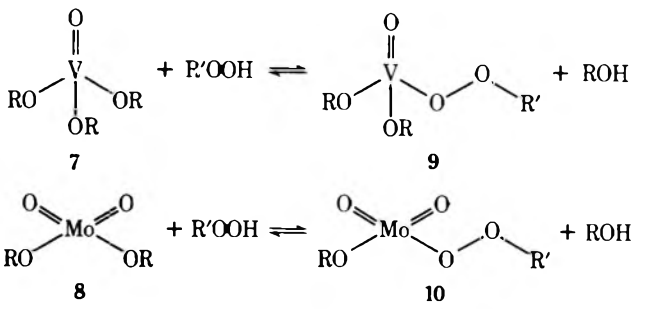
Scheme IV. Epoxidation of Allylic Alcohols



Although mechanisms I and II fail to account for the enhanced reactivity of allylic alcohols in these systems, we have noted a variant on this mechanistic theme which would be consonant with the special reactivity observed with allylic alcohols. This mechanism is shown in VII of Scheme IV, and, like the mechanisms in I and II of Scheme III, involves coordination of the hydroperoxide by the oxygen proximal to the alkyl group. A key feature of this process is the hydrogen transfer from the hydroperoxide oxygen to the oxygen of the coordinated allylic alcohol. Whatever objections might be raised to this mechanism, it at least meets our criterion of geometrical feasibility.

The present work has provided good evidence that the intact hydroperoxide is involved in the epoxidation step. As discussed above, we favor activation of the hydroperoxide by coordination to the metal through the oxygen distal to the alkyl group. Oxo alkoxides such as **7** and **8** are well known[16] for vanadium(V) and molybdenum(VI) and such species are substitution labile. Thus it seems logical to assume that in the presence of alkyl hydroperoxides equilibria such as those indicated in Scheme V would be set up. These equilibria would

Scheme V



generate the peroxidic species (e.g., **9** and **10**) which we believe to be responsible for these epoxidations.

In the process of designing chiral polydentate ligands for these epoxidation catalysts,[17] it is hoped that these mechanistic concepts can be further refined.

Experimental Section

Oxygen-18 enriched water (66 atom %) was procured from Miles Laboratories. The *tert*-butyl hydroperoxide (ca. 90%) was obtained from the Lucidol Division of the Pennwalt Corp.; it was dried over anhydrous magnesium sulfate just before use. Commercial samples of $Mo(CO)_6$ (Pressure Chemical Co.), $VO(acac)_2$ (Alfa), (*E*)-cyclododecene (Chemical Samples), and geraniol (Aldrich) were used as obtained. Dioxane was distilled from sodium metal under nitrogen just prior to use.

The "combustion tubes" were obtained from the Lab Crest Scientific Division of the Fischer and Porter Co. The combustion tube consisted of a thick-walled glass tube fitted with a Teflon-lined, screw-on metal cap.

Preparative GLC was performed on a Varian Model 920 instrument. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer. Isotopic analysis of the *tert*-butyl alcohol was carried out by GC–MS using a 6 ft × 1 mm Porapak QS column.

Molybdenum Catalyzed Epoxidation of Cyclododecene in Oxygen-18 Enriched Water/Dioxane. To a solution of 25 mg (27 μL, 0.15 mmol) of (*E*)-cyclododecene in 0.5 mL of freshly distilled dioxane contained in a combustion tube (Fischer and Porter, 0.375 in. i.d., 3 in. length) were added 50 μL of 66 atom % oxygen-18 enriched water, 18 μL (18 mg, 0.18 mmol) of 90% *tert*-butyl hydroperoxide, and 0.4 mg (0.0015 mmol, 1% based on olefin) of molybdenum hexacarbonyl. The combustion tube was capped tightly and immersed in an oil bath at 115 °C for 24 h with periodic shaking. The blue reaction mixture was then cooled to room temperature and a small portion was reserved for GC–MS analysis of the *tert*-butyl alcohol formed. The solvent from the remaining portion of the reaction mixture was removed under reduced pressure and the residue was taken up in 15 mL of methylene chloride. The resultant solution was washed with 10% aqueous sodium bisulfite (1 × 15 mL) followed by water (1 × 15 mL), then dried ($MgSO_4$) and concentrated to give a light-yellow oil. Mass spectral analysis of the *trans*-cyclododecene epoxide, isolated from the oil by preparative GLC (a 15 ft × 0.25 in. column packed with 10% UCW-98 on 45/60 mesh Chromosorb W, 175 °C) indicated no incorporation of oxygen-18 into the epoxide. The mass spectra of the authentic unlabeled epoxide and the epoxide from this labeling experiment were identical. However, since the parent ion (*m/e* 182) was small the accuracy of the measurement was not great. For this reason the epoxide was opened ($HClO_4$, H_2O, THF) to the diol, which was further transformed (acetone, $HClO_4$) to the acetonide. The acetonide exhibited an intense $M^+ - CH_3$ ion at *m/e* 225 which was ideal for determination of the ^{18}O content. Again the acetonide derived from the labeling experiment and an authentic unlabeled specimen gave identical spectra, confirming the original conclusion that no ^{18}O had been incorporated.

GC–MS analysis (using a Porapak QS column) of the original crude reaction mixture indicated 74% incorporation of oxygen-18 into the *tert*-butyl alcohol formed. The $M^+ - CH_3$ ion (*m/e* 59) was used to calculate ^{18}O content.

Control. A control reaction was performed to indicate whether *tert*-butyl alcohol exchanges oxygen with water under the reaction conditions. To a solution of 25 mg (27 μL, 0.15 mmol) of (*E*)-cyclododecene in 0.5 mL of freshly distilled dioxane contained in a combustion tube were added 50 μL of 66 atom % oxygen-18 enriched water, 18 μL (18 mg, 0.18 mmol) of *tert*-butyl alcohol, and 0.4 mg (0.0015 mmol) of dioxobis(acetylacetonato)molybdenum(VI) [$MoO_2(acac)_2$]. The tube was capped tightly and immersed in an oil bath at 115 °C for 24 h with periodic shaking. GC–MS analysis of the reaction mixture indicated 68% incorporation of oxygen-18 in the *tert*-butyl alcohol.

Vanadium Catalyzed Epoxidation of Geraniol in Oxygen-18 Enriched Water/Dioxane. To a solution of 46 mg (52 μL, 0.3 mmol) of geraniol in 0.5 mL of freshly distilled dioxane and 50 μL of 66 atom % oxygen-18 enriched water were added 18 μL (18 mg, 0.18 mmol) of 90% *tert*-butyl hydroperoxide and 0.4 mg (0.0015 mmol) of vanadyl acetylacetonate [$VO(acac)_2$]. The initially red mixture was stirred in a small test tube (capped with a rubber septum) at 25 °C for 12 h, by which time the solution had become green-yellow. A small portion of this reaction mixture was reserved for GC–MS analysis of the *tert*-butyl alcohol formed. To the remaining portion of the reaction mixture were added 1.0 mL of pyridine and 0.5 mL of acetic anhydride and the mixture was stirred at 25 °C for 3 h. To this mixture was then added 0.5 mL of water and after stirring for a further 0.5 h, the mixture was taken up in 10 mL of chloroform and washed with water (3 × 10 mL). The chloroform layer was dried ($MgSO_4$) and concentrated to give a yellow oil. Mass spectral analysis of the 2,3-epoxygeranyl acetate, isolated from the oil by preparative GLC (a 20 ft × 0.375 in. column packed with 20% OV-17 on 45/60 mesh Chromosorb W, 180 °C) indicated no incorporation of oxygen-18 into the epoxide. The intense $M^+ - HOAc$ ion at *m/e* 152 was used to calculate the ^{18}O content. GC–MS analysis of the original crude reaction mixture revealed no ^{18}O incorporation into the *tert*-butyl alcohol formed.

Acknowledgment. We are indebted to Dr. Catherine Costello of Professor Biemann's laboratory for determining the isotopic composition of our products by GC–MS. A. O. Chong is grateful to the Upjohn Co. for a graduate fellowship, and we thank the National Science Foundation (MPS 74-21260) for supporting this research.

Registry No.—(*E*)-cyclododecene, 1486-75-5; *tert*-butyl hydroperoxide, 75-91-2; molybdenum hexacarbonyl, 13939-06-5; geraniol, 106-24-1; vanadyl acetylacetonate, 3153-26-2.

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(6) K. B. Sharpless and J. M. Townsend, unpublished results.
(7) R. A. Sheldon, *Recl. Trav. Chim. Pays-Bas*, **92**, 367 (1973).
(8) Oxo groups are ubiquitous in the chemistry of d^0 vanadium and molybdenum compounds.
(9) The following references reveal that oxo transition metal compounds generally undergo exchange with $H_2{}^{18}O$ at reasonable rates even at 25 °C. Under the conditions of our experiments (Scheme II) we would expect at least partial exchange of any oxo groups to occur. Since *no ^{18}O incorporation* was observed in the epoxide and alcohol products (Scheme II), we feel that the peroxo mechanisms of Scheme I must be considered extremely unlikely. (a) R. K. Murmann and P. R. Robinson, *Inorg. Chem.*, **14**, 203 (1975); (b) H. Goff and R. K. Murmann, *J. Am. Chem. Soc.*, **93**, 6058 (1971); (c) R. K. Murmann, *J. Phys. Chem.*, **71**, 964 (1967); (d) R. K. Murmann, *J. Am. Chem. Soc.*, **96**, 7836 (1974); (e) R. K. Murmann, *Inorg. Chem.*, in press; (f) J. A. McClaskey and M. J. McClelland, *J. Am. Chem. Soc.*, **87**, 5090 (1965).
(10) Because of the inhibition by dioxane and water, these conditions were necessary for the reaction to proceed. Less severe conditions might have been possible with a more reactive olefin such as geraniol (used with vanadium in experiment 1, Scheme II); however, we wanted to know the outcome with both a simple olefin and an allylic alcohol to be sure that there were no differences between these two types of substrates.
(11) (a) M. N. Sheng and J. G. Zajacek, *J. Org. Chem.*, **35**, 1839 (1970); also M. N. Sheng and J. G. Zajacek, *Adv. Chem. Ser.*, **76**, 418 (1968); (b) E. S. Gould, R. Hiatt and K. C. Irwin, *J. Am. Chem. Soc.*, **90**, 4573 (1968); also C.-C. Su, J. W. Reed, and E. S. Gould, *Inorg. Chem.*, **12**, 337 (1973); (c) R. A. Sheldon, *Recl. Trav. Chim. Pays-Bas*, **92**, 253 (1973); (d) R. A. Sheldon and J. A. Von Doorn, *J. Catal.*, **31**, 427 (1973).
(12) This mechanism is indicated in a figure labeled IV in our earlier publication (ref 4). *IV is incorrect as it appears in that work;[4] an oxo group (Mo = O) is missing.* The similarity between peroxo species **1**, which is known to epoxidize olefins, and the putative active oxidants in mechanisms III and IV is another attractive feature of these new proposals.
(13) The approach of a nucleophile to a peroxide linkage has long been assumed to occur in this manner (see, e.g., J. O. Edwards in "Peroxide Reaction Mechanisms", J. O. Edwards, Ed., Wiley, New York, N.Y., 1962, pp 67–106. All the evidence is consistent with the proposal of backside attack, but to the best of our knowledge, no one has yet designed an experiment which would provide a rigorous test of this hypothesis. What is needed here is

an approach modeled after the elegant work of Eschenmoser and coworkers, wherein they demonstrate the angular depencence of displacements at saturated carbon [L. Tenud, S. Faroog, J. Seible, and A. Eschenmoser, *Helv. Chim. Acta*, **53**, 2059 (1970)].
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(15) It must be pointed out that all our mechanistic considerations, as well as those of others (ref 11), are predicated on the assumption that a single metal center is acting as the catalyst. This is by no means a foregone conclusion, especially in the case of high valent V, Mo, and W oxo species which are well known for their tendencies to form exotic oligomers. Even if metal clusters do turn out to play a role in these oxidations, we feel that the results with allylic alcohols would support the involvement of only one metal center at a time. Unless the allylic alcohol and the hydroperoxide coordinate to the same metal, it is, in our opinion, difficult to rationalize the exceptional syn selectivities observed[13c,e] in epoxidations of cyclic allylic alcohols.
(16) (a) R. J. H. Clark, "The Chemistry of Titanium and Vanadium", Elsevier, Amsterdam, 1968, Chapter 10; (b) ref 7; (c) K. M. Sarma and S. K. Anand, *J. Prakt. Chem.*, **317**, 540 (1975).
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Kinetics and Mechanism of the Epoxidation of Maleic and Fumaric Acids by Hydrogen Peroxide in the Presence of Sodium Orthovanadate as Catalyst

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The kinetics and mechanism of epoxidation of maleic and fumaric acids by hydrogen peroxide in the presence of sodium orthovanadate have been studied. The epoxidation rate of fumaric acid into *trans*-epoxysuccinic acid is faster than that for the epoxidation of maleic acid into *cis*-epoxysuccinic acid. The reaction is first order with respect to unsaturated acid and catalyst and zero order with respect to hydrogen peroxide. Based on substituent, solvent, and salt effects, the mechanism of the epoxidation step is believed concerted with considerable polar (electrophilic) character.

Although organic peracids[1] are generally used for the epoxidation of alkenes, compounds having strong electron-withdrawing substituents adjacent to the double bonds are not readily epoxidized by them.[2] More recently hydroperoxides[3-7] are being used for the epoxidation of such alkenes, but these are limited to only nonaqueous medium. In these cases hydroperoxide–metal [V(V), Mo(VI), and W(VI)] complexes[5-7] bring about epoxidation through metal–hydroperoxide–olefin complexes, whereas aqueous hydrogen peroxide in the presence of tungstate or molybdate epoxidizes through peroxy acid.[8-10] And contrary to expectation, the pH dependence of the epoxidation rate shows that vanadate-catalyzed epoxidation by aqueous hydrogen peroxide is still different from the molybdate- or the tungstate-catalyzed process.

The epoxydicarboxylic acids should be of potential commercial interest because of their easy conversion into dialkyltin epoxysuccinates which are important plasticizer-stabilizers for polyvinyl chlorides[11] as well as for cross-linkable epoxy-containing film-forming polyamides.[12] This paper, therefore, presents a quantitative and comparative kinetic study of the epoxidation of maleic and fumaric acids by hydrogen peroxide in the presence of sodium orthovanadate as catalyst.

Experimental Section

All the chemicals used were reagent (B. D. H.) grade. Maleic and fumaric acid solutions were standardized using the bromate–bromide procedure.[13] The ionic strength of the reaction mixture was maintained by the addition of sodium perchlorate solution. The progress of the reaction was followed spectrophotometrically as detailed elsewhere.[10] Triethanolamine was used to adjust the pH of the reaction mixture. Every run was followed until reaction was at least 75% complete. The plots of concentration of hydrogen peroxide vs. time were good straight lines, and the rates were obtained from the slopes of these lines. No plot contained less than ten points. Pseudo-zero-order rates are reported here as k_{obsd}.

Decomposition of Hydrogen Peroxide by Sodium Orthovanadate. Aqueous solutions of hydrogen peroxide, catalyst, and hydrochloric acid were mixed under experimental conditions and hydrogen peroxide was estimated after 4 h. In the presence of vanadate, the decomposition of hydrogen peroxide was negligible between pH 4 and 7 and significant at about pH 7.

Identification of Products. The epoxysuccinic acid formed in the reaction was measured quantitatively by the pyridinium chloride–pyridine method described by Jungnickel et al.[14] Instead of methanolic sodium hydroxide, an aqueous solution was used for the titration. Maleic and fumaric acids, at pH 6.0, gave their corresponding epoxides in 93 and 86% yields, respectively. No tartaric acid could be detected in the reaction mixture above pH 5. However, below pH 5 the test for tartaric acid[15] was positive and its form was identified by Buchanan's chromatographic method.[16] The R_f values suggest that maleic and fumaric acids give *dl* and meso forms of tartaric acid, respectively.

Results and Discussion

Straight line plots of hydrogen peroxide concentration against time with identical slopes (Table I) indicated zero-order dependence of rate on the hydrogen peroxide concentration. k_{obsd} (Tables II and III) is directly proportional to the concentrations of substrate and catalyst. The standard deviation of k_{obsd} is 0.02.

Preliminary studies have shown that under our experimental conditions, hydrogen peroxide does not bring about epoxidation of maleic and fumaric acids without the catalyst (vanadate) and also the catalyst alone (without the oxidant) fails to bring about the epoxidation. This clearly suggests the involvement of some more oxygenated form of vanadium in the process as oxygen carrier. Jander and Jahr[17] have shown that in the acidic medium, orthovanadate changes into vanadium pentoxide, which according to Flood and co-workers[18] dissolves in aqueous hydrogen peroxide giving peroxyvanadic acid. It is thus presumed here that in the system under investigation, peroxyvanadic acid is the epoxidizing species and in a rate-controlling step it reacts with the unsaturated acids giving epoxysuccinic acid and regenerating vanadic acid. Vanadic acid is then reconverted into peroxyvanadic acid by hydrogen peroxide. The following seems to be the most probable mechanism.

Table I. Pseudo-Zero-Order Rates for the Epoxidation of Maleic and Fumaric Acids with Hydrogen Peroxide in the Presence of Sodium Orthovanadate[a]

$[H_2O_2] \times 10^4$, M	Maleic acid $k_{obsd} \times 10^7$, mol L^{-1} min^{-1}	Fumaric acid $k_{obsd} \times 10^6$, mol L^{-1} min^{-1}
6.00	8.35	3.14
8.00	8.33	3.16
10.00	8.36	3.17
12.50	8.34	3.16
15.00	8.32	3.18
20.00	8.33	3.19
25.00	8.30	3.18
30.00	8.32	3.16
35.00	8.34	3.19
40.00	8.33	3.17

[a] $[Na_3VO_4] = 2.00 \times 10^{-4}$ M; [maleic acid] = [fumaric acid] = 6.00×10^{-2} M; temp, 40 °C; pH 6.0.

Table II. First-Order Dependence of Vanadate Catalyzed Epoxidation Rates of Maleic and Fumaric Acids on the Concentration of Unsaturated Acid[a]

[Maleic acid] $\times 10^2$, M	$k_{obsd} \times 10^7$, mol L^{-1} min^{-1}	[Fumaric acid] $\times 10^2$, M	$k_{obsd} \times 10^6$, mol L^{-1} min^{-1}
6.00	8.33	6.00	3.18
8.00	11.50	8.00	4.28
10.00	14.01	10.00	5.10
12.00	16.23	12.00	6.78
14.00	19.85	14.00	7.35

[a] $[H_2O_2] = 2.50 \times 10^{-3}$ M; $[Na_3VO_4] = 2.00 \times 10^{-4}$ M; temp, 40 °C; pH 6.0.

Table III. First-Order Dependence of Vanadate-Catalyzed Epoxidation Rate of Maleic and Fumaric Acids on Catalyst Concentration[a]

$[Na_3VO_4] \times 10^4$, M	Maleic acid $k_{obsd} \times 10^7$, mol L^{-1} min^{-1}	Fumaric acid $k_{obsd} \times 10^6$, mol L^{-1} min^{-1}
2.00	8.33	3.19
4.00	15.78	6.20
6.00	24.01	9.89
8.00	34.35	12.40
10.00	41.02	16.35

[a] $[H_2O_2] = 2.50 \times 10^{-3}$ M; [maleic acid] = [fumaric acid] = 6.00×10^{-2} M; temp, 40 °C; pH 6.0; $\mu = 60.0 \times 10^{-4}$ M.

$$H_3VO_5 \underset{}{\overset{K_1}{\rightleftharpoons}} H_2VO_5^- + H^+ \quad (1)$$

$$H_2M \text{ or } H_2F + H_3VO_5 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} (\text{intermediate complex}) \quad (2)$$

$$(\text{intermediate complex}) \xrightarrow{k_3} H_2E + H_3VO_4 \quad (3)$$

H_2M, H_2F, and H_2E are maleic, fumaric, and epoxysuccinic acid, respectively.

Assuming steady state for the complex concentration,

$$\text{epoxidation rate} = k'[H_2M \text{ or } H_2F][H_3VO_5] \quad (4)$$

where

$$k' = \frac{k_2k_3}{k_{-2} + k_3}$$

Table IV. Dependence of Vanadate-Catalyzed Epoxidation Rate of Maleic and Fumaric Acids on the pH of the Medium[a]

	Maleic acid		Fumaric acid	
Epoxidation pH	$k_{obsd} \times 10^7$ (calcd), mol L^{-1} min^{-1}	$k_{obsd} \times 10^7$ (exptl), mol L^{-1} min^{-1}	$k_{obsd} \times 10^7$ (calcd), mol L^{-1} min^{-1}	$k_{obsd} \times 10^6$ (exptl), mol L^{-1} min^{-1}
4.00	—	—	4.98	4.98
5.00	9.31	9.32	4.76	4.77
5.50	9.07	9.09	4.32	4.35
6.00	8.37	8.33	3.33	3.19
6.50	6.73	6.62	1.93	1.88
7.00	4.15	4.16	0.83	0.83

[a] [Maleic acid] = [fumaric acid] = 6.00×10^{-2} M; $[Na_3VO_4] = 2.00 \times 10^{-4}$ M; $[H_2O_2] = 2.50 \times 10^{-3}$ M; temp, 40 °C.

Table V. Dependence of Vanadate-Catalyzed Epoxidation Rate of Maleic or Fumaric Acid in Ethanol-Water Mixture on the Composition of the Solvent[a]

% of ethanol	Dielectric constant[b]	Maleic acid $k_{obsd} \times 10^7$, mol L^{-1} min^{-1}	Fumaric acid $k_{obsd} \times 10^6$, mol L^{-1} min^{-1}
0	78.5	8.32	3.19
15.4	69.5	6.93	2.76
31.5	60.0	5.20	2.35
50.0		2.74	1.08

[a] [Maleic acid] = [fumaric acid] = 6.00×10^{-2} M; $[Na_3VO_4] = 2.00 \times 10^{-4}$ M; $[H_2O_2] = 2.50 \times 10^{-3}$ M; pH 6.0; temp, 40 °C. [b] The dielectric constant values have been taken from A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", 2nd ed, Wiley, New York, N.Y., 1961, p 146.

The catalyst (Na_3VO_4), at any stage in the process, is distributed in three forms according to eq 5.

$$[Na_3VO_4] = [H_3VO_5] + [H_2VO_5^-] + [\text{intermediate complex}] \quad (5)$$

The concentration of the intermediate complex in eq 5 is negligible in comparison to other terms of eq 5. Hence,

$$[Na_3VO_4] = [H_3VO_5] + [H_2VO_5^-] \quad (6)$$

Substituting for $[H_3VO_5]$ from eq 1 and 6 in eq 4, we get

$$\text{epoxidation rate} = \frac{k'[H^+][Na_3VO_4][H_2M \text{ or } H_2F]}{K_1 + [H^+]} \quad (7)$$

This explains the order of the reaction with respect to the substrate, catalyst, and hydrogen peroxide. The pH dependency of the process (Table IV) is also very well explained by eq 7. The straight-line plot between inverse of epoxidation rate and inverse of $[H^+]$ is in agreement with eq 7. Using the measured epoxidation rate values at pH 5.0 and 7.0 (Table IV) and eq 7, pK_1 and k' were calculated both for maleic and fumaric acids. For maleic acid pK_1 is 6.90 and k' is 0.08, and for fumaric acid pK_1 is 6.30 and k' is 0.42. The two values of pK_1 are different due to the large difference in the dissociation constants of maleic and fumaric acids. Substituting these values of K_1 and k' in eq 7, epoxidation rates at different pH's were calculated. The calculated epoxidation rates compare well (Table IV) with the observed ones. The un-ionized substrate maleic or fumaric acid will no doubt be in equilibrium with its ionized forms. But as reaction 2 involves only the double bond, k_2 for the ionized and un-ionized forms will not be different and the same will be true for k_{-2}. Hence, H_2M or

Table VI. Dependence of Vanadate-Catalyzed Epoxidation Rate of Maleic and Fumaric Acid on the Ionic Strength of the Medium[a]

Ionic strength, $\mu \times 10^4$ M	Maleic acid $k_{obsd} \times 10^7$, mol L^{-1} min^{-1}	Fumaric acid $k_{obsd} \times 10^6$, mol L^{-1} min^{-1}
12.0	8.33	3.19
16.0	8.32	3.18
20.0	8.29	3.19
24.0	8.34	3.20
36.0	8.33	3.19

[a] [Maleic acid] = [fumaric acid] = 6.00×10^{-2}; M; [Na_3VO_4] = 2.00×10^{-4} M; [H_2O_2] = 2.50×10^{-3} M; temp, 40 °C; pH 6.0.

Table VII. The Substituent Effect on the Epoxidation of Maleic and Fumaric Acid by Hydrogen Peroxide[a]

$[H_2O_2] \times 10^3$, M	Citraconic acid $k_{obsd} \times 10^7$, mol L^{-1} min^{-1}	Mesoconic acid $k_{obsd} \times 10^6$, mol L^{-1} min^{-1}
2.00	16.52	6.32
2.50	16.51	6.35
3.00	16.52	6.33
3.50	16.53	6.32

[a] [Citraconic acid] = [mesoconic acid] = 6.00×10^{-2} M; [Na_3VO_4] = 2.00×10^{-4} M; temp, 40 °C; pH 6.0.

H_2F in eq 7 stand for the total concentration of the ionized and un-ionized acid.

Above pH 5, *cis*- and *trans*-epoxysuccinic acids are stable, but below pH 5 they change into *dl*- and *meso*-tartaric acids, respectively. The *dl* form reacts with the catalyst[19] whereas the meso form does not. Hence, in the case of maleic acid, epoxidation kinetics were not studied below pH 5.

Increase in ionic strength did not affect the rate. The faster epoxidation rate of citraconic acid as compared to that of maleic acid and of mesaconic acid as compared to that of fumaric acid under identical conditions show that the presence of methyl group at the double bond is rate enhancing. This points to an electrophilic addition which is generally observed in the corresponding reaction of olefins with organic peracids and in other three-center-type additions.[20,21] The epoxidation rate decreased as the percentage of water in alcohol–water mixture decreased (dielectric constant lowered) but no linear relation between rate and dielectric constant was obtained. Solvent and salt effects described above give an insight into the nature of the transition state of the oxygen transfer from the peracids to the double bond of the olefinic substrate as described elsewhere.[10]

The two carboxylic groups on the same side of the double bond offer hindrance in the formation of the intermediate complex and this explains why the epoxidation rate of maleic acid is slower than that of fumaric acid.

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Registry No.—Maleic acid, 110-16-7; fumaric acid, 110-17-8; H_2O_2, 7722-84-1; Na_3VO_4, 13721-39-6.

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Secondary Amine Catalysis of the Oximation of Acetone[1a]

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The equilibrium constants for addition of hydroxylamine to acetone to give a carbinolamine and for oxime formation have been found to be 0.59 and 4.65×10^5 M^{-1}, respectively, in water at 35 °C. The pK_a of the protonated oxime is 1.54. The kinetics of oxime formation have been studied over the pH range 4.5–12.7 and the reaction found to be catalyzed by pyrrolidine, dimethylamine, and morpholine. These secondary amines act as catalysts by transforming acetone to iminium ions that then react with hydroxylamine to give acetoxime. Over the pH range studied (~8.5–~10.3) the amines are in rapid equilibrium with intermediates of the type $Me_2C(OH)NR_2$, which then undergo uncatalyzed loss of hydroxide ions to give iminium ions. The efficiency of capture of the iminium ion derived from pyrrolidine was observed to increase with increasing concentrations of hydroxylamine, above pH 9, at least. Under the conditions used, capture of the iminium ions derived from dimethylamine and morpholine was almost complete. Rate constants for formation of iminium ions from pyrrolidine, dimethylamine, and morpholine are 4.25, 0.0504, and 0.00109 M^{-1} s^{-1} in water at 35 °C. These relative reactivities are rationalized in terms of polar effects and steric effects that are similar to those seen in the solvolysis of tertiary chlorides, another reaction in which an atom at the reaction center acquires a positive charge and changes its hybridization from sp^3 to sp^2.

Several publications from this laboratory have described bifunctional catalysis of the removal of α hydrogen from an aldehyde or ketone.[2] All the bifunctional catalysts used contain a primary amino group, whose function is to transform the carbonyl compound into the iminium ion, whose α-hydrogen atoms are more acidic than those in the original carbonyl compound. Secondary amines should also give iminium ions and should not have the disadvantage that primary amines have in some cases, of transforming most of the carbonyl compound into imine ("nonproductive binding"). The ability of alkyl substituents to stabilize double bonds, well known in the cases of carbon–carbon and carbon–oxygen double bonds,[3] might make equilibrium constants for iminium ion formation larger for secondary than for primary amines if steric effects are not too unfavorable. Under conditions where primary amines catalyze the dedeuteration of isobutyraldehyde-2-*d* largely via iminium ion formation,[4] dimethylamine, morpholine, piperazine, and piperidine gave no evidence for such catalysis, acting only as simple bases.[5] However, it was suggested that this result may reflect a steric effect arising from the branching at the α-carbon atom of isobutyraldehyde. Accordingly, we are interested in learning how rapidly acetone is transformed to an iminium ion by simple secondary amines and whether such iminium ions lead to significant amounts of α-hydrogen exchange.

Many reactions at or near carbonyl groups are catalyzed by primary and secondary amines and seem to involve the intermediate formation of iminium ions.[6,7] Cordes and Jencks showed that moderate concentrations of semicarbazide or hydroxylamine are sufficient to capture almost all the intermediate imine formed from some primary amines and *p*-chlorobenzaldehyde under at least some conditions.[8] This provides a method for determining the rate of imine formation that is particularly valuable when the equilibrium constant for imine formation is so small that the amount of imine present at equilibrium in aqueous solution is too small to measure reliably. Hydroxylamine has been used as the capturing agent in studying the kinetics of imine formation from acetone and a number of primary amines.[9-11] We are not aware of hydroxylamine or semicarbazide capture having been used to measure the rate of formation of iminium ions from a secondary amine and a carbonyl compound. In fact, the rate of morpholine-catalyzed semicarbazone formation by pyridoxal was found to be linear in semicarbazide concentration up to the highest concentration (0.1 M) used, showing that this concentration is nowhere near enough for complete capture of the intermediate iminium ion.[12] Nevertheless, pyridoxal has certain special structural features that might make it an exceptional case. Therefore we have studied hydroxylamine capture as a method of measuring the rate of iminium ion formation from acetone and secondary amines.

Results and Discussion

Equilibrium Constants for Carbinolamine and Oxime Formation. In previous studies we ignored the amounts of acetone and hydroxylamine that were tied up as carbinolamine in the relatively rapid equilibrium that precedes direct oxime formation.[10,11]

$$Me_2CO + H_2NOH \overset{K_{Ca}}{\rightleftharpoons} Me_2C(OH)NHOH \qquad (1)$$

A value of 1 M^{-1} was obtained for K_{Ca} for acetone at 25 °C and ionic strength 3.2 by spectral measurements extrapolated to zero time.[12] This value promised that the fraction of reactants present as carbinolamine would probably be small at the reactant concentrations we used. However, the oximation of acetone is so fast that the extrapolation used to determine K_{Ca} at 25 °C was rather large, so that the value obtained was said to be less reliable than those obtained for other carbonyl compounds.[13] Furthermore, it was necessary to use larger concentrations of hydroxylamine in the present study than we had used previously. We therefore determined K_{Ca} under our conditions, 35 °C and ionic strength 0.3. The reactants were mixed in a stopped flow spectrophotometer and absorbance measurements over about the first second were extrapolated to zero time. The K_{Ca} value of 0.59 M^{-1} obtained had a standard deviation of 0.13 M^{-1}. The formation of carbinolamine involves the transformation of two molecules to one molecule and must therefore be accompanied by a large negative change in entropy. Hence, K_{Ca} could be as large as the reported values only if the reaction is exothermic. Therefore K_{Ca} should decrease with increasing temperature. Our value at 35 °C is smaller than the value obtained at 25 °C[13] and also smaller than a value (1.0 M^{-1}) determined by flow UV spectroscopic measurements at 30 °C and ionic strength 1.96,[14] which was reported after our experiments were completed.

To assure that reversibility in oxime formation may be neglected under our conditions in aqueous solution at 35 °C (as had been assumed to be the case previously[9,10] on the basis of an equilibrium constant determined at 25 °C[15,16]), the equilibrium constant was determined. With the abbreviations Ox, Ac, and Hx for acetoxime, acetone, and hydroxylamine,

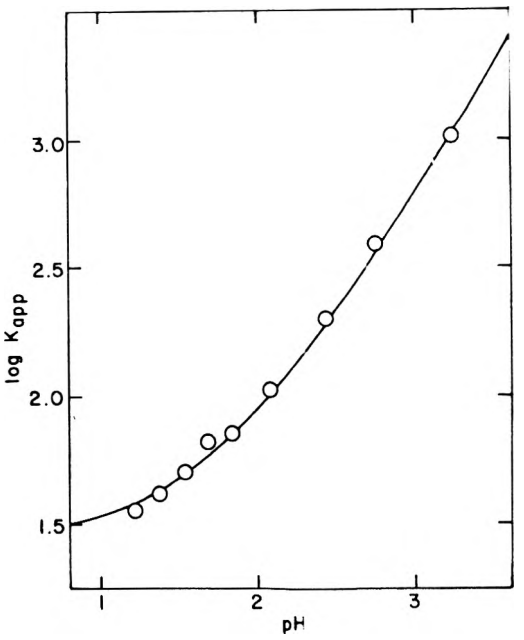

Figure 1. Plot of log K_{app} for the oximation of acetone in water at 35 °C vs. pH.

respectively, the equilibrium constant sought is defined by

$$K_{Ox} = [Ox]/([Ac][Hx]) \quad (2)$$

The constant determined directly in a given experiment, however, is K_{app}, which is defined by

$$K_{app} = [Ox]_t/([Ac][Hx]_t) \quad (3)$$

in which the subscript t refers to all states of protonation of the species in question. Values of K_{app} were determined by dissolving known amounts of acetoxime in water at various pH's from 1.2 to 3.2 and measuring the absorbance at 277 nm, where the oxime absorbs negligibly, but acetone absorbs almost as strongly as at its 264-nm absorption maximum. The resulting values are plotted logarithmically against the pH in Figure 1. The value of K_{Ca} we have obtained shows that under the present conditions, where less than 1% of the hydroxylamine is ever present in the unprotonated form, the formation of carbinolamine may be neglected. Analogy with studies of the addition of protonated and unprotonated amines to formaldehyde[17] shows that the formation of protonated carbinolamine may also be neglected. Therefore, K_{app} may be expressed as shown in

$$K_{app} = \frac{K_{Ox}K_{HxH}(K_{OxH} + [H^+])}{K_{OxH}(K_{HxH} + [H^+])} \quad (4)$$

in terms of K_{Ox} and of K_{HxH} and K_{OxH}, the thermodynamic acidity constants for hydroxylammonium ions and protonated acetoxime. Values of pK_{HxH} over the ionic strength range 0.06–0.24 used in the experiments were obtained by interpolation between the values 5.73 and 5.76 reported for ionic strengths 0.00 and 0.25, respectively.[18] Least-squares treatment of the K_{app} values obtained gave values of 4.65×10^5 M^{-1} and 1.54 for K_{Ox} and pK_{OxH}, with standard deviations of 0.30×10^{-5} M^{-1} and 0.05, respectively. The line in Figure 1 is based on these values and an average ionic strength of 0.15.

Oximation in the Absence of Amines. The previous study[10] of the kinetics of the reaction of acetone with hydroxylamine in water at ionic strength 0.3 and 35 °C had been limited to the pH range 6.6–10.7, and had neglected the transformation of part of the reactants to carbinolamine; also, the first-order rate constants obtained using an excess of hydroxylamine had been transformed to second-order rate constants by dividing by the initial hydroxylamine concentration. By use of stopped flow kinetic measurements we have now extended the pH range to 4.5–12.7. The total initial concentration of hydroxylamine, in all states of protonation, was 7.5–12 times that of the acetone. Hence the hydroxylamine concentration was taken as a constant [Hx] equal to its average value during the kinetic run. Then the second-order rate constant for oximation in a given run, k_{ox}, may be expressed in terms of the observed first-order rate constant, k_{obsd}, as shown by

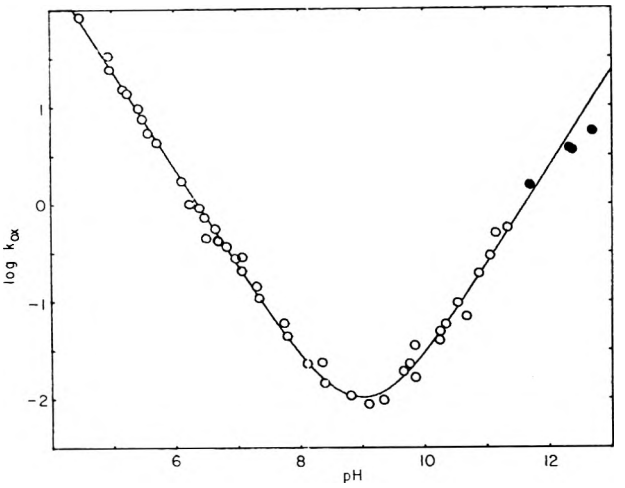

Figure 2. Plot of log k_{ox} vs. pH for the oximation of acetone in water at 35 °C and ionic strength 0.3. The solid circles are for points not used in the least-squares treatment for the values of the rate constants in eq 6 on which the line is based.

$$k_{ox} = k_{obsd}(1 + K_{Ca}[Hx])/[Hx] \quad (5)$$

The values obtained previously were recalculated using this equation and all the k_{ox} values are plotted logarithmically against pH in Figure 2. The variation of k_{ox} with pH was assumed to follow

$$k_{ox} = k_H[H^+] + k_h[OH^-] + k_w \quad (6)$$

which allows for hydrogen ion catalyzed, hydroxide ion catalyzed, and uncatalyzed reactions. A least-squares treatment of the values obtained below pH 11.4 gave k_H, k_h, and k_w values of 1.64×10^6 M^{-1} s^{-1}, 80 M^{-1} s^{-1}, and 5.66×10^{-3} s^{-1} with standard deviations of 4.2, 7.2, and 19.4%, respectively. The line in Figure 2 is based on these values. The points obtained above pH 11.6 were not included in the least-squares treatment because the increase in transmittance used to obtain the rate constant was preceded by a rapid unexplained decrease in transmittance, and because in calculating [Hx] a correction had to be made for that part of the hydroxylamine present as its conjugate base. To make this correction the pK value of 13.74 at 25 °C[19] was assumed to change with temperature in the same way that pK_w does, giving a hydroxylamine pK of 13.42 at 35 °C. The values of k_H and k_w are near those obtained previously,[10] but the previous k_h value was 36% smaller than the present one.

The second-order rate constant k_{ox} is the product of the equilibrium constant for carbinolamine formation and k_d,

$$Me_2C(OH)NHOH \xrightarrow{k_d} Me_2C{=}NOH \quad (7)$$

the rate constant for dehydration of the carbinolamine. The k_H and k_h terms in eq 6 correspond to hydrogen ion and hydroxide ion catalysis of the dehydration of the carbinolamine. Jencks showed that dehydration of this carbinolamine is subject to general acid catalysis by $H_2PO_4^-$ but not signifi-

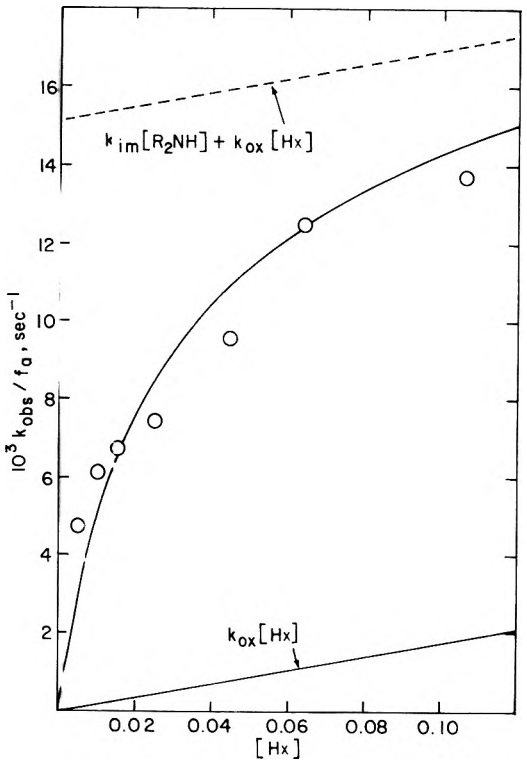

Figure 3. Plot of k_{obsd}/f_a for the oximation of acetone at pH 9.70 ± 0.01 in the presence of 0.103 ± 0.004 M total pyrrolidine vs. the average concentration of hydroxylamine present in the run.

cantly by hydroxylammonium ions (even though these are more acidic than $H_2PO_4^-$); no evidence for general base catalysis was found.[13] This is consistent with our lack of evidence for catalysis by the components of the triethylamine, trimethylamine, *N*-methylmorpholine, and hydroxylamine buffers used. It is inconsistent with a recently reported flow-NMR study of the reaction of acetone with hydroxylamine, in which the carbinolamine was observed directly and the rate constant for its dehydration said to increase by more than 110% as the total hydroxylamine concentration was increased from 0.2 to 0.5 M at 30 °C and pH 7.70.[14] However, these rate constants seem clearly to have been miscalculated. They appear to be first-order rate constants for overall disappearance of carbinolamine, but when the carbinolamine is in equilibrium with substantial concentrations of acetone and hydroxylamine the rate of its disappearance depends on the equilibrium constant for carbinolamine formation and the concentrations of acetone and hydroxylamine as well as on the rate constant for dehydration. This error accounts for the value of k_d extrapolated to zero phosphate concentration being reported as 0.012 s^{-1} in the flow-NMR study at 30 °C[14] in contrast to Jencks' value of 0.03 s^{-1} at 25 °C and our value of 0.09 s^{-1} at 35 °C. Recalculation of all the k_d values in the flow-NMR report gives results consistent with the present study and the work of Jencks. It might be mentioned that the same method of calculation seems to have been used in a flow-NMR study of the reaction of hydroxylamine with acetaldehyde.[20] However, the equilibrium constant for carbinolamine formation in that case appears to be so large that the limiting reactant is transformed almost entirely to carbinolamine, so that the resulting error in k_d is small.

Secondary Amine Catalysis of Oximation. The oximation of acetone in the presence of secondary amines was usually carried out with substantial excesses of hydroxylamine over acetone and treated as a first-order reaction of acetone in any given run. Equilibrium constants for addition of simple amines to carbonyl groups are so much smaller than for addition of hydroxylamine[21] that the amount of reactants tied up by such addition may be neglected. If the secondary amine is transforming acetone to an iminium ion with the second-order rate constant k_{im}, and if the iminium ion is being transformed quantitatively to oxime by the hydroxylamine present, the first-order rate constant for the disappearance of acetone could be expressed as shown in

$$k_{obsd}/f_a = k_{im}[R_2NH] + k_{ox}[Hx] \quad (8)$$

in which f_a, the fraction of acetone present as such, rather than in the form of the carbinolamine derived from hydroxylamine, may be expressed as shown in

$$f_a = 1/(K_{Ca}[Hx] + 1) \quad (9)$$

The value of f_a was always between 0.88 and 1.00, so that k_{obsd}/f_a is just a slightly "corrected" form of k_{obsd}. According to eq 8, at a given concentration of secondary amine and a given pH, a plot of k_{obsd}/f_a vs. the hydroxylamine concentration should give a straight line of slope k_{ox} and intercept $k_{im}[R_2NH]$. In Figure 3 data obtained at pH 9.70 in the presence of 0.10 M total pyrrolidine are plotted. The points do not describe a straight line and the best straight line through the points would certainly have a much larger slope than k_{ox}; the straight line at the bottom of the figure is a plot of the first-order rate constant for the uncatalyzed oximation reaction and has a slope of k_{ox}. The experimental points suggest that capture of the intermediate iminium ion by hydroxylamine is incomplete but that increasing hydroxylamine concentrations are making such capture more nearly complete.

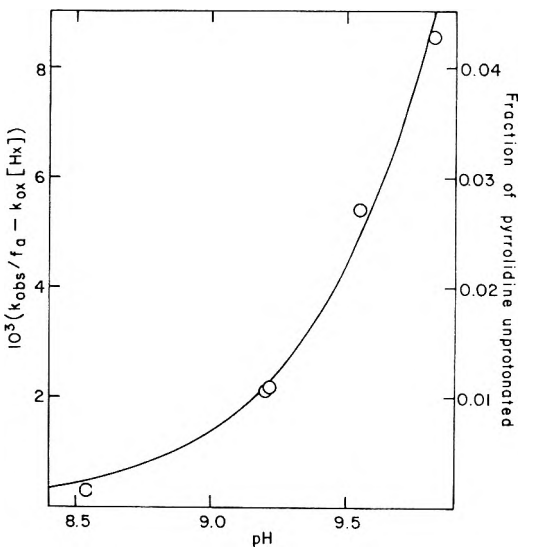

Figure 4. Kinetics of oximation of acetone in the presence of 0.156 M hydroxylamine and 0.049 M total pyrrolidine. The scale for the points is on the left-hand side and the scale for the line is on the right-hand side of the graph.

In Figure 4 is a plot of k_{obsd}/f_a for 0.049 M pyrrolidine in the presence of 0.156 M hydroxylamine, which is enough to make capture of the iminium ion almost complete. The line shown, whose ordinates refer to the scale on the right-hand side of the graph, is the fraction of pyrrolidine present in the unprotonated form. The close agreement between the points and the line shows the iminium ion formation is largely a reaction of the free amine, that is, that dehydration of the intermediate carbinolamine is largely uncatalyzed.

$$Me_2C(OH)NR_2 \rightleftharpoons Me_2C{=}NR_2^+ + OH^- \quad (10)$$

This conclusion is supported by studies of the pyrrolidine-catalyzed dedeuteration of acetone-d_6, which show that even at pH 7 there is no significant acid catalysis of iminium ion

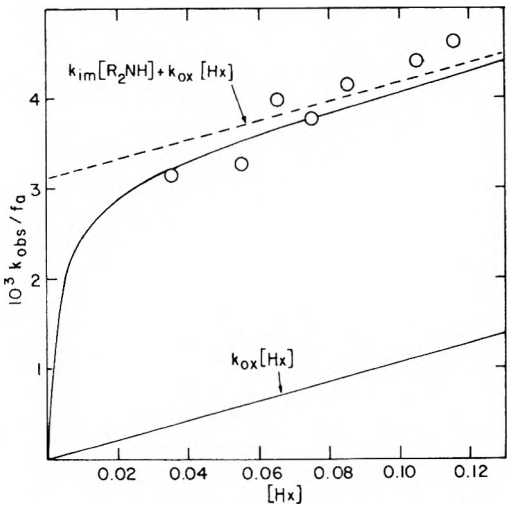

Figure 5. Plot of k_{obsd}/f_a for the oximation of acetone at pH 8.83 ± 0.01 in the presence of 0.150 M total pyrrolidine vs. the average concentration of hydroxylamine in the run.

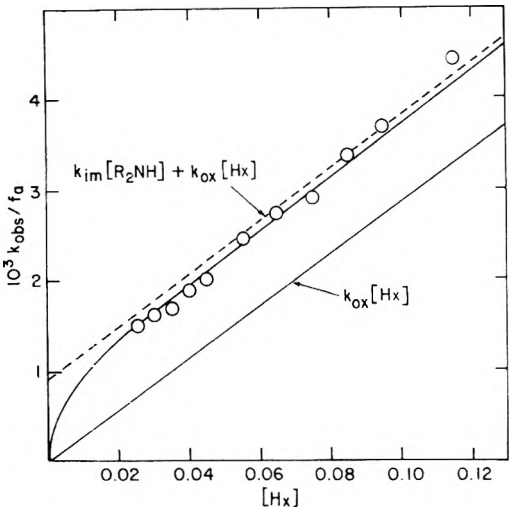

Figure 6. Plot of k_{obsd}/f_a for oximation of acetone at pH 9.98 ± 0.03 in the presence of 0.100 M total dimethylamine vs. the average concentration of hydroxylamine present during the run.

formation from acetone and pyrrolidine.[22] Application of the principle of microscopic reversibility to eq 10 shows that, in capturing the iminium ion, hydroxylamine must compete with hydroxide ions. In this regard let us examine Figure 5, a plot of k_{obsd}/f_a vs. hydroxylamine concentration in the presence of 0.15 M total pyrrolidine at pH 8.83, where there are less than one-seventh as many hydroxide ions as at pH 9.70. The experimental points describe a line almost parallel to the line at the bottom of the figure, which refers to the rate of uncatalyzed oximation. This shows that capture of the iminium ions by hydroxylamine is almost complete. Such capture was much less complete at pH 9.70 (Figure 3). Apparently the hydroxylamine captures the iminium ion more efficiently at pH 8.83 than at pH 9.70 because it has fewer hydroxide ions to compete with.

The preceding evidence suggests eq 11 and 12

$$Me_2CO + R_2NH \underset{k_r}{\overset{k_{im}}{\rightleftharpoons}} Me_2C{=}NR_2^+ + OH^- \quad (11)$$

$$Me_2C{=}NR_2^+ + H_2NOH \xrightarrow{k_x} Me_2C{=}NOH + R_2NH_2^+ \quad (12)$$

for the secondary amine catalyzed oximation of acetone. Inasmuch as reaction of hydroxylamine with acetone is subject to base catalysis, the possibility of hydroxide ion catalysis of the capture of iminium ions by hydroxylamine is also included in the proposed mechanism (eq 13).

$$Me_2C{=}NR_2^+ + H_2NOH + OH^- \xrightarrow{k_b} Me_2C{=}NOH + R_2NH \quad (13)$$

This mechanism, and allowance for that fraction of the acetone tied up as $Me_2C(OH)NHOH$, gives

$$k_{obsd}/f_a = \frac{k_{im}[R_2NH][Hx](k_x/k_r + (k_b/k_r)[OH^-])}{[OH^-] + [Hx](k_x/k_r + (k_b/k_r)[OH^-])} \quad (14)$$

for the observed first-order rate constants. Least-squares treatment of 78 values of k_{obsd} for 0.048–0.150 M total pyrrolidine and 0.0055–0.244 M hydroxylamine over the pH range 8.54–9.81 using values of k_{ox} and f_a calculated from eq 6 and 9, respectively, gave values of 4.25 ± 0.11 M^{-1} s^{-1}, 0.0065 ± 0.0047, and 2.1 ± 30 M^{-1} for k_{im}, k_x/k_r, and k_b/k_r, respectively, where the ± figures are standard deviations. From these values the k_{obsd} values can be calculated with a standard deviation of 11.0%. There is obvious doubt as to the reality of base catalysis of the hydroxylamine reaction because k_b/k_r is so much smaller than its standard deviation. When k_b/k_r was set equal to zero the least-squares treatment gave k_{im} and k_x/k_r values of 4.24 ± 0.10 M^{-1} s^{-1} and 0.0068 ± 0.0006, respectively, which also fit the k_{obsd} values with a standard deviation of 11.0%. When k_x/k_r was set equal to zero k_{im} rose only to 4.44 ± 0.17 M^{-1} s^{-1}, k_b/k_r became 47 ± 6 M^{-1}, and the standard deviation in the fit to the k_{obsd} values was 12.6%. Thus there is great uncertainty as to the details concerning the capture of iminium ions by hydroxylamine, i.e., as to the values of k_b/k_r and k_x/k_r, but this results in little uncertainty in k_{im}, whose value was the principal objective of the study. The solid curved lines in Figures 3 and 5 are based on the k_{im}, k_x/k_r, and k_b/k_r values of 4.25 M^{-1} s^{-1}, 0.0065, and 2.1 M^{-1}, respectively. They are, therefore, samples of how the proposed mechanism fits all 78 values of k_{obsd}. The dashed lines at the top of the figures are plots of $k_{im}[R_2NH] + k_{ox}[Hx]$, the rate constants for oximation that would be observed if capture of the iminium ions by hydroxylamine were perfect, vs. the hydroxylamine concentration. These lines are asymptotes that are approached by the solid curved lines.

Dimethylamine catalysis of oximation was also studied, as illustrated by the plot in Figure 6 of k_{obsd}/f_a vs. hydroxylamine concentration for 0.10 M total amine at pH 9.98. Dimethylamine is so much poorer than pyrrolidine as a catalyst that for none of the points shown in the figure does the added amine as much as double the reaction rate. From inspection of the points in the figure it is not clear whether iminium ion capture is essentially complete or not. Application of eq 14 to 120 values of k_{obsd} for 0.10 or 0.20 M total dimethylamine and 0.026–0.116 M hydroxylamine over the pH range 8.97–10.33 gave plausible values for k_{im} and k_b/k_r but a small negative value for k_x/k_r. Hence, k_x/k_r was set equal to zero and least-squares values of 0.0504 ± 0.0029 M^{-1} s^{-1} and 313 ± 235 M^{-1} obtained for k_{im} and k_b/k_r, respectively. These values fit the 120 k_{obsd} values with a standard deviation of 9.0% and were the basis of the solid curved line in Figure 6. Since this curve fits the experimental points only slightly better than the dashed line does (and the situation is similar at other pH's), we have not learned anything very reliable about how hydroxylamine captures the iminium ion derived from acetone and dimethylamine. This does not affect the reliability of the k_{im} value obtained, however.

Catalysis of the oximation of acetone by morpholine was studied in less detail than catalysis by pyrrolidine or dimethylamine. Figure 7 is a plot of k_{obsd}/f_a vs. hydroxylamine

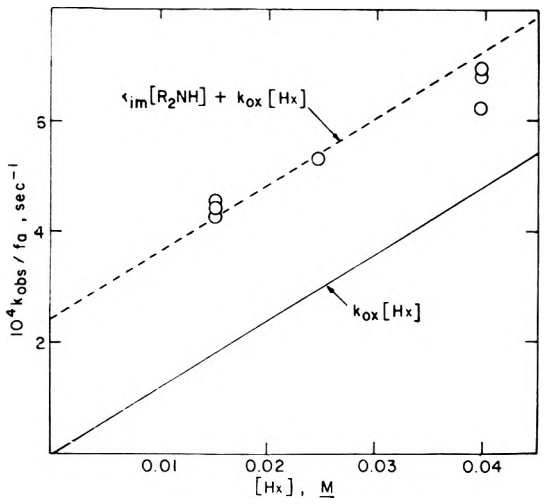

Figure 7. Plot of k_{obsd}/f_a for the oximation of acetone at pH 9.35 in the presence of 0.25 M total morpholine vs. the average concentration of hydroxylamine present in the run.

Table I. Rate Constants for Iminium Ion Formation from Acetone and Secondary Amines in Water at 35 °C[a]

Amine	k_{im}, M^{-1} s^{-1}	Std dev, M^{-1} s^{-1}	pK
Pyrrolidine	4.25	0.11	10.99
Dimethylamine	0.0504	0.0029	10.49
Morpholine	0.00109	0.00004	8.27

[a] At ionic strength 0.3.

concentration for 0.25 M total morpholine at pH 9.35. As in the case of dimethylamine, much of the total rate observed is seen to be that of the uncatalyzed reaction. The best straight line through the points would certainly not be steeper than the solid line shown, representing the rate constant for uncatalyzed oximation. Capture of the intermediate iminium ions by hydroxylamine was therefore assumed to be complete over the concentration range shown. The data in the figure and nine other k_{obsd} values at pH 9.03–9.77 with a total morpholine concentration of 0.25 M and a hydroxylamine concentration of 0.15 M were fitted to eq 8. The value of k_{im} obtained was 1.09×10^{-3} M^{-1} s^{-1} with a standard deviation of 4×10^{-5} M^{-1} s^{-1} and the standard deviation of the calculated from the observed rate constants was 6.7%. The dashed line in Figure 7 is based on this k_{im} value.

The values of k_{im} and standard deviations obtained for pyrrolidine, dimethylamine, and morpholine are listed in Table I with the pK_a values of the protonated amines. The k_{im} values are seen to increase with increasing amine basicity, as might be expected since both iminium ion formation and protonation put a positive charge on the amine nitrogen atom. However, the ability to stabilize a positive charge on nitrogen seems to be an incomplete explanation of the observed structural effects on k_{im}. In Figure 8 log k_{im} values for the three secondary amines we have studied are plotted as open circles against the pK_a values of the conjugate acids of the amines. The solid circles are log k_{im} values for primary amines of the type RCH_2NH_2 (also reacting with acetone in water at 35 °C).[10] The points for the primary amines, in which steric effects have been held much more nearly constant, describe a line of slope 0.59. It is plausible that polar effects should give a slope less than 1.0 because only a partial positive charge has been put on the nitrogen atom in the transition state for iminium ion formation. The points for the secondary amines do not lie near any straight line but the best such line would have

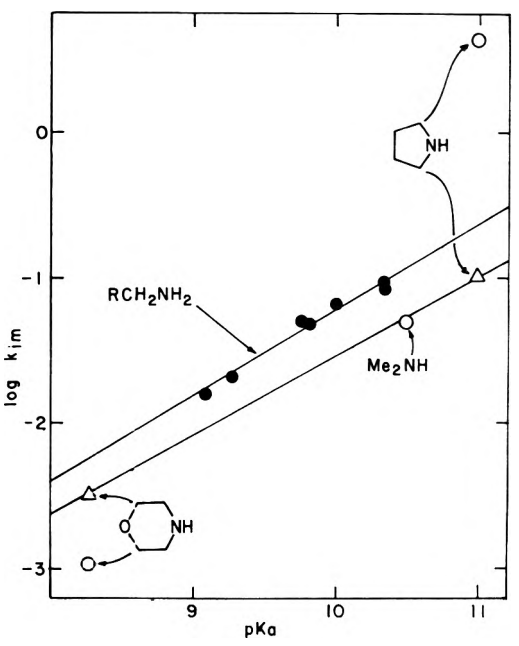

Figure 8. Plot of log k_{im} for iminium ion formation from acetone and amines in water at 35 °C vs. pK_a for the protonated amines: ●, primary amines of the type RCH_2NH_2; ○, secondary amines; △, secondary amines corrected for a five- or six-membered ring effect.

a slope considerably larger than 1.0 and hence would be an implausible description of polar effects. The observed reactivity pattern bears some similarity to that observed in the solvolysis of tertiary chlorides in 80% ethanol at 25 °C. If the >NH groups of pyrrolidine and dimethylamine are transformed to $>C(Cl)CH_3$ groups the compounds become 1-methyl-1-chlorocyclopentane and *tert*-butyl chloride, respectively. In the solvolysis of these compounds the carbon atom acquires a positive charge and changes its hybridization from sp^3 to sp^2 just as the analogous nitrogen atom does in the amines. The cyclopentane derivative hydrolyzes faster than *tert*-butyl chloride does, the log of the ratio of the rate constants being 1.62.[23] If the value of log k_{im} for pyrrolidine is corrected for this "five-membered ring effect" by subtracting 1.62 from it the triangular point for pyrrolidine is obtained. Transformation of the >NH groups of morpholine to $>C(Cl)CH_3$ gives 4-methyl-4-chlorotetrahydropyran, whose solvolysis rate does not appear to have been measured. However, we may define the log of the ratio of the rate constant for 1-methyl-1-chlorocyclohexane to that for *tert*-butyl chloride as the "six-membered ring effect". This value is −0.48 and subtraction from log k_{im} for morpholine gives the triangular point shown. The two corrected (triangular) points and the points for dimethylamine, the reference species, describe an excellent straight line whose slope (0.54) is not far from that of the line through the primary amine points. The quality of the line is, no doubt, largely coincidence, but the fact that the corrections gave an improved correlation shows that the factors governing the relative magnitudes of k_{im} are very probably similar to those that govern the relative rates of solvolysis of the tertiary chlorides.

Experimental and Data Treatment Section

Acetoxime was vacuum distilled at 68–70 °C giving white crystals, mp 60–61 °C. Amine hydrochlorides were recrystallized before use. Purities of liquids were checked by GLC. A Radiometer Model 26 pH meter was used to obtain the pH, which was taken to be $-\log a_{H^+}$. Ionic activity coefficients were calculated from the Davies equation.[24] First-order rate constants were calculated from spectrophotometric data by a nonlinear regression that minimized the unweighted sum of the squares of $A_{obsd} - A_{calcd}$, where the A's are absorbances, and

Table II. Pyrrolidine-Catalyzed Oximation of Acetone[a]

pH	$10^4 k_{obsd}$, s^{-1}	$[R_2NH]_t$,[b] M	[Hx],[c] M	n[d]	$10^4 k_{obsd}/f_a$, s^{-1} Exptl	$10^4 k_{obsd}/f_a$, s^{-1} Calcd[e]
9.705	61.0	0.1145	0.0104	2	61.3	56.6
9.691	62.2	0.0487	0.0642	4	64.6	64.2
9.697	79.9	0.0503	0.0851	4	83.9	74.0
9.703	80.6	0.0499	0.1053	4	85.6	80.4
9.700	87.6	0.0462	0.1340	4	94.6	82.8
9.702	102.3	0.0503	0.2438	3	117.1	112.5

[a] In water at 35 °C and ionic strength 0.3. [b] In all states of protonation. [c] Average hydroxylamine concentration throughout the run. [d] Number of runs made. [e] From eq 14 and the least-squares values of k_{im}, k_b/k_r, and k_x/k_r.

Table III. Dimethylamine-Catalyzed Oximation of Acetone[a]

pH	$10^4 k_{obsd}$, s^{-1}	[Hx],[b] M	n[c]	$10^4 k_{obsd}/f_a$, s^{-1} Exptl	$10^4 k_{obsd}/f_a$, s^{-1} Calcd[d]
8.971	4.38[e]	0.026	2	4.44	4.54
8.996	5.22[e]	0.036	2	5.34	5.47
8.982	6.14[e]	0.046	3	6.30	6.76
8.983	7.07[e]	0.056	3	7.30	7.82
8.991	7.74[e]	0.066	3	8.04	8.91
8.995	8.93[e]	0.076	4	9.33	9.98
9.615	8.24	0.026	3	8.36	7.96
9.601	11.3	0.026	4	11.5	7.78
9.632	11.2	0.046	3	11.5	11.4
9.616	14.5	0.066	4	15.0	14.7
9.614	15.8	0.066	2	16.4	14.6
9.620	19.2	0.096	2	20.3	19.7
9.629	19.5	0.096	2	20.6	19.9
10.312	29.5	0.026	3	29.9	28.3
10.328	35.6	0.036	2	36.4	35.2
10.326	40.5	0.046	3	41.6	41.0
10.322	47.9	0.056	3	49.4	46.4
10.322	56.2	0.066	3	58.4	52.1
10.322	62.0	0.076	2	64.8	57.8
10.320	67.6	0.086	2	71.0	63.2
10.310	76.5	0.096	3	80.8	67.5

[a] In water at 35 °C and ionic strength 0.3, and, unless otherwise noted, a total dimethylamine concentration of 0.100 M. [b] Average hydroxylamine concentration throughout the run. [c] Number of runs. [d] From eq 14, a k_x/k_r value of zero, and the least-squares values of k_{im} and k_b/k_r. [e] 0.200 M total dimethylamine.

Table IV. Morpholine-Catalyzed Oximation of Acetone[a]

pH	$10^4 k_{obsd}$, s^{-1}	$[Am]_t$,[b] M	[Hx],[c] M	n[d]	$10^4 k_{obsd}/f_a$, s^{-1} Exptl	$10^4 k_{obsd}/f_a$, s^{-1} Calcd[e]
9.030	3.96	0.250	0.016	3	3.99	3.81
9.578	5.02	0.250	0.015	3	5.06	4.85
9.767	5.37	0.252	0.015	3	5.42	5.68

[a] In water at 35 °C and ionic strength 0.3. [b] In all states of protonation. [c] Average hydroxylamine concentration throughout the run. [d] Number of runs. [e] From eq 8.

gave values for three parameters, the rate constant and the initial and infinite absorbances.

Determination of the Equilibrium Constant for Carbinolamine Formation. In a typical run one syringe of the stopped-flow spectrophotometer contained 0.600 M hydroxylamine hydrochloride and the other 0.600 M sodium hydroxide–0.0100 M acetone. The voltages observed often showed rather random variations as large as 1% in magnitude for about 1 s before settling into a slow increase that was essentially linear in time and amounted to 2–5% over the first 5 s of reaction. Voltages were extrapolated to zero time and compared with similar values obtained when one or the other of the two syringes contained only water or when the first syringe contained sodium hydroxide but no acetone. The assumption that the carbinolamine absorbs negligibly at the wavelength (275 nm) at which measurements were made gives

$$K_{Ca} = \frac{\log V_1V_2 - \log V_3V_4}{[Hx] \log (V_4/V_1)} \quad (15)$$

where V_1 is the voltage when the acetone, hydroxylamine hydrochloride, and sodium hydroxide had all been added, V_2 is the voltage when only the sodium hydroxide had been added, V_3 is the voltage when the acetone and sodium hydroxide had been added, and V_4 is the voltage when hydroxylamine hydrochloride and sodium hydroxide had been added.

Determination of the Equilibrium Constant for Oximation. Extinction coefficients for acetoxime in water at 35 °C were deter-

mined in the presence of 0.25 M hydroxylamine–0.25 M hydroxylamine hydrochloride to suppress hydrolysis to acetone. Values of 1.5 and 0.4 M^{-1} cm^{-1} were obtained at 264 and 270 nm, respectively, but the value at 277 nm was too small to measure. The values obtained for acetone at these three wavelengths were 18.0, 16.9, and 13.7 M^{-1} cm^{-1}, respectively. Absorbance measurements were then made on 0.15 M solutions of acetoxime in the presence of 0.013–0.19 M hydrochloric acid and 0.05 M sodium chloride in most cases after 7 h and in all cases after about 13 h. The absorbances after 13 h, which ranged from 0.16 to 0.88, never differed from the values at 7 h by more than 0.011. The pH of the solution was measured after 13 h and ranged from 1.221 to 3.241. The apparent equilibrium constant may be expressed as

$$K_{app} = \frac{[Ox]_t - A/\epsilon_{Ac}}{(A/\epsilon_{Ac})^2} \quad (16)$$

in which A is the absorbance and ϵ_{Ac} is the extinction coefficient at 277 nm. This equation may be solved to give A as a function of K_{app} and the known quantities $[Ox]_t$ and ϵ_{Ac}, and then K_{app} may be replaced by the right-hand side of eq 3. A nonlinear least-squares treatment[25] was then used to obtain the values of K_{OxH} and K_{Ox} that minimized the sum of the squares of $A_{obsd} - A_{calcd}$. Inasmuch as the uncertainty in the absorbance values was thought to be about the same for the various values obtained, all the values were weighted equally.

Stopped-Flow Kinetic Measurements. In a typical run aqueous hydroxylamine hydrochloride was in one syringe and a mixture of acetone and sodium hydroxide and/or a buffer in aqueous solution in the other syringe of the stopped-flow spectrophotometer. The ionic strength of the mixed solution was 0.30, which often required addition of sodium chloride to the solution in one syringe. In the runs below pH 4.95 the initial total concentrations of acetone and hydroxylamine were 0.0020 and 0.0150 M, respectively. In all other runs the acetone concentration was 0.0050 M, with the hydroxylamine concentration being 0.100 M in most of the runs between pH 9.5 and 11.4 and 0.060 M in all the other runs. Most of the rate constants plotted in Figure 2 are the averages of three runs, with about 20 points being taken per run. The buffer was the hydroxylamine in the runs below pH 7, 0.10 M total triethylamine from pH 9.6 to 11.4, and sodium hydroxide at higher pHs.

Oximation of Acetone in the Presence of Added Secondary Amines. These kinetic runs were carried out in essentially the same manner described previously for the reaction in the presence of primary amines. The pH was controlled by the secondary amine buffer except in the dimethylamine runs below pH 9.4 and the pyrrolidine runs around pH 8.8, where a trimethylamine buffer with a total concentration of 0.10 M was used. In the runs using morpholine and most of those using pyrrolidine about 10–20 absorbance values were read from the chart recording. In the runs using dimethylamine and pyrrolidine around pH 8.8 about 40 values were transferred from the Cary 1605 spectrophotometer to a Nicolet Model 1090 digital oscilloscope and later read into the memory of a Hewlett-Packard calculator, Model 9830. In all cases the initial acetone concentration was 0.010 M. The concentrations of hydroxylamine listed and plotted in the various kinetic runs are the average concentrations present over that part of the reaction that was followed (usually the first 80%, but less than this in the case of the runs using the lowest concentrations of hydroxylamine). The thermodynamic pK_a values used for the conjugate acids of morpholine and pyrrolidine in water at 35 °C were 8.268[26] and 10.994,[27] respectively. For dimethylamine the value 10.491 was interpolated from measurements at 30 and 40 °C.[28] The standard deviations of the rate constants obtained in individual runs were used in the weight matrix when these constants were fit to eq 14 by a nonlinear least-squares treatment.[24]

Kinetic results not plotted in the various figures are summarized in Tables II, III, and IV for pyrrolidine, dimethylamine, and morpholine, respectively.

Registry No.—Acetone, 67-64-1; acetoxime, 127-06-0; hydroxylamine, 7803-49-8; acetone carbinolamine derivative, 31558-18-7; pyrrolidine, 123-75-1; dimethylamine, 124-40-3; morpholine, 110-91-8.

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Structure of the Substance $C_{27}H_{38}O$ Formed by the Base-Catalyzed Self-Condensation of Isophorone[1a]

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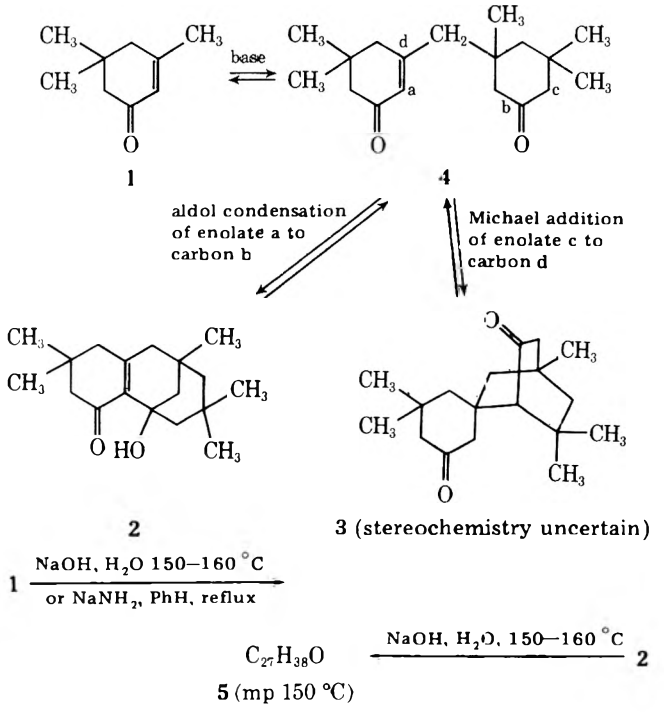
The yellow, crystalline product, $C_{27}H_{38}O$, formed by reaction of isophorone (1) with hot concentrated aqueous alkali, has been shown to possess structure **13** both by a total synthesis and by determination of its crystal structure by x-ray diffraction. The synthetic scheme used supports the idea that this trienone **13** is formed by the base-catalyzed dehydration of the isophorone dimer **2** to form an intermediate dienone **9** with a bridgehead double bond. Michael addition of the isophorone enolate **10b** to this dienone **9** followed by an aldol condensation provides a reasonable reaction path for the formation of the trienone **13**.

Following two early structural studies,[2,3] it is now known that many 3-methylcyclohexenone derivatives such as isophorone (1, Scheme I) undergo a base-catalyzed condensation

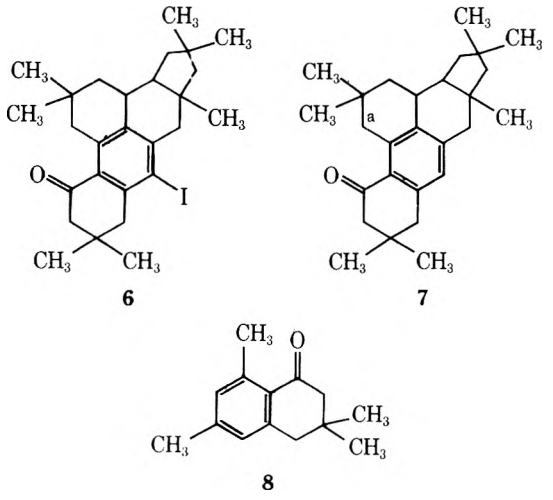
Scheme I



reaction to form dimeric structures of the types **2** and **3**.[4,5] These dimers **2** and **3** are presumably formed via the Michael adduct **4** followed either by an aldol condensation to form the ketol **2** or by a second Michael addition to form the diketone **3**. Although both dimerization processes have been shown to be reversible, generally the use of a metal hydroxide in a protic solvent (e.g., H_2O) favors production of the ketol dimer **2** while use of $NaNH_2$ in an aprotic solvent (e.g., Et_2O, PhH) favors the diketone dimer **3**.

In the course of studying the base-catalyzed dimerization of isophorone (1), heating this enone **1** to 155–160 °C with aqueous NaOH[4] or with $NaNH_2$ in boiling PhH[5] was found also to yield a yellow, crystalline solid **5** (mp 150 °C) with a composition $C_{27}H_{38}O$ corresponding to an isophorone trimer minus two molecules of H_2O. This same product **5** was also formed along with isophorone (1) when the ketol dimer **2** was heated with aqueous NaOH[4]. Subsequently, a "trimer" with the same composition was obtained by passing isophorone vapor through a tube packed with MgO pellets and heated to 380 °C.[6] Although these authors gave no melting point or other description of the physical properties of their "trimer", the product would appear to correspond to the substance **5** (mp 150 °C) obtained from isophorone and other basic reagents. These workers stated that they had examined the IR, Raman, UV, NMR, and mass spectra of this "trimer" **5** but did not report this spectral data because they regarded the data as inconclusive. Instead, the "trimer" was treated with I_2 and CF_3CO_2Ag in CCl_4 to produce two monoiodo derivatives.[6,7] Since the authors were unsuccessful in obtaining a crystal structure for the major monoiodo derivative (melting point not recorded), they determined the crystal structure **6** (617 independent reflections, R factor 11.8%) for the minor monoiodo derivative (mp 140–143 °C).[7] Based upon this structure **6** for the minor monoiodo derivative, the structure **7** (Scheme II) was assigned to the isophorone "trimer" **5**. Some

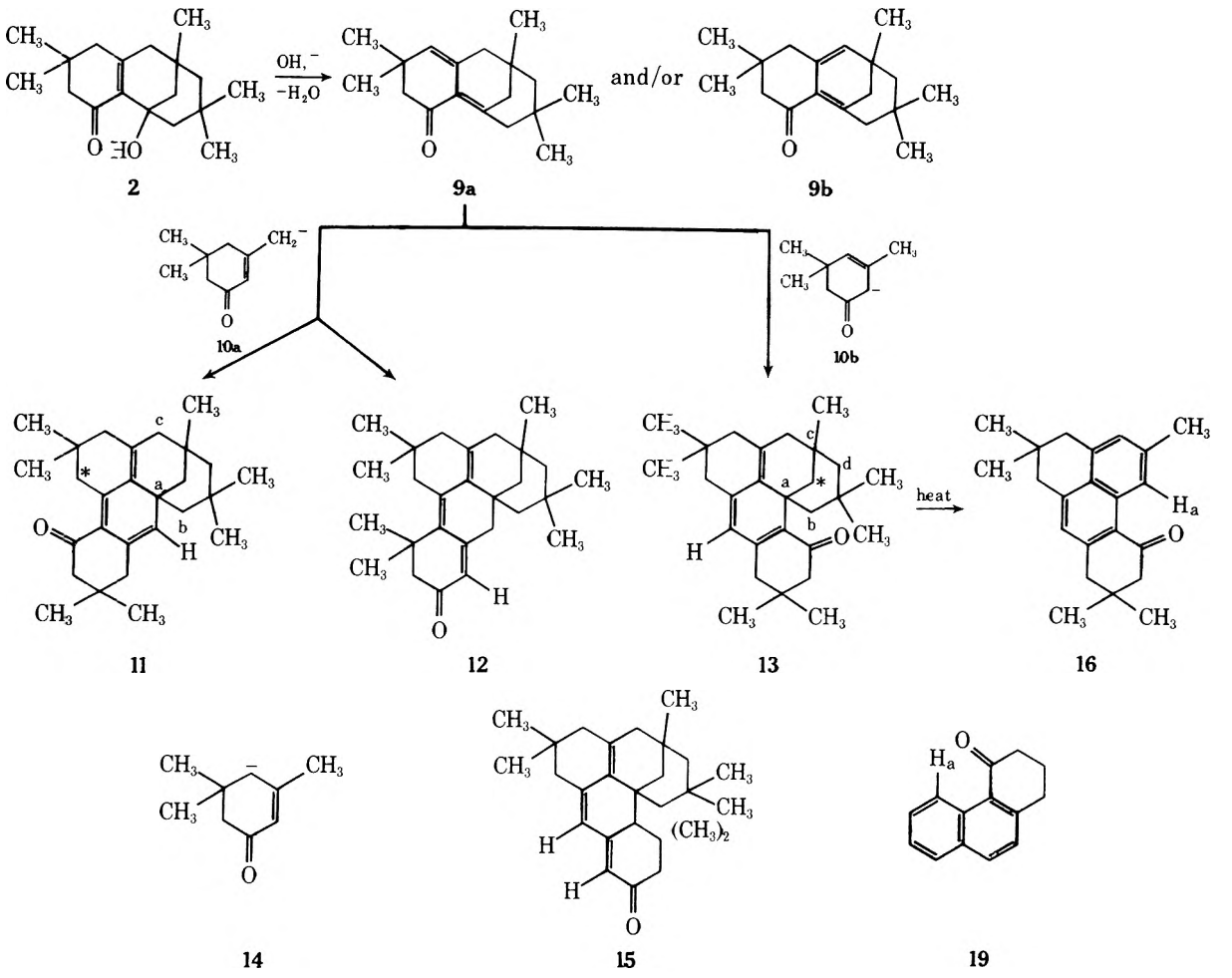
Scheme II



support for this structure **7** was obtained by an NMR study with the added lanthanide shift reagent $Yb(DPM)_3$.[8] This study indicated that two H atoms in the "trimer" **5** were held close to the O atom of the carbonyl group; these H atoms were suggested to be located at the position designated "a" in structure **7**.[8]

During the course of other studies in which isophorone (1) was passed over heated metal oxide catalysts,[9] samples of the "trimer" **5** were again shown to be present in the reaction products and the spectra of the material were determined. Among the salient spectroscopic features were infrared bands at 1642 (C=O), 1628 (C=C), and 1618 cm^{-1} (C=C) and ultraviolet maxima (95% EtOH) at 242 nm (ϵ 12 000) and 390 (8400). The ^1H NMR spectrum had distinctive absorption at δ 5.42 (1 H) and 2.92 (1 H, doublet, J = 12.5 Hz) and the mass

Scheme III



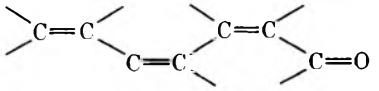
spectrum exhibited a molecular ion peak at *m/e* 378 with an intense fragment peak at *m/e* 307. The natural abundance ^{13}C NMR spectrum (see Table II) exhibited a low field signal at 196.0 ppm (C=O) with six additional lines in the region 120.2–147.0 ppm attributable to sp^2 hybridized C atoms. Only one of these signals (120.2 ppm) exhibited multiplicity in an off-resonance decoupling experiment indicating a C–H grouping. The remaining 20 ^{13}C NMR lines were in the aliphatic region (25.4–53.4 ppm); some of the lines were sufficiently close together that their multiplicities in off-resonance decoupling measurements were ambiguous (see Table II).

Although certain of these spectral data are compatible with structure **7**, other data are difficult to reconcile. In particular, the ^1H NMR signal at δ 5.42 seems more appropriate for a vinyl CH grouping rather than the aryl CH grouping (typically at δ 6.8–7.5) present in structure **7** and the intense ultraviolet maximum at 390 nm (responsible for the bright yellow color of the "trimer" **5**) seems inappropriate for structure **7**. For comparison, the tetralone **8** (a reasonable spectral model for structure **7**) exhibits aryl CH ^1H NMR absorption at δ 6.88 with ultraviolet maxima (95% EtOH) at 261 nm (ϵ 14 000) and 300 (2000). In addition to the above difficulties with spectral data, any mechanistic scheme we were able to devise to account for the formation of structure **7** from isophorone (**1**) in a base-catalyzed process required some rather bold mechanistic proposals.

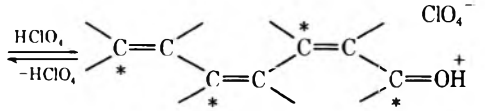
The above observations caused us to question the assignment of structure **7** to the isophorone "trimer" **5** and to consider other possible structures. A particularly appealing idea arose from the possibility that β-hydroxy ketone dimer **2** might undergo the characteristic base-catalyzed dehydration when treated with base to form one of the dienones **9** (Scheme III). Although these conjugated systems **9** possess a bridgehead double bond and will be strained, it is clear from other studies[10] that these intermediates are capable of existence. The Michael addition of one of the isophorone enolate anions **10** to the strained C=C of one of these enone systems **9** followed by an intramolecular aldol condensation could lead to three isomeric structures **11**, **12**, and **13**, each of which is compatible with the IR and NMR data observed for the "trimer" **5**. A fourth structure **15**, formed by Michael addition of the enolate **14** to enone **9**, can be excluded because this structure **15** has two vinyl CH groups. The ultraviolet maximum calculated for structure **12** (397 nm) is in better agreement with the observed value (390 nm) than the value calculated for structure **13** (417 nm); since structure **11** contains a cross-conjugated system, a simple prediction of its ultraviolet maximum is not possible. In any event, any one of these structures **11**–**13** is more compatible with the observed UV absorption for the "trimer" **5** than is structure **7**. In both structures **11** and **13** (but not **12**) there is one CH_2 group (designated*) that is held close to the O atom of the carbonyl group and could account for both the unique low-field ^1H NMR signal (doublet at δ 2.92) that we observed and the earlier lanthanide shift reagent results.[8] It is also of interest to note that if an intermediate formed by addition of CF_3CO_2I to structure **11** were to ionize, the resulting carbonium ion might fragment at bond a–b in structure **11** and then undergo suitable double bond migration and recyclization to form a new bond b–c (see structure **11**). Such a sequence could account for the formation of the monoiodo derivative **6** from structure **11**.

Two additional observations tended to reinforce our belief in the foregoing analysis and to give us a distinct preference for structure **13** as the correct structure for isophorone "trimer" **5**. When a solution of the yellow "trimer" **5** in CH_2Cl_2

was treated with aqueous 70% $HClO_4$, a deep red solution was formed from which a red solid could be isolated; treatment of this red solid with aqueous acetone regenerated the starting "trimer" **5**. The ^{13}C NMR spectrum of a $CDCl_3$ solution of the red solid (see Table II) was similar to the ^{13}C NMR of the "trimer" **5** except that the carbonyl carbon signal had been shifted upfield by 3 ppm and three of the six vinyl C atom signals had been shifted downfield by ca. 20–30 ppm. These observations are most compatible with the presence in the



17



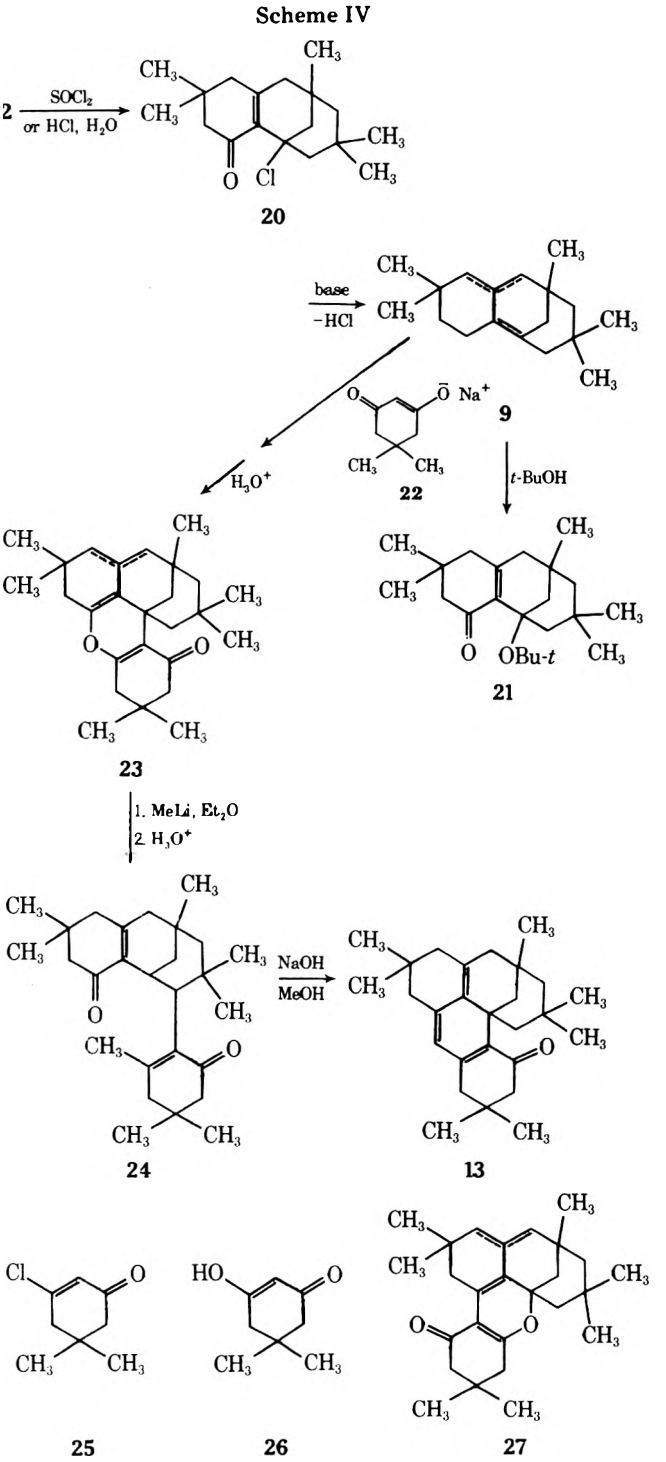
18

"trimer" **5** of a linearly conjugated trienone system **17** that is converted reversibly to its perchlorate salt **18**. In the cation **18**, the bulk of the positive charge would be centered on the designated (*) C atoms accounting for a distinct downfield shift of only three of the six vinyl C atoms. It will be noted that structures **12** and **13** (but not **11**) possess such a linearly conjugated trienone system **17**.

The fact that the mass spectrum of the "trimer" **5** exhibited a molecular peak (*m/e* 378) and one major fragment peak (*m/e* 307, $M^+ - 71$) indicated that the "trimer" **5** had a strong tendency to lose one or more fragments of total mass 71 corresponding to C_5H_{11}. We were, therefore, prompted to heat a sample of the "trimer" **5** to its boiling point at which time vigorous gas evolution was observed. A new ketone ($C_{22}H_{26}O$, mol wt 306) was isolated from this mixture in 34% yield. The various spectral properties of this product (see Experimental Section) indicated it to be a naphthyl ketone. One especially low-field ^1H NMR signal at δ 9.18 indicated that one aryl CH group was uniquely deshielded by the carbonyl function as has been observed previously[11] for a proton H_a in the naphthyl ketone **19** (Scheme III). Among the structures **11–13** being considered, it is apparent that cleavage of bonds a–b and c–d in structure **13** accompanied by loss of two H atoms can produce a naphthyl ketone **16** that would possess an aryl proton H_a with such a unique NMR signal. Thus, the data available at this stage of our investigation clearly favored formula **13** as the structure of the "trimer" **5**.

To make these assignments more secure we embarked upon a combination of a total synthesis of structure **13** and an x-ray crystal structure determination on the "trimer" **5** in order to avoid the possibility of a molecular rearrangement that might accompany the preparation of a heavy-atom derivative. Our synthetic plan utilized the observation[4] that the ketol dimer **2** could be converted to the chloro ketone **20** (Scheme IV) by reaction with either $SOCl_2$ or aqueous 12 M HCl. Our expectation that this chloro ketone **20** would undergo base-catalyzed elimination to form the bridgehead dienone **9** was readily supported by reaction of the chloro ketone **20** with *t*-BuOK in *t*-BuOH to form the *tert*-butyl ether **21**. Since the chloro ketone **20** is stable in boiling *t*-BuOH in the absence of base, it is clear that the ether **21** is not being formed by a solvolytic S_N1 reaction and the structure of the chloro ketone **20** precludes the possibility that the ether is formed in an S_N2 reaction. Thus, the elimination–addition sequence **20** → **9** → **21** is the only reasonable pathway for the formation of the ether **21**. Treatment of the chloro ketone **20** with NaH in DMF containing the enolate **22** of dimedone (**26**) yielded an initial base-soluble product that formed the keto enol ether **23** upon treatment with acid. The ^{13}C NMR spectrum of this synthetic

Scheme IV



20 **9** **22** **21** **23** **24** **13** **25** **26** **27**

intermediate was used to confirm the idea that this substance possessed structure **23** rather than a possible alternative structure **27**. The ^{13}C NMR spectrum exhibited two low-field signals (165.2 and 142.5 ppm) attributable to the two sp^2 carbon atoms bound to oxygen in structure **23**; structure **27** has only one carbon atom of this type. Furthermore, the spectrum lacked a signal at about 70 ppm (e.g., 70.9 ppm in the spectrum of ketol **2**) expected for an sp^3 carbon atom bound to one oxygen atom and three alkyl groups; this structural feature is present in structure **27** but not in structure **23**. After addition of MeLi to the carbonyl group of the keto enol ether **23**, acid-catalyzed hydrolysis produced the diketone **24** and a subsequent base-catalyzed aldol condensation yielded the trienone **13**. This product was identical in all respects with the "trimer" **5** formed from isophorone and aqueous NaOH.

As alternative synthetic routes to the trienone **13**, we also

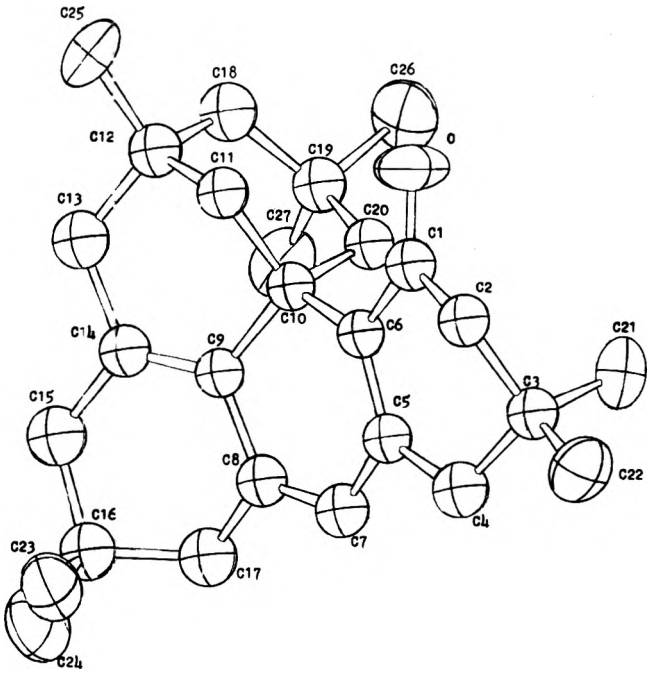


Figure 1. A perspective view of the molecular structure of the trienone **13**.

explored briefly the reaction of the chloro ketone **20** with the β-chloro enone **25** in an effort to form an enol ether precursor to enone **23** and the reaction of the chloro ketone **20** with dimedon (**26**) and $AgClO_4$ in CH_3NO_3.[12] The first process led to recovery of the starting materials and the second procedure formed a relatively complex mixture of reaction products that was not investigated further.

The structure of the "trimer" **5**, obtained from a single-crystal x-ray diffraction study, is shown in Figure 1. The list of bond lengths and bond angles is given in Table I; the values are consistent with structure **13**. The estimated standard deviations of the bond lengths and angles are ca. 0.005 Å and 0.4°, respectively.

For the conjugated system extending from the carbonyl group (C1) to C14, the carbon–carbon double bond lengths are 1.353 (C_5–C_6), 1.329 (C_7–C_8), and 1.334 Å (C_9–C_{14}) while the remaining bond lengths are 1.481 (C_1–C_6), 1.452 (C_5–C_7), and 1.450 Å (C_8–C_9). Although these values are reasonable for a delocalized system, there is some distortion from planarity and these distortions may be responsible for the difference in the calculated (417 nm) and observed (390 nm) positions of the ultraviolet maximum. The nature and extent of the distortion is shown by dihedral angle calculations for the three-atom planes at each end of a bond; bonds C1–C6, C5–C7, and C8–C9 all show approximately 15° twists from planarity. Some of this distortion is apparently caused by repulsion between the carbonyl oxygen and a methylene proton at C11; the H11–O distance of 2.32 Å is less than the sum of the van der Waals radii of oxygen and hydrogen (ca. 2.5 Å). This close approach is consistent with the observation of a low-field ^1H NMR signal.

Experimental Section[13]

Preparation of the Trienone 13. A mixture of 200 g (1.45 mol) of the enone **1**, 70 g of NaOH, and 30 mL of H_2O was heated to 150 °C with stirring for 20 h and then cooled and partitioned between Et_2O and H_2O. The ethereal layer was washed with aqueous NaCl, dried, and concentrated to leave 198 g of crude product as a dark red liquid. The relatively volatile materials were removed from this mixture by distillation at 0.3 mm and temperatures up to 170 °C. When an EtOH solution of the residue from this distillation was cooled, the crude trienone **13** separated as a yellow solid, mp 138–144 °C. Recrystallization from EtOH gave 25.1 g (14%) of the trienone **13** as yellow prisms, mp 147–148 °C. When this material was allowed to crystallize very slowly from EtOH, the trienone **13**, mp 149–150 °C, separated as large yellow prisms (lit.[4] mp 150–152 °C): IR ($CHCl_3$) 1642 (conjugated C=O), 1628, and 1618 cm^{-1} (C=C); UV max (95% EtOH) 242 nm (ε 12 000) and 390 (8400); ^1H NMR ($CDCl_3$) δ 5.42 (1 H, broad, vinyl CH), 2.92 (1 H, d, J = 12.5 Hz, aliphatic CH), and 0.8–2.4 (36 H, m, aliphatic CH); mass spectrum m/e (rel intensity) 378 (M^+, 24), 363 (11), 308 (25), and 307 (100).

Anal. Calcd for $C_{27}H_{38}O$: C, 85.66; H, 10.12. Found: C, 85.70; H, 10.13.

The EtOH mother liquors remaining after the above crystallization of the trienone **13** were concentrated to leave a brown, viscous liquid containing (TLC, silica gel coating with an EtOAc–hexane eluent, 1:4 v/v) two or more rapidly eluted components with R_f values of 0.59

Table I. Molecular Geometry of the Trienone 13

A. Bond Lengths

Atoms	Distance, Å (standard deviation)	Atoms	Distance, Å (standard deviation)
O–C1	1.213 (4)	C13–C14	1.495 (5)
C5–C6	1.353 (4)	C14–C15	1.518 (5)
C7–C8	1.329 (5)	C15–C16	1.514 (5)
C9–C14	1.334 (4)	C16–C17	1.523 (5)
C1–C6	1.481 (4)	C8–C17	1.508 (5)
C5–C7	1.452 (5)	C10–C20	1.557 (5)
C8–C9	1.450 (5)	C12–C18	1.534 (5)
C1–C2	1.506 (5)	C18–C19	1.537 (6)
C2–C3	1.524 (5)	C19–C20	1.544 (5)
C3–C4	1.516 (5)	C3–C21	1.520 (5)
C4–C5	1.511 (5)	C3–C22	1.520 (5)
C9–C10	1.526 (5)	C16–C23	1.530 (6)
C6–C10	1.543 (5)	C16–C24	1.517 (6)
C10–C11	1.534 (5)	C12–C25	1.520 (6)
C11–C12	1.529 (5)	C19–C26	1.527 (6)
C12–C13	1.524 (5)	C19–C27	1.529 (6)

B. Bond Angles

Atoms	Angle, deg (standard deviation)	Atoms	Angle, deg (standard deviation)
O–C1–C2	119.9 (4)	C9–C10–C20	109.9 (3)
O–C1–C6	123.1 (3)	C11–C10–C20	107.8 (3)
C2–C1–C6	117.0 (3)	C10–C11–C12	111.0 (3)
C1–C2–C3	112.5 (3)	C11–C12–C13	107.7 (3)
C2–C3–C4	106.1 (3)	C11–C12–C18	108.7 (3)
C2–C3–C21	110.1 (3)	C11–C12–C25	110.5 (3)
C2–C3–C22	110.5 (3)	C13–C12–C18	113.2 (3)
C4–C3–C21	110.7 (3)	C13–C12–C25	109.1 (3)
C4–C3–C22	110.3 (3)	C18–C12–C25	107.7 (3)
C21–C3–C22	109.2 (4)	C12–C13–C14	116.3 (3)
C3–C4–C5	116.1 (3)	C13–C14–C9	122.6 (3)
C4–C5–C6	123.0 (3)	C13–C14–C15	115.1 (3)
C4–C5–C7	115.8 (3)	C9–C14–C15	122.2 (3)
C6–C5–C7	121.2 (3)	C14–C15–C16	116.7 (3)
C5–C6–C10	119.5 (3)	C15–C16–C17	107.3 (3)
C1–C6–C5	118.2 (3)	C15–C16–C23	110.3 (4)
C1–C6–C10	122.0 (3)	C15–C16–C24	109.3 (4)
C5–C7–C8	121.6 (3)	C17–C16–C23	110.0 (4)
C7–C8–C9	120.6 (3)	C17–C16–C24	110.6 (3)
C7–C8–C17	122.8 (3)	C23–C16–C24	109.3 (4)
C9–C8–C17	116.6 (3)	C16–C17–C8	112.5 (3)
C8–C9–C10	117.4 (3)	C12–C18–C19	119.5 (3)
C8–C9–C14	120.4 (3)	C18–C19–C20	110.8 (3)
C10–C9–C14	122.2 (3)	C18–C19–C26	108.8 (3)
C6–C10–C9	110.8 (3)	C18–C19–C27	111.6 (3)
C6–C10–C11	113.4 (3)	C20–C19–C26	107.9 (3)
C6–C10–C20	106.0 (3)	C20–C19–C27	111.7 (3)
C9–C10–C11	108.9 (3)	C26–C19–C27	105.7 (4)
		C19–C20–C10	116.3 (3)

Table II. Natural Abundance ^{13}C NMR Spectra in $CDCl_3$ Solution of the Trienone 13 and Its Perchlorate Salt

Signal in order of increasing field	Signal for trienone 13, ppm (multiplicity in off-resonance decoupling)[a]	Signal for the salt, ppm (multiplicity in off-resonance decoupling)[a]
1	196.0 (s)	193.4 (s)
2	147.0 (s)	178.3 (s)
3	141.1 (s)	163.3 (s)
4	135.8 (s)	153.8 (s)
5	132.4 (s)	132.0 (s)
6	131.4 (s)	127.7 (s)
7	120.2 (d)	124.5 (d)
8	53.4 (t)	51.8 (t)
9	52.4 (t)	46.5[b] (t, ?)
10	45.8 (t)	46.4[b] (t, ?)
11	44.8[b] (t, ?)	46.4[b] (t, ?)
12	44.7[b] (t, ?)	46.3[b] (t, ?)
13	43.9 (t, ?)	45.0 (t)
14	43.1 (t)	44.0 (t)
15	39.8[b] (s)	40.3[b] (s)
16	39.7[b] (t)	40.3[b] (?)
17	37.5 (q, ?)	40.2[b] (?)
18	33.2 (q)	37.3 (q)
19	32.6 (s)	32.8[b] (s)
20	31.1 (q, ?)	32.7[b] (?)
21	30.3[b] (s, ?)	32.1 (?)
22	30.3[b] (s, ?)	30.4[b] (?)
23	29.9 (s)	30.3[b] (?)
24	29.2[b] (q, ?)	29.9 (?)
25	28.9[b] (q, ?)	29.5 (?)
26	26.6 (q)	26.9 (q)
27	25.4 (q)	25.2 (q)

[a] Where the multiplicity designation is accompanied by a question mark, the close spacing of two or more lines made the splitting pattern ambiguous. [b] Only partial resolution of these closely spaced peaks was attained.

(corresponds to the trienone **13**) and 0.62 as well as several more polar components with smaller R_f values. A portion of this crude mixture was subjected to a preparative TLC separation to obtain a sample of the materials with R_f values of 0.59 and 0.62. GLC analysis (silicone DC-710 on Chromosorb P) of the sample indicated the presence of comparable amounts of four components with the following retention times: 26.6, 31.0 (corresponds to the trienone **13**), 38.0, and 48.4 min. Thus, this base-catalyzed condensation of isophorone (**1**) produces components other than the trienone **13** but with similar properties. These by-products may include one or more of the structural isomers **11**, **12**, and **15**.

The natural abundance ^{13}C NMR spectrum of the trienone **13** ($CDCl_3$ solution) exhibited the peaks listed in Table II. The results of off-resonance decoupling measurements (s, d, t, etc.) are indicated in parentheses beside each peak. In cases where close spacing of two peaks made the splitting pattern ambiguous, the multiplicity is designated with a question mark.

When a solution of 2.25 g (5.95 mmol) of the trienone **13** in 10 mL of CH_2Cl_2 was treated with 5 mL of aqueous 70% $HClO_4$, the organic layer immediately became deep red in color. After the mixture had been stirred at 25 °C for 30 min, the organic layer was separated, dried, and concentrated to leave 2.83 g of the crude perchlorate salt of the trienone **13** as a red solid: IR ($CHCl_3$) a series of weak bands in the 6-μ region at 1642, 1605, and 1585 cm^{-1} (C=C); UV max (CH_2Cl_2) 272 nm (ϵ ca. 11 000), 329 (ca. 2900), and 511 (ca. 15 000); ^1H NMR ($CDCl_3$) δ 6.09 (1 H, broad, vinyl CH) and 0.8–3.0 (5.7 H, m, aliphatic CH). The natural abundance ^{13}C NMR data obtained for a $CDCl_3$ solution of this crude salt are summarized in Table II; in some cases, designated (?), we were unable to discern the splitting patterns obtained with off-resonance decoupling. When a solution of 104 mg of this crude salt in 5 mL of acetone was treated with H_2O, the red color was discharged to leave a yellow solution. After this solution had been partitioned between H_2O and CH_2Cl_2, the organic layer was dried and concentrated to leave 83 mg of the crude trienone **13**, mp 143.5–144.5 °C, that was identified with the starting trienone **13** by comparison of IR and UV spectra. Recrystallization from EtOH raised the melting point of the recovered trienone **13** to 148–149 °C; a mixture melting point determination of the starting and recovered trienone samples was not depressed.

Table III. Natural Abundance ^{13}C NMR Spectrum of Ketone 16 in $CDCl_3$ Solution

Signals in order of increasing field	^{13}C NMR signal, ppm (multiplicity in off-resonance decoupling measurement)
1	199.1 (s)
2	143.9 (s)
3	141.7 (s)
4	137.7 (s)
5	134.2 (s)
6	131.0 (s)
7	126.5 (d)
8	126.4 (s)
9	124.9 (d)
10	123.5 (s)
11	123.2 (d)
12	54.5 (t)
13 and 14	45.2 (t)
15	44.7 (t)
16	33.3 (s)
17	30.5 (s)
18, 19, 20, and 21	27.8 (q)
22	22.1 (q)

Pyrolysis of the Trienone 13. A 2.00-g (5.29 mmol) sample of the trienone **13** was heated to boiling (ca. 320–330 °C) under an N_2 atmosphere during 30 min and then maintained at this temperature for 50 min. A solution of the product, a viscous brown liquid, in CH_2Cl_2 was filtered through a bed of silica gel and then chromatographed on silica gel with a PhH–hexane eluent (3:1 v/v). After removal of the early fractions containing 1.13 g of viscous yellow liquid, subsequent fractions contained an oily solid that was triturated with pentane to leave 564 mg (34%) of the ketone **16** as a pale green solid, mp 141–143 °C. Recrystallization from EtOH afforded 475 mg of the pure ketone **16** as pale yellow-green needles, mp 143–144 °C, and an additional recrystallization raised the melting point to 143.5–145 °C: IR ($CHCl_3$) 1660 cm^{-1} (conjugated C=O); UV max (95% EtOH) 218 nm (ϵ 31 000), 258 (22 000), and 343 (8000);[14] ^1H NMR ($CDCl_3$) δ 9.18 (1 H, broad s, aryl CH), 7.07 (1 H, broad s, aryl CH), 6.93 (1 H, broad s, aryl CH), 2.93 (2 H, s, benzylic CH_2), 2.83 (4 H, s, benzylic CH_2), 2.57 (2 H, s, benzylic CH_2), 2.49 (3 H, s, aryl CH_3), 1.09 (6 H, s, CH_3), and 0.99 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 306 (M^+, 100), 250 (53), 222 (10), 207 (13), and 192 (10).

Anal. Calcd for $C_{22}H_{26}O$: C, 86.23; H, 8.55. Found: C, 86.04; H, 8.59.

The natural abundance ^{13}C NMR spectrum of a $CDCl_3$ solution of the ketone **16** exhibited the peaks listed in Table III.

Preparation of the Hydroxy Ketone 2. Following a previous procedure,[2] a mixture of 117 g (0.849 mol) of isophorone (**1**), 20 g of NaOH, and 10 mL of H_2O was heated to 100–125 °C with stirring for 2 h. After the reaction mixture had been partitioned between $CHCl_3$ and aqueous 3 M HCl, the organic layer was washed with aqueous NaCl, dried, and concentrated. The residual liquid was fractionally distilled to separate 14.3 g of pale yellow liquid, bp 100 °C (15 mm), and 86.63 g of a viscous yellow liquid fraction, bp 110–133 °C (0.3 mm), that solidified on standing. Repeated recrystallization of this material from hexane separated 51.8 g (44%) of the pure ketol **2** as colorless prisms: mp 83–84 °C (lit. mp 84–85,[5] 86–88 °C[4]); IR (CCl_4) 3470 (OH), 1656 (shoulder), 1650 (conjugated C=O), and 1632 cm^{-1} (C=C); UV max (95% EtOH) 250 nm (ϵ 8300); ^1H NMR (CCl_4) δ 4.76 (1 H, broad, OH), 1.1–2.2 (12 H, m, CH_2), 1.03 (6 H, s, CH_3), 0.98 (3 H, s, CH_3), 0.92 (3 H, s, CH_3), and 0.72 (3 H, s, CH_3); mass spectrum *m/e* (rel intensity) 276 (M^+, 2), 261 (6), 206 (16), 205 (100), 163 (22), and 121 (19). The natural abundance ^{13}C NMR spectrum of the ketol **2** in $CDCl_3$ solution is summarized in Table IV.

Preparation of the Chloro Ketone 20. A solution of 9.78 g (35.4 mmol) of the ketol **2** in 50 mL of $CHCl_3$ (EtOH free) was treated with 4.9 g (41 mmol) of $SOCl_2$ and the resulting solution was stirred at 25 °C for 16 h. After the resulting solution had been washed successively with H_2O and with aqueous $NaHCO_3$ it was dried and concentrated to leave 10.6 g of the crude chloro ketone **20** as an orange solid. Recrystallized from MeOH afforded 8.02 g of pure chloro ketone **20** as

Table IV. Natural Abundance ^{13}C NMR Spectrum of Ketol 2 in $CDCl_3$ Solution

Signals in order of increasing field	^{13}C NMR signal, ppm (multiplicity in off-resonance decoupling measurement)
1	199.4 (s)
2	156.3 (s)
3	134.7 (s)
4	70.9 (s)
5	51.9 (t)
6	51.5 (t)
7	50.1 (t)
8	46.4 (t)
9	45.5 (t)
10	44.4 (t)
11	36.9 (q)
12	32.5 (q)
13	32.2 (s)
14	32.0 (s)
15	31.2 (s)
16	29.5 (q)
17	28.1 (q)
18	26.6 (q)

pale orange prisms, mp 137–138.5 °C (lit.[4] mp 135–136 °C), as well as 0.97 g of less pure product: mp 136–138 °C (total yield 8.99 g or 86%); IR (CCl_4) 1638, 1678 (C=O), and 1627 cm^{-1} (C=C); UV max (95% EtOH) 244 nm (ϵ 8000); NMR (CCl_4) δ 1.1–2.8 (12 H, m, CH_2), 1.08 (3 H, s, CH_3), 1.00 (6 H, s, CH_3), 0.93 (3 H, s, CH_3), and 0.73 (3 H, s, CH_3); mass spectrum *m/e* (rel intensity) 296 (M^+, 2), 294 (M^+, 5), 258 (40), 243 (33), 203 (25), 202 (40), 201 (100), 187 (30), 119 (24), 55 (25), and 41 (38).

Preparation of the *tert*-Butoxy Ketone 21. To a boiling solution of 700 mg (2.58 mmol) of the chloro ketone **20** in 5 ml of *t*-BuOH was added, dropwise and with stirring during 5 min, 5 mL of a *t*-BuOH solution containing 2.69 mmol of *t*-BuOK. During this addition the solution turned deep red and a fine precipitate (presumably KCl) separated. After the reaction mixture had been refluxed for 30 min, it was neutralized by addition of 0.5 g (9 mmol) of solid NH_4Cl and then diluted with Et_2O, filtered, and concentrated. The residue was partitioned between pentane and H_2O and the pentane solution was dried and concentrated to leave 687 mg of the crude product as a light orange solid, mp 110–118 °C. Chromatography on silica gel with an EtOAc–hexane eluent (1:9 v/v) separated 484 mg (61%) of the *tert*-butoxy ketone **21**, mp 126–129 °C. Recrystallization from an EtOH–H_2O mixture afforded the pure *tert*-butoxy ketone **21** as colorless needles: mp 131–132 °C; IR (CCl_4) 1671, 1680 (conjugated C=O), 1630, and 1620 cm^{-1} (weak, conjugated C=C); UV max (95% EtOH) 248 nm (ϵ 6500); NMR (CCl_4) δ 1.3–2.5 (10 H, m, aliphatic CH) and 0.6–1.3 [26 H, m, aliphatic CH including singlets at 1.17 (*t*-BuO), 1.05 (CH_3), 0.98 (two CH_3), 0.81 (CH_3), and 0.74 (CH_3)]; mass spectrum *m/e* (rel intensity) 302 (2), 258 (12), 243 (10), 231 (10), 205 (30), 187 (15), 146 (14) 56 (39), 55 (28), 41 (100), and 39 (35).

Anal. Calcd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.92. Found: C, 79.44; H, 10.93.

In a similar experiment, a solution of 800 mg (2.72 mmol) of the chloro ketone **20** in 5 mL of THF was added to 5 mL of a *t*-BuOH solution containing 3.67 mmol of *t*-BuOK. The mixture, which turned red and deposited a white precipitate (KCl), was stirred at 25 °C for 12 h and then subjected to the previously described isolation and purification procedures. The yield of the *tert*-butyl ether **21**, mp 130–132 °C, was 581 mg (64%).

As a control experiment, a solution of 150 mg (0.51 mmol) of the chloro ketone **20** in 2 mL of *t*-BuOH was refluxed for 25 min and then concentrated under reduced pressure. The recovered chloro ketone **20** (150 mg, mp 137–138.5 °C) was identified with an authentic sample by comparison of IR spectra.

Preparation of the Chloro Ketone 25. Following a previously described procedure,[15] a suspension of 20.0 g (0.14 mol) of dimedone **26** in 40 mL of $CHCl_3$ (EtOH free) was treated with 6.7 g (0.049 mol) of PCl_3 and the resulting mixture was refluxed for 2.2 h. After the reaction mixture had been concentrated under reduced pressure, the residue was partitioned between Et_2O and aqueous 10% NaOH and the ethereal phase was dried and concentrated. Fractional distillation of the crude organic product afforded 13.6 g (61%) of the chloro ketone **25** as a colorless liquid: bp 99–100 °C (16 mm); $n^{25}D$ 1.4943 [lit. bp 72 °C (5 mm),[16] 105 °C (20 mm),[17]]; IR (CCl_4) 1700 (shoulder), 1682, 1670 (shoulder, conjugated C=O), and 1615 cm^{-1} (C=C); UV max (hexane) 233 nm (ϵ 13 000); NMR (CCl_4) δ 6.13 (1 H, t, J = 1.5 Hz, vinyl CH), 2.55 (2 H, d, J = 1.5 Hz, allylic CH_2), 2.18 (2 H, s, CH_2CO), and 1.10 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 160 (M^+, 9), 158 (M^+, 25), 143 (6), 104 (33), 102 (100), 67 (28), and 39 (16).

Properties of the Tetralone 8. As a spectroscopic model for the structure **7**, a sample of the tetralone **8** was prepared from acetone by a previously described procedure.[18] The product was obtained as colorless prisms: mp 56–57 °C (lit. mp 56.5–57,[18b] 54–55 °C[18c]); IR (CCl_4) 1670 cm^{-1} (conjugated C=O); UV max (95% EtOH) 261 nm (ϵ 14 000) and 300 (2000); NMR ($CDCl_3$) δ 6.88 (2 H, broad s, aryl CH), 2.76 (2 H, s, CH_2), 2.60 (3 H, s, aryl CH_3), 2.41 (2 H, s, CH_2), 2.28 (3 H, s, aryl CH_3), and 1.00 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 202 (M^+, 34), 146 (100), and 118 (9).

Preparation of the Keto Enol Ether 23. To a cold (0 °C) suspension of 21 mmol of NaH (from 956 mg of a 52% dispersion that was washed with pentane) in 5 mL of DMF was added, dropwise and with stirring, a solution of 1.39 g (9.94 mmol) of dimedone (**26**) in 5 mL of DMF. After the addition was complete, during which time the temperature of the mixture rose to 5 °C, a solution of 1.40 g (4.76 mmol) of the chloro ketone **20** in 10 mL of DME was added dropwise and with stirring during 5 min. During this addition the mixture became red-brown in color and gas was evolved. The resulting mixture was stirred at 5 °C for 20 min and at 25 °C for 80 min. The resulting mixture was diluted with H_2O and then partitioned between Et_2O and aqueous 1 M HCl. After the ethereal solution had been washed with H_2O, dried, and concentrated, the residual crude product (2.00 g of viscous yellow liquid) was dissolved in 20 mL of THF containing 0.2 mL of aqueous 70% $HClO_4$ and stirred at 25 °C for 1.5 h. The resulting mixture was partitioned between Et_2O and aqueous 5% NaOH and the ethereal layer was washed with water, dried, and concentrated. Recrystallization of the residual crude product (1.39 g of tan solid, mp 140–150 °C) from EtOH separated 956 mg (53%) of the ketone **23** as colorless prisms, mp 160–162 °C. An additional recrystallization gave the pure ketone **23**: mp 161–162 °C; IR (CCl_4) 1680 (enol ether C=C), 1661 (conjugated C=O), and 1610 cm^{-1} (conjugated C=C); UV max (95% EtOH) 240 nm (ϵ 18 000) and 318 (2300); NMR (CCl_4) δ 5.15 (1 H, s, broad vinyl CH), 2.71 (1 H, d, J = 12 Hz, aliphatic CH), 1.2–2.5 (13 H, m, aliphatic CH), and 0.7–1.2 (21 H, m, CH_3); mass spectrum *m/e* (rel intensity) 380 (M^+, 9), 365 (14), 310 (14), 309 (100), 83 (10), 55 (10), 43 (9), and 41 (9).

Anal. Calcd for $C_{26}H_{36}O_2$: C, 82.06; H, 9.54. Found: C, 81.98; H, 9.55.

The natural abundance ^{13}C NMR spectrum of the ketone **23** ($CDCl_3$ solution) exhibited the peaks listed in Table V.

Table V. Natural Abundance ^{13}C NMR Spectrum of the Ketone 23 in $CDCl_3$ Solution

Signals in order of increasing field	^{13}C NMR signal, ppm (multiplicity in off-resonance decoupling measurement)[a]
1	197.0 (s)
2	165.2 (s)
3	142.5 (s)
4	132.0 (d)
5	129.8 (s)
6	116.5 (s)
7	114.4 (s)
8	53.0 (t)
9 and 10	49.3 (2t)
11	43.8 (t)
12	42.1 (t)
13 and 14	40.7 (2t)
15	37.1 (q)
16	33.9 (s)
17	33.0 (s)
18	31.4 (s)
19, 20, 21, and 22	30.2 (2s, 2q, ?)
23 and 24	29.5 (2q, ?)
25	27.2 (q)
26	26.1 (q)

[a] Where the multiplicity designation is accompanied by a question mark, the close spacing of two or more lines made the splitting pattern ambiguous.

Table VI. Natural Abundance ^{13}C NMR Spectrum of the sp^2 Carbon Atoms in Diketone 24

Signals in order of increasing field	^{13}C NMR signal, ppm (multiplicity in off-resonance decoupling measurement)
1	200.3 (s)[a]
2	198.7 (s)[b]
3	196.6 (s)[b]
4	194.6 (s)[a]
5	152.2 (s)[a]
6	149.8 (s)[b]
7	144.4 (s)[b]
8	143.6 (s)[a]
9	140.8 (s)[b]
10	139.9 (s)[a]
11	137.4 (s)[b]
12	137.1 (s)[a]

[a] Less intense signal. [b] More intense signal.

Preparation of the Diketone 24 and the Trienone 13. To 3.1 mL of a cold (0 °C) ethereal solution containing 2.26 mmol of MeLi was added a solution of 588 mg (1.55 mmol) of the keto enol ether **23** in 7 mL of Et_2O. After the resulting mixture had been stirred at 25 °C for 20 min, it was partitioned between Et_2O and H_2O. The ethereal solution was dried and concentrated to leave a colorless, viscous liquid that was dissolved in 10 mL of cold (0 °C) THF. This cold solution was treated with 2 mL of aqueous 12 M HCl in 5 mL of THF and the resulting solution was stirred at 25 °C for 1.5 h. The resulting yellow solution was partitioned between aqueous NaCl and Et_2O. The ethereal layer was washed successively with aqueous $NaHCO_3$ and with aqueous NaCl, dried, and concentrated to leave 614 mg of viscous yellow liquid containing (TLC, silica gel with an EtOAc–hexane eluent, 1:9 v/v) the diketone **24** (R_f 0.32), the keto enol ether **23** (R_f 0.52), the trienone **13** (R_f 0.56), and two unidentified components (R_f 0.64 and 0.75). Chromatography on silica gel with an EtOAc–hexane eluent (2:23 v/v) separated the crude diketone **24** as a colorless liquid that solidified on standing. Recrystallization from MeOH separated 353 mg (57%) of the diketone **24** as colorless prisms, mp 99–100 °C. An additional recrystallization from H_2O–EtOH raised the melting point to 99.5–100.5 °C: IR (CCl_4) 1665 (conjugated C=O), 1632, and 1600 cm^{-1} (C=C); NMR (CCl_4) δ 1.2–2.6 (19 H, m, aliphatic CH) and 0.6–1.2 (21 H, m, CH_3); UV max (95% EtOH) 256 nm (ε 13 000); mass spectrum *m/e* (rel intensity) 396 (M^+, 100), 381 (47), 340 (32), 325 (59), 307 (45), 201 (30), 141 (49), 83 (49), 69 (36), 55 (52), 43 (48), and 41 (61).

Anal. Calcd for $C_{27}H_{40}O_2$: C, 81.76; H, 10.17. Found: C, 81.73; H, 10.03.

After a solution of 200 mg (0.51 mmol) of the diketone **24** and 650 mg (16 mmol) of NaOH in 8 mL of MeOH had been refluxed for 15 h under an N_2 atmosphere, the resulting dark yellow reaction mixture was concentrated and then partitioned between Et_2O and H_2O. The ethereal layer was dried and concentrated to leave 180 mg of the crude product as a yellow solid, mp 144–147 °C; this material contained (TLC, silica gel coating with an EtOAc–hexane eluent, 1:9 v/v) the trienone **13** (R_f 0.49) and a minor identified impurity (R_f 0.53) but none of the starting diketone **24** (R_f 0.25) was detected. Recrystallization from MeOH separated 154 mg (81%) of the trienone **13** as yellow prisms, mp 147–149 °C. This product was allowed to crystallize from EtOH very slowly to give 90 mg of the pure trienone **13**, mp 149–150 °C, that was identified with the previously described sample by a mixture melting point determination and by comparison of IR, UV, and NMR spectra.

When the natural abundance ^{13}C NMR spectrum of the diketone **24** was determined in $CDCl_3$ solution at ca. 40 °C, the six lines expected for the sp^2 carbon atoms in structure **24** (Table VI) were accompanied by six additional less intense lines corresponding to a second conformer of structure **24**. Because of the presence of two rotational isomers with different ^{13}C NMR signals, we were unable to resolve satisfactorily the complex multiplet from the sp^3 carbon atoms in this spectrum. To establish that these extra NMR signals arose from two slowly equilibrating conformers (presumably caused by restricted rotation about the C–C bond joining the two ring systems in structure **24**), the ^1H NMR spectrum of the diketone **24** in PhCl solution was examined at ca. 35 °C and at 95 °C. At ca. 35 °C, the highest field CH_3 signal appeared as a less intense singlet at δ 0.68 and a more intense singlet at δ 0.74. When this solution was warmed to 95 °C, the two signals collapsed to a single line at δ 0.77; upon cooling this solution to ca. 35 °C the original spectrum was obtained.

Structure Determination of "Trimer" 5. A platelike crystal fragment with approximate dimensions 0.5 × 0.7 × 0.3 mm was mounted on a glass fiber with epoxy cement. Unit cell parameters and the orientation matrix were determined on a Syntex $P2_1$ four-circle diffractometer equipped with a graphite monochromator (Bragg 2θ angle 12.2°) using Mo Kα radiation at a takeoff angle of 6.5°. Fifteen reflections whose 2θ values ranged from 11.72° to 21.90° were machine centered and used in least-squares refinement of the lattice parameters and orientation matrix. Unit cell parameters obtained were[19] a = 12.196 (2) Å, b = 11.247 (3) Å, c = 10.740 (2) Å, α = 94.45 (2)°, β = 110.76 (2)°, γ = 119.04 (2)°, and V = 1146.9 (4) Å^3. The calculated density of 1.10 g cm^{-3} for two molecules per unit cell agrees with the experimetnal density of 1.09 (1) g cm^{-3} measured by the flotation method using aqueous zinc chloride solution at room temperature. Omega scans of several low 2θ angle reflections gave peak widths at half-height of less than 0.30°, indicating a satisfactory mosaic spread for the crystal.

Intensity data were collected using θ–2θ scans with x-ray source and monochromator settings identical with those used for determination of the unit cell parameters. A variable scan rate of from 4.88 to 29.3°/min was used and a scan width of 2.3° was sufficient to collect all of the peak intensity. Stationary background counts were measured at the beginning (bgd1) and at the end (bgd2) of each scan with a total background to scan time ratio of 1.0. No significant fluctuations were observed in the intensities of three standard reflections (-3,3,-3; 4,-4,-4; 2,2,-2) monitored every 97 reflections. Intensities (I) were calculated by subtracting the sum of the two background counts (bgd1 + bgd2) from the total scan count (CT). Standard deviations were assigned to the intensities according to the formula

$$\sigma(I) = (\mathrm{CT} + \mathrm{bgd1} + \mathrm{bgd2})^{1/2}$$

From a total of 4274 reflections collected in a complete hemisphere ($h \geq 0$) of data out to 2θ = 50°, 2223 were accepted as statistically above background [$I \geq 3\sigma(I)$]. Lorentz and polarization corrections were made in the usual way; no corrections were made for absorption.

The structure was solved[20] by direct methods utilizing the program MULTAN to generate phases. E values were calculated for all nonzero reflections and the 336 largest E values were used as input for MULTAN. When the program was allowed to choose three origin-fixing reflections, it was unable to produce a set of phases that led to a solution. Three alternate origin-setting reflections chosen manually produced a set of phases with an absolute figure-of-merit of 1.152 and Ψ_0 of 0.29 × 10^3; the resulting E map revealed the positions of all nonhydrogen atoms. After three cycles of full-matrix least-squares refinement, a difference Fourier revealed positions of all nonmethyl hydrogens. Further refinement, followed by another difference Fourier, located methyl hydrogen positions. After three additional cycles of least-squares refinement, varying a scale factor, coordinates of all atoms, anisotropic temperature parameters for the oxygen and methyl carbons, isotropic temperature factors for all other carbon atoms, and fixing the isotropic temperature parameters of all hydrogen atoms at 4.0, the refinement converged[24] to R = 0.064 and R_w = 0.055 (262 variables, 2223 reflections). Final positional and thermal parameters and a list of calculated and observed structure factors are available as supplementary material.

Registry No.—**1**, 78-59-1; **2**, 6244-16-2; **8**, 5409-55-2; **13**, 61528-42-5; **13** $HClO_4$, 61528-43-6; **16**, 61528-44-7; **20**, 6244-19-5; **21**, 61528-40-3; **23**, 61528-46-9; **24**, 61528-41-4; **25**, 17530-69-7; **26**, 3471-13-4; *t*-BuOH, 75-65-0; PCl_3, 7719-12-2.

Supplementary Material Available. Tables of atomic coordinates and isotropic temperature factors (Table VII), anisotropic thermal parameters (Table VIII), and observed and calculated structure amplitudes (Table IX) (15 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) This research has been supported in part by Public Health Service Grant RO1-GM-20197 from the National Institute of General Medical Science. 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. (b) Georgia Institute of Technology. (c) Union Carbide Corp.
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(13) All melting points are corrected and 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 Cary Model 14 or 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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(19) Numbers in parentheses here and elsewhere in this paper indicate estimated standard deviations in the least significant digit(s).
(20) All computations were carried out on the CDC Cyber 74 system. Standard programs utilized included: Germain, Main, and Woolfsons' MULTAN, Zalkin's FORDAP, Iber's NUCLS modification of Busing, Martin, and Levy's least-squares program, Busing and Levy's ORFFE, and Johnson's ORTEP. Scattering factors were taken from Cromer and Waber's tabulation[21] for carbon and oxygen; Stewart's hydrogen atom scattering factors[22] were used. Anomalous dispersion factors employed were those given by Cromer.[23]
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(24) $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w(|F_o|)^2]^{1/2}$.

Total Synthesis of (±)-Acorone

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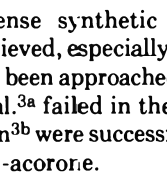
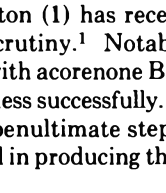
(±)-Acorone (**3**) has been synthesized by an efficient sequence beginning with 4-methyl-3-cyclohexenecarboxaldehyde (**5**). The imine of the aldehyde was alkylated with trimethylsilylpropargyl bromide. The acetylene moiety was hydrated with dilute acid and mercuric sulfate which also removed the trimethylsilyl group to give 1-(2-oxopropyl)-4-methyl-3-cyclohexenecarboxaldehyde which was cyclized with base to 8-methylspiro[4.5]deca-1,7-dien-3-one (**4**). Base-induced condensation of **4** with ethyl formate followed by acetic anhydride yielded 1-(*anti*-acetoxymethylene)-8-methylspiro[4.5]deca-3,7-dien-2-one (**14**). Two successive treatments of **14** with lithium dimethylcuprate followed by hydroboration and oxidation afforded a mixture consisting almost entirely of (±)-acorone and (±)-isoacorone (**21**) from which pure (±)-acorone could be isolated by crystallization.

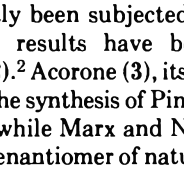
The acorane skeleton (**1**) has recently been subjected to intense synthetic scrutiny.[1] Notable results have been achieved, especially with acorenone B (**2**).[2] Acorone (**3**), itself, has been approached less successfully. The synthesis of Pinder et al.[3a] failed in the penultimate step, while Marx and Norman[3b] were successful in producing the enantiomer of natural (+)-acorone.



1

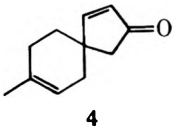


2



3

Spirocyclopentenone (**4**) appeared to be a very attractive intermediate. Indeed, we have synthesized crystalline (±)-acorone via **4** without a single chromatographic separation. A problem in preparing **4** is that most methods of cyclopentenone construction are not sufficiently versatile to incorporate the quaternary carbon necessary for a spiro skeleton.[4]



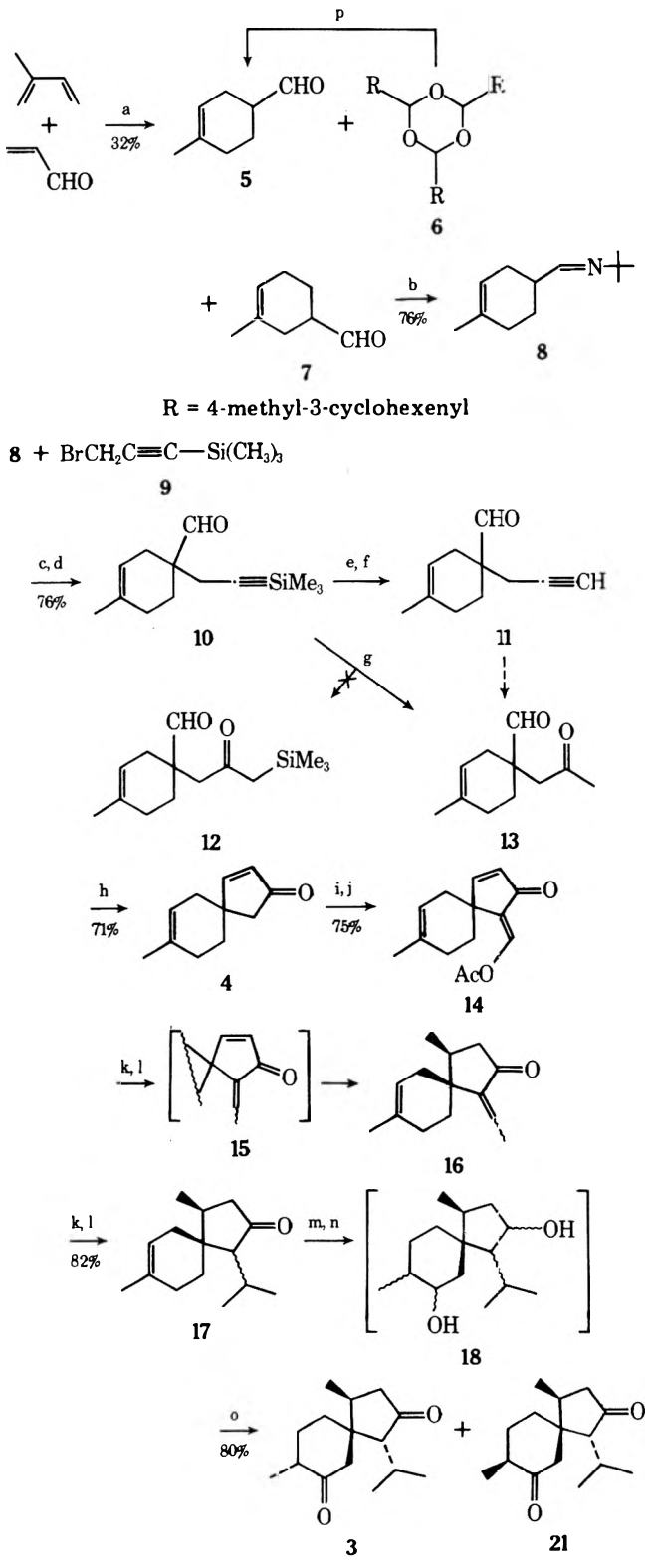
4

Regiospecific hydration of an acetylenic carbonyl compound to generate the 1,4-dicarbonyl precursor avoids this problem. Alkylation of the appropriate enolate anion with a propargyl halide should provide the quaternary carbon readily. A communication by Stork and Borch[5a] appeared in 1964 describing the regiospecific hydration of acetylenic ketones. Both 1,4 and 1,5 diketones were prepared, and a synthesis of *cis*-jasmone was delineated.[5b] We have begun an extended study of this reaction, with special regard for its synthetic utility.[6]

The synthesis (Scheme I) was begun with 4-methyl-3-cyclohexene-1-carboxaldehyde (**5**).[7a,b] Lewis acid catalyzed Diels–Alder reaction of isoprene and acrolein gave **5**, accompanied by the symmetrical trioxane (**6**) which was pyrolyzed in the presence of acid to regenerate **5**. The poor yield obtained at our hands (32%) was mitigated by the ready availability of the starting materials. As reported earlier,[7b] the expected 3-methyl isomer (**7**) could not be separated by GLC nor was it distinguishable by NMR, and was assumed to comprise ≤5% of the product.

The *tert*-butyl imine (**8**) was generated in 76% yield without incident. Alkylation was accomplished using the imine alkylation procedure of House.[8,9] Treatment of imine **8** with *n*-butyllithium in dimethoxyethane (DME) to form the anion followed by addition of 3-bromo-1-trimethylsilyl-1-propyne (**9**)[10] and then by acid hydrolysis gave the alkylated aldehyde **10** (76%).

Scheme I



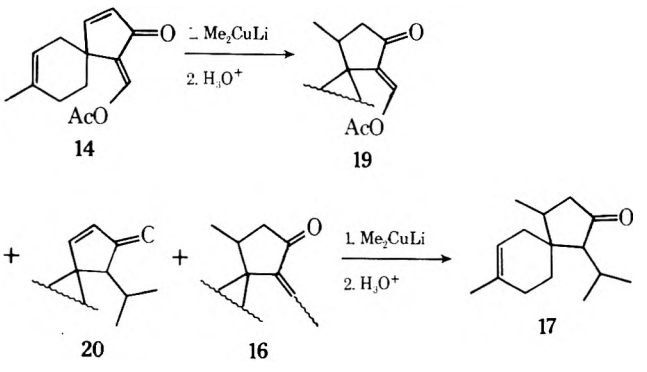
a, $SnCl_4 \cdot 5H_2O/C_6H_6$; b, *t*-$BuNH_2$/4A molecular sieves/pentane; c, *n*-BuLi/DME; d, HCl/H_2O; e, $AgNO_3$/EtOH/H_2O; f, 2 M HCN; g, $HgSO_4/H_2SO_4$/aq THF; h, NaOEt/EtOH; i, NaOMe/ethyl formate; j, Ac_2O; k, Me_2CuLi; l, H_3O^+; m, $BH_3 \cdot SMe_2$; n, H_2O_2/OH^-; o, Jones reagent; p, $TsOH/\Delta/C_6H_6$

Our first thoughts were to remove the trimethylsilyl protecting group, then to hydrate the acetylene generating the required keto aldehyde. Compound **10** was treated with 1.1 equiv of ethanolic $AgNO_3$, followed by aqueous KCN.[11] GLC analysis of the product mixture revealed one major peak (about 85% of the total) corresponding to the propynylaldehyde **11** and several minor unidentified compounds. Rather than attempting to optimize this reaction, we hoped that mercuric ion might play the same role as silver ion in the release of the trimethylsilyl group. However, we did not expect the mercuric complex to precipitate from the reaction as did the silver acetylide. In this case, hydration could conceivably occur generating the keto aldehyde **13** in a single step. At worst we expected to obtain the α-trimethylsilyl ketone **12**, which would not be disastrous. Compound **10** was treated with 0.06 equiv of $HgSO_4$ and a trace of H_2SO_4 in aqueous THF, which cleanly gave **13** (≥93% pure by GLC). The unstable oil was immediately cyclized with 1 M NaOEt/EtOH to produce 8-methylspiro[4.5]deca-1,7-dien-3-one (**4**) in 71% distilled yield from **10**. Deprotection and hydration of the acetylene were accomplished in a single, very clean reaction.

Realizing the difficulties attendant to direct isopropylation, we proceeded to treat **4** with ethyl formate and NaOMe, then with excess acetic anhydride.[2b] This produced crystalline 1-(*anti*-acetoxymethylene)-8-methylspiro[4.5]deca-3,7-dien-2-one (**14**) in 75% yield after sublimation (mp 116–119 °C). The anti stereochemical assignment was based on the downfield position of the C-11 vinyl proton (δ 8.10), in agreement with other workers.[2b] We found no evidence (NMR, GLC) of the syn isomer.

A priori, treatment of **14** with excess lithium dimethylcuprate could be expected to produce a number of 1,4-addition products (**16, 19, 20**) following workup (Scheme II). Further

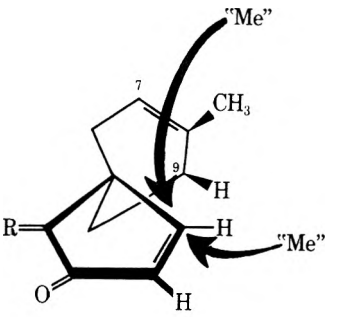
Scheme II



treatment of **16, 19,** and **20** with lithium dimethylcuprate should give the thrice-alkylated compound **17**. We hoped to titrate the reaction mixture containing the enolate anions of **16, 19,** and **20** with 1 equiv of AcOH, add lithium dimethylcuprate, and obtain **17** in a one-pot procedure.

This sequence generates two chiral centers with the attendant possibilities for complication. Examination of molecular models suggested that the required stereochemistry at C-4 should be favored. The active methyl transfer agent was expected to approach past the Δ^7 double bond giving the desired stereochemistry. Approach past C-9 to the opposite face of the five-membered ring is subject to a skew butane type interaction and, hence, is not as favorable. The required configuration at C-1 is known to be much the more stable.[12] The epimerizable center thus posed no problems. In the event, treatment of **14** with 6 equiv of lithium dimethylcuprate produced two major compounds in a ratio of 7:1, ≥98% pure by GLC. These proved to be the *Z* and *E* isomers of **16**, respectively. Only one of the C-4 epimers was present by NMR. The absorption arising from the C-4 methyl group was a sharp doublet (δ 0.88, J = 7 Hz) with no indication of a second doublet for the other epimer. That this was the desired diastereomer was confirmed by conversion to acorone.

It appears that the first equivalent of lithium dimethylcuprate adds to **14** at C-11, followed by elimination of acetate to give intermediate **15**. At this point, the second equivalent



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adds to the endo double bond rather than the exo double bond. Using the method of House,[13] the difference in reduction potentials of the two possible α,β-unsaturated carbonyl systems may be estimated. We calculate the endocyclic system to be ~0.1 V more positive than the exocyclic system, hence the more reactive as confirmed by isolation of **16** as the major product.

All attempts at a one-pot reaction sequence failed. The only major compound produced was **16**. Instead, crude **16** was treated with 3 equiv more of lithium dimethylcuprate to give **17** as a clear oil, 98% pure by GLC, as a mixture of C-1 epimers (82% from **14**).

With acorone almost in hand, we elected not to purify **17**, but treated it with borane–dimethyl sulfide complex to give, after oxidative workup, a compound presumed to be diol **18**, which was not characterized. The crude oil was oxidized with Jones reagent to produce an oil containing (±)-acorone and (±)-isoacorone (96%), and one unidentified component (4%) by GLC in a total yield of 80% from **17**.[3b] The oil was taken up in hexane/chloroform and stored overnight at −5 °C, yielding a crystalline material (mp 101.5–103.5 °C) which proved identical with an authentic sample of (+)-acorone[14] by NMR, IR, and GLC after sublimation and recrystallization.

Experimental Section

General. Melting points were determined on a Koefler hot stage and are uncorrected. Infrared spectra were run on Beckman IR-7 or IR-10 instruments as CCl_4 solutions. NMR spectra were run on Varian HA-100 or XL-100-15 spectrometers as solutions in $CDCl_3$. Chemical shifts are reported in δ units downfield of internal reference Me_4Si. Mass spectra and elemental analysis were performed by Dr. R. Wielesek of the University of Oregon Microanalytical Laboratory.

All reactions were performed under an atmosphere of dry nitrogen and were routinely followed by GLC of small aliquots. All GLC analyses were run on an F & M Model 700 equipped with a thermal conductivity detector and a 6 ft × 0.25 in. 20% DC 410, Chromosorb W AW column unless otherwise noted.

4-Methyl-3-cyclohexene-1-carboxaldehyde (5).[7] In a 500-mL round-bottom flask were placed 19 g (0.054 mol) of $SnCl_4 \cdot 5H_2O$ and 150 mL of benzene. To the rapidly stirred suspension was added 67 mL (1.0 mol) of acrolein (bp 53 °C) at which time the $SnCl_4$ dissolved to give a clear solution. The temperature was reduced to −8 °C on a NaCl/ice bath and isoprene (100 mL, 1.0 mol) was added at a rate of ≤1 drop/s. More rapid rates lead to a temperature rise and attendant polymerization. After 5.5 h, the resulting pale yellow slush was poured onto 200 mL of H_2O. The emulsion which formed proved completely intractable. The material was vacuum filtered to yield a white solid which proved to be trioxane **6**. The two-phase filtrate (benzene/H_2O) was separated, and the benzene layer was washed with brine and dried (Na_2SO_4). The white solid was dissolved in benzene with a trace of acid and heated to 120–130 °C (5 mm), which distilled over a clear liquid. The combined organics were distilled on a tantalum spiral column to yield 40.0 g (32.4%) of **5**, ≥99% pure by GLC:[15] bp 64–65 °C (10 mm); IR 2715, 1730, 1435 cm^{-1}; NMR δ 1.66 (br s, 3 H, vinyl $-CH_3$), 1.80–2.60 (complex, 7 H), 5.43 (br s, 1 H, vinyl H), 9.68 (s, 1 H, –CHO); 2,4-DNP, mp 178.5–180 °C (lit. 176.4–177.5 °C).

Recrystallization of a sample of the solid (ethanol/pentane, 4:1) produced short, fluffy crystals (mp 162–164 °C). The very simple NMR spectrum showed no evidence of an aldehyde. The IR showed no carbonyl absorbtion: IR 3030, 1440, 1135 cm^{-1}; NMR δ 1.65 (br s, 3 H, vinyl $-CH_3$), 1.70–2.40 (complex, 7 H), 4.65 (d, J = 5 Hz, 1 H, acetal H), 5.38 (br s, 1 H, vinyl H). A possible parent ion at m/e 248 in the mass spectrum was appropriate for a dimer. However, the peak at m/e 249 (M + 1) was 60% of m/e 248, too large for natural ^{13}C abundance. This evidence suggested that the compound was in fact the symmetric trimer. Pyrolysis of a sample in an NMR tube at 220 °C produced **5**.

***N-tert*-Butyl-4-methyl-3-cyclohexene-1-carboxaldehyde Imine (8).** A 500-mL round-bottom flask was charged with 100 g of 4A molecular sieves, 25.4 mL (0.242 mol) of dry *tert*-butylamine (distilled from KOH), and 100 mL of pentane. Aldehyde **5** (30.0 g, 0.242 mol) in 150 mL of pentane was added dropwise at a rate sufficient to maintain reflux. The mixture was held at reflux for 4 h, filtered, and distilled to yield 33.4 g (77%) of **8** (>99% pure by GLC): bp 90–91 °C (16 mm); IR 3035, 1668 cm^{-1}; NMR δ 1.16 (s, 9 H, $-CH_3$), 1.65 (br s, 3 H, vinyl $-CH_3$), 1.70–2.50 (complex, 7 H), 5.40 (br s, 1 H, vinyl H), 7.50 (d, J = 5 Hz, 1 H, N=CH).

1-(3-Trimethylsilyl-2-propynyl)-4-methyl-3-cyclohexene-1-carboxaldehyde (10).[10] Lithium diisopropylamide was generated by adding *n*-butyllithium (0.167 mol) to 23.6 mL (0.167 mol) of diisopropylamine (KOH) and 60 mg of phenanthroline in 100 mL of DME (distilled from Na/benzophenone) at −30 °C. After 30 min **8** (30 g, 0.167 mol) was added dropwise, then stirred for 1.25 h as the temperature rose to 20 °C. 3-Bromo-1-trimethylsilyl-1-propyne (**9**, 30.3 g, 0.159 mol) was added dropwise to the red-brown solution. The temperature was kept below 20 °C with judicious application of an ice bath. After 21 h the pale yellow slurry was quenched with 200 mL of 10% HCl and refluxed for 4 h. The mixture was saturated with NaCl and extracted with 3 × 100 mL of ether. The combined organics were washed with brine, dried ($MgSO_4$), and distilled to yield 24.3 g (68.5%) of **10**: >95% pure by GLC; bp 102–107 °C (0.85 mm); IR 2710, 2160, 1730, 1435, 1245 cm^{-1}; NMR δ 0.14 (s, 9 H, $-CH_3$), 1.66 (br s, 3 H, vinyl $-CH_3$), 1.70–2.60 (complex, 6 H), 2.38 (s, 2 H, propargylic H), 5.41 (br s, 1 H, vinyl H), 9.60 (s, 1 H, –CHO); mol wt (calcd for $C_{14}H_{22}OSi$, 234.144), 234.144.

1-(2-Propynyl)-4-methyl-3-cyclohexene-1-carboxaldehyde (11).[11] A 50-mL round-bottom flask was equipped with a magnetic stirrer and addition funnel to which was added 234 mg (1.0 mmol) of **10** in 5 mL of absolute EtOH. $AgNO_3$ (187 mg, 1.1 mmol) in 3 mL of 70% EtOH was added dropwise, precipitating a white material; 0.5 h later 2 mL of 2 M KCN was added to dissolve all the precipitate. The mixture was extracted with 2 × 10 mL of pentane and dried ($MgSO_4$). After the solvent was removed (distillation), GLC analysis showed a complex mixture of products. Preparative GLC of the major peak (85%) provided an analytical sample: NMR δ 1.67 (br s, 3 H, vinyl $-CH_3$), 2.01 (t, J = 2.25 Hz, 1 H, acetylenic H), 2.37 (d, J = 2.25 Hz, 2 H, propargylic H), 1.70–2.50 (complex, 6 H), 5.40 (br s, 1 H, vinylic H), 9.61 (s, 1 H, –CHO); mol wt (calcd for $C_{11}H_{14}O$, 162.104), 162.102.

8-Methylspiro[4.5]deca-1,7-dien-3-one (4). $HgSO_4$ (891 mg, 3.0 mmol), concentrated H_2SO_4 (300 mg), H_2O (12 mL), and THF (60 mL) were placed in a 250-mL round-bottom flask and stirred. Compound **10** (11.7 g, 0.050 mol) was added to the yellow suspension and stirred for 1 h during which time the mixture became homogeneous. The solution was poured onto 50 mL of H_2O and extracted with 2 × 50 mL of CH_2Cl_2. The aqueous phase was saturated with NaCl and extracted with 2 × 25 mL of CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and stripped of solvent under vacuum to yield 1-(2-oxopropyl)-4-methyl-3-cyclohexene-1-carboxaldehyde (**13**). An analytical sample was purified by GLC: NMR δ 1.66 (br s, 3 H, vinyl $-CH_3$), 2.12 (s, 3 H, O=CCH_3), 1.70–2.60 (complex, 6 H), 2.77 (d, J = 2 Hz, O=CCH_2), 5.40 (br s, 1 H, vinylic H), 9.70 (s, 1 H, –CHO); mol wt (calcd for $C_{11}H_{16}O_2$, 180.115), 180.115. No detectable amounts of dialdehyde were observed (≤5%).

Crude **13** was dissolved in 100 mL of absolute EtOH in a 250-mL round-bottom flask. To the stirred solution was added 50 mL of 1 M NaOEt/EtOH (0.05 mol). The reaction mixture was stirred for 1 h. The red-brown solution was neutralized with 2 N H_2SO_4, the color changing to pale yellow. The mixture was worked up as above yielding 5.75 g (71%) of **4** (94% pure by GLC) after distillation: bp 59–60 °C (0.15 mm); IR 1720, 1590, 1450, 1440 cm^{-1}; NMR δ 1.72 (br s, 3 H, vinyl $-CH_3$), 2.19 (s, 2 H, O=CCH_2), 1.60–2.40 (complex, 6 H), 5.42 (br s, 1 H, vinylic H), 6.07 (d, J = 6 Hz, C-2 H), 7.57 (d, J = 6 Hz, C-1 H); mol wt (calcd for $C_{11}H_{14}O$, 162.104), 162.102.

1-(*anti*-Acetoxymethylene)-8-methylspiro[4.5]deca-3,7-dien-2-one (14).[26] In a flamed 100-mL round-bottom flask equipped with a mechanical stirrer was placed 1.94 g (36 mmol) of commercial NaOMe (Mallinckrodt) in 50 mL of dry ether (distilled from $LiAlH_4$). Ethyl formate (7.25 mL, 90 mmol) was syringed into the cold (−7 °C) slurry, followed by dropwise addition of **4** (2.92 g, 18 mmol) in 5 mL of dry ether. After 4 h the reaction was quenched with 15 mL of acetic

anhydride (distilled from Mg) to give a yellow suspension. After 1 h of stirring, the mixture was poured onto 50 mL of H_2O, neutralized with solid NH_4Cl, and extracted with 3 × 25 mL of ether. The combined organics were washed with brine and dried (Na_2SO_4). Solvent was removed under aspirator pressure to give crude yellow crystals. The solid was recrystallized twice from hexane and sublimed (80–90 °C bath temperature, 0.01 mm) to yield 2.387 g. The mother liquors were concentrated and chilled (−5 °C) to give a second crop of solid that was recrystallized and sublimed as above and combined with the first crop to yield 3.137 g (75%) of **14**. An analytical sample recrystallized from ether melted at 116–119 °C; IR 1785, 1720, 1660, 1450 cm^{-1}; NMR δ 1.77 (br s, 3 H, vinyl $-CH_3$), 2.14 (s, 3 H, $-O_2CCH_3$), 1.80–3.00 (complex, 6 H), 5.48 (br s, 1 H, vinylic H), 6.25 (d, J = 6 Hz, 1 H, C-3 H), 7.66 (d, J = 6 Hz, 1 H, C-4 H), 8.10 (s, 1 H, C-11 H). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.06; H, 7.12.

1-Ethylidene-4,8-dimethylspiro[4.5]dec-7-one (16).[2b] In a 100-mL round-bottom flask was placed 5.71 g (30.0 mmol) of anhydrous CuI (Fischer) in 20 mL of ether (distilled from $LiAlH_4$). The mechanically stirred slurry was cooled to −70 °C in a dry ice/2-propanol bath and MeLi (64.5 mL, 59.5 mmol) was added via syringe. After 0.5 h **14** (1.14 g, 5.0 mmol) in 25 mL of ether was added over 5 min giving an orange slurry. The mixture was quenched 1 h later by addition of 5% HCl and poured onto 50 mL of H_2O, and the organic layer separated. The aqueous layer was extracted with 4 × 40 mL of ether. The combined organics were washed with saturated $Na_2S_2O_3$ (100 mL) and brine, dried (Na_2SO_4), and distilled to remove solvent yielding a gold-brown oil, shown by GLC to be two major components (95%) in a ratio of 7:1. Preparative GLC of the major peak provided an analytical sample [NMR δ 0.88 (d, J = 7 Hz, 3 H, C-4 methyl), 1.65 (br s, 3 H, vinyl $-CH_3$), 2.05 (d, J = 7 Hz, 3 H, ethylidene $-CH_3$), 1.96–2.10 (complex, 8 H), 2.66 (dd, J = 8, 18 Hz, 1 H, C-3 H), 5.47 (br s, 1 H, vinylic H), 6.00 (q, J = 7 Hz, 1 H, C-11 H)] interpreted as the Z isomer.[2b] The minor peak was identified as the E isomer having the ethylidene resonances at δ 1.85 (d, J = 7 Hz, 3 H, ethylidene $-CH_3$) and 6.77 (q, J = 7 Hz, 1 H, ethylidene H).

1-Isopropyl-4,8-dimethylspiro[4.5]dec-7-en-2-one (17).[16] As above, 15 mmol of lithium dimethylcuprate was prepared at 0 °C. The crude oil **15** in 5 mL of ether was added dropwise and the reaction mixture stirred for 1 h. After an identical workup 2.25 mg of oil was obtained, 98% pure by GLC (82.5% yield): IR 1740, 1467, 2452 cm^{-1}; NMR δ 0.88 (dd, J = 2, 7 Hz, 6 H, isopropyl CH_3), 1.09 (d, J = 7 Hz, 3 H, C-4 $-CH_3$), 1.63 (br s, 3 H, vinyl $-CH_3$), 1.70–2.70 (complex, 11 H), 5.38 (br s, 1 H, vinylic H); mol wt (calcd for $C_{15}H_{24}O$, 220.183), 220.184.

(±)-Acorone (3). In a flamed 25-mL round-bottom flask was placed 500 mg (2.28 mmol) of **17** in 10 mL of THF (Na/benzophenone). BH_3·SMe_2 (Aldrich, 150 μL, 1.61 mmol) was added via a septum inlet and the solution stirred for 2 h. One milliliter of 3 N NaOH followed by 1 mL of 30% H_2O_2 were added and the reaction mixture stirred for an additional 1 h. The solution was poured onto 15 mL of H_2O and the organic layer separated. The aqueous layer was extracted with 2 × 5 mL of ether, saturated with NaCl, and reextracted with 2 × 5 mL of ether. The combined organics were washed with brine, dried (Na_2SO_4), and stripped of volatiles under vacuum to yield 519 mg of pale yellow oil. No starting material was present by GLC and NMR.

The crude oil was dissolved in 15 mL of acetone and treated dropwise with Jones reagent until a faint red color persisted.[3b] Water (15 mL) was added and the mixture extracted with 4 × 5 mL of CH_2Cl_2. The combined organics were washed with brine, dried (Na_2SO_4), and stripped of solvent to yield 447 mg of yellow oil (80%). GLC analysis (15 ft × 0.125 in., 20% Carbowax 20M on Chromosorb W AW, 200 °C, FID detector) indicated the oil to be a mixture of acorone (55%) and isoacorone (45%), accounting for 96% of the total (identical with authentic samples[14]) and 4% of an unidentified component. The oil was dissolved in hexane/$CHCl_3$ and placed in a freezer overnight. Crystals were deposited which were recrystallized from hexane/$CHCl_3$ and sublimed (80 °C bath temperature, 0.1 mm) to yield 47 mg, mp 98–102 °C. Crystals (10.2 mg) were dissolved in heptane with a trace of ether and chilled. The crystals which were deposited were recrystallized from heptane to yield 6.7 mg of long needles, mp 101.5–103.5 °C, identical with authentic (+)-acorone (mp 96.0–97.5 °C)[3b] by NMR, IR, and GLC. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.26; H, 9.89. Found: C, 76.14; H, 9.97.

Registry No.—**3**, 61475-94-3; **4**, 61426-14-0; **5**, 61426-17-3; **6**, 6739-07-7; **8**, 61426-15-1; **9**, 38002-45-8; **10**, 61426-16-2; **11**, 61426-18-4; **13**, 61426-19-5; **14**, 61426-20-8; **15** isomer A, 61426-21-9; **15** isomer B, 61426-22-0; (*Z*)-**16**, 61426-23-1; (*E*)-**16**, 61475-95-4; **17** isomer A, 61426-24-2; **17** isomer B, 61475-96-5; **21**, 61475-97-6; acrolein, 107-02-8; isoprene, 78-79-5; *tert*-butylamine, 75-64-9; ethyl formate, 109-94-4; lithium dimethylcuprate, 15681-48-8.

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Purine *N*-Oxides. 66. Synthesis of 9-Hydroxyadenine[1]

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The synthesis of 9-hydroxyadenine, by a variation of the Shaw purine synthesis, involved the condensation of ethyl *N*-(dicyanomethyl)formimidate tosylate (**2**) with benzyloxyamine to a cyanoimidazole derivative **3** which was then ring closed to the purine derivative. This is the third adenine *N*-oxide isomer available for carcinogenicity testing.

The biological studies on the oncogenicity of purine *N*-oxides have demonstrated that adenine 1-*N*-oxide[2] is a mild oncogen with respect to the strong oncogen, 3-hydroxyxanthine,[3] whereas adenine 3-*N*-oxide is not oncogenic.[4] 9-Hy-

droxyadenine was required to shed further light on the relationship between the structure and oncogenicity of adenine *N*-oxides.

Of the routes to purine *N*-oxides, the simplest is the direct oxidation of a purine with peroxy acids and only one isomer is obtained from a given purine. Adenine is oxidized to adenine 1-*N*-oxide[5] while guanine yields guanine 3-*N*-oxide.[6] From these two *N*-oxides, many other purine 1- and 3-*N*-oxides have been derived.[7,6] Adenine 3-oxide has been obtained by two routes. In one, 7-aminothiazolo[5,4-d]pyrimidine was oxidized to its 6-oxide, in analogy to oxidation of adenine at position 1. With base, the 7-aminothiazolopyrimidine 6-oxide is rearranged to 6-mercaptopurine 3-oxide,[8] which can be oxidized to the 6-sulfono- and that aminated to the adenine 3-oxide.[9] Amination of 6-chloropurine 3-oxide also yields adenine 3-oxide.[10]

Recently the synthesis of the 6-oxopurines 9-hydroxyhypoxanthine, xanthine, and guanine has been accomplished[11] from a common starting material, namely 2-amino-2-cyanoacetamide via 5-amino-1-benzyloxyimidazole-4-carboxamide. However, an imidazole carboxamide is not applicable in synthesis of 6-amino derivatives, which require an appropriate imidazole carboxamidine or carbonitrile.

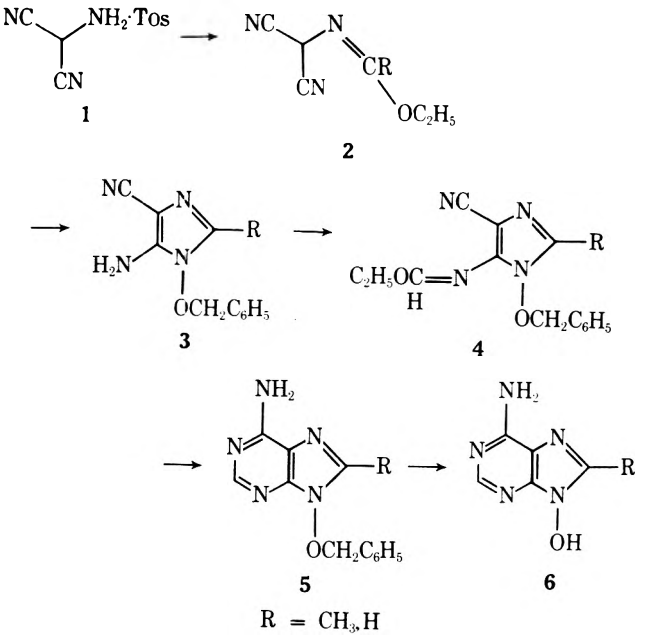
In the course of studies on prebiotic syntheses, Orgel[12] prepared aminomalononitrile and found it to be stable as the *p*-toluenesulfonate. By treating this compound with formamidine acetate, 5-aminoimidazole-4-carbonitrile was obtained and then ring closed to adenine.

Shaw[13] has used the free aminomalononitrile in his synthetic route and has prepared 5-amino-1-cyclohexylimidazole-4-carbonitrile. The synthesis of 9-hydroxyadenine was therefore first attempted from aminomalononitrile. Initially the free amino compound obtained from the tosylate was used to prepare the imino ether but this resulted in complete failure due to the polymerization of the aminomalononitrile on heating in triethyl ortho esters.

Martin[14] has shown that 2-amino-3-methylamino- and 2-methylamino-3-aminopropionic acids can be cyclized to 1-methyl-2-imidazoline-4- and -5-carboxylic acids, respectively, in triethyl orthoformate in the presence of a catalytic trace of hydrochloric acid. These ring closure reactions must have taken place via the imino ether hydrochloride intermediates shown. From previous findings on the catalytic effect of a trace of HCl in the synthesis of 5-amino-1-benzyloxyimidazole-4-carboxamide from an imino ether and benzyloxyamine hydrochloride,[11] coupled with those of Martin,[14] it was decided to first heat the aminomalononitrile tosylate with triethyl orthoacetate on a steam bath. The reaction was monitored by TLC, a new spot of high R_f was observed, and on eluting with ethanol, the UV spectrum showed the characteristic phenyl absorption at 250–260 nm plus a high absorption at 228 nm which is characteristic of imino ethers. This imino ether tosylate, **2** (R = CH_3) (Scheme I), was then refluxed in ethanol with 2 equiv of benzyloxyamine for 4 h to give a good yield of 5-amino-2-methyl-1-benzyloxyimidazole-4-carbonitrile (**3**, R = CH_3). The best yield of 5-amino-1-benzyloxyimidazole-4-carbonitrile (**3**, R = H) was obtained when equimolar quantities of **2** (R = H) and benzyloxyamine were used and reaction time reduced to 1.5 h. The **3** was then treated with triethyl orthoformate on a steam bath for 1 h to give the ethoxymethyleneaminoimidazole derivative (**4**, R = CH_3). 9-Benzyloxy-8-methyladenine (**5**, R = CH_3) was obtained by heating **4** in a steel bomb with ethanolic ammonia at 120 °C for 2 h. Removal of the benzyl group was accomplished with 32% HBr in acetic acid giving a high yield of 9-hydroxy-8-methyladenine (**6**, R = CH_3).

By the same sequence of reactions used for the preparation of 9-hydroxy-8-methyladenine, the desired 9-benzyloxyadenine (**5**, R = H) and 9-hydroxyadenine (**6**, R = H) were

Scheme I



synthesized. The UV spectrum of the anion of 9-hydroxyadenine has a strong absorption (ϵ 20.8 × 10^{-3}) at 234 nm which is over twice that of the second maximum at 262 nm. The absorption of the neutral species, ϵ 11.8 × 10^3 at 245 nm, compared to the value at 234 nm for the monoanion indicates that the neutral species has a considerable proportion of the *N*-oxide tautomer, presumably with a proton on N-7. The predominant tautomer in the neutral species is the *N*-hydroxy derivative, whereas in the monoanion the *N*-oxide form predominates, in agreement with the deductions previously made for the strong absorption in the 215–240-nm range for purine *N*-oxides that are considered to be due to >N→O or the enol anion >N–O^-.[15–17]

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. NMR spectra were determined on a Varian A-60 spectrometer in $(CH_3)_2SO$-d_6 as solvent with Me_4Si as internal standard. Chemical shifts are reported in parts per million (δ), and signals are quoted as s (singlet), d (doubled), t (triplet), and q (quartet). UV spectra were measured using a Unicam Model SP800. Elemental analyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. For TLC Eastman chromatographic silica gel sheets were used with solvent systems indicated and viewed under UV or developed with iodine. The pK_a values were determined spectrophotometrically by methods described.[18,19] The silica gel used is grade 923 (100–200 mesh, Davison).

5-Amino-2-methyl-1-benzyloxyimidazole-4-carbonitrile (3, R = CH_3). Aminomalononitrile *p*-toluenesulfonate (12.67 g, 0.05 mmol) and 75 ml of triethyl orthoacetate were warmed on a steam bath for about 1 h, or when TLC (1:1 petroleum ether–ether) of the reaction mixture indicated that the reaction was complete, that is, until the absence of aminomalononitrile tosylate. The excess triethyl orthoacetate was removed in vacuo and benzyloxyamine (12 g, 0.1 mol) in 250 ml of ethanol was added to the residue. The solution was heated under reflux for ~4 h until the TLC (1:1 petroleum ether–ether) indicated that **2** had completely disappeared and a new UV absorbing spot was present. The ethanol was removed in vacuo and the residue was chromatographed on silica gel. Elution with 1:1 petroleum ether–ether gave two compounds; the first was ethyl *N*-benzyloxyacetimidate and the second the excess benzyloxyamine. Elution with anhydrous ether removed a non-UV-absorbing material of unknown structure which could be detected only when TLC was developed with I_2. On eluting with ether, containing 3.5% EtOH, the required imidazole was obtained. Evaporation of the solvent and recrystallization from ethyl acetate–petroleum ether gave white needles of **3** (R = CH_3): yield 4.5 g (39%); mp 144–145 °C; UV λ_{max} (EtOH) 217 nm (ϵ 7.3 × 10^3), 247 (10.0 × 10^3); NMR δ 7.40 (s, 5, $OCH_2C_6H_5$), 4.24 (bs, 2, NH_2), 5.09 (s, 2, $OCH_2C_6H_5$), 2.02 (s, 3, CCH_3).

Anal. Calcd for $C_{12}H_{12}N_4O$: C, 63.15; H, 5.30; N, 24.55. Found: C, 63.30; H, 5.34; N, 24.47.

9-Benzyloxy-8-methyladenine (5, R = CH_3). A solution of 5-amino-1-benzyloxy-2-methylimidazole-4-carbonitrile (456 g, 0.002 mmol) in triethyl orthoformate was warmed on a steam bath until TLC (1:1 petroleum ether–$CHCl_3$) showed the absence of **3**. The excess triethyl orthoformate was removed in vacuo and the residue was dissolved in saturated ethanolic ammonia and heated in a steel bomb at 120 °C for 3 h. The mixture was evaporated to dryness and the residual gum was chromatographed over silica gel. Elution with 9:1 $CHCl_3$–EtOH gave pure **5** (R = CH_3). Recrystallization from ethyl acetate–petroleum ether afforded white needles of 9-benzyloxy-8-methyladenine (391 mg, 76%): mp 174–175 °C; UV λ_{max} (pH 1) 210 nm (ϵ 23.5 × 10^3), 263 (13.4 × 10^3); NMR δ 8.33 (s, 1, 2-CH), 7.73 (s, 5, $CH_2C_6H_5$), 6.60 (bs, 2 NH_2), 5.40 (s, 2, $OCH_2C_6H_5$), 2.10 (s, 3, CCH_3).

Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43. Found: C, 61.04; H, 4.94; N, 27.37.

9-Hydroxy-8-methyladenine (6, R = CH_3). 9-Benzyloxy-8-methyladenine (**5**, R = CH_3) (255 mg, 0.001 mmol) was warmed on a steam bath in 4 ml of 32% HBr in glacial acetic acid for 3.5 h. The reaction mixture was cooled and the HBr salt was collected and washed thoroughly with ether. The product was dissolved in hot water containing a few drops of concentrated ammonia, treated with charcoal, and precipitated by the addition of glacial acetic acid. The 9-hydroxy-8-methyladenine (**6**, R = CH_3) was collected, washed with water, ethanol, and ether, and dried at 78 9 °C over P_2O_5: yield 126 mg (79%); UV λ_{max} (pH 1) (+) 217 nm (ϵ 16.0 × 10^3), 263 (12.2 × 10^3); pH 5.0 (0) 246 nm (ϵ 10.6 × 10^3), 261 (11.5 × 10^3), pH (−), 235 nm (ϵ 20.2 × 10^3), 265 (9.0 × 10^3); pK_a's 3.95 (±0.07), 6.00 (±0.1).

Anal. Calcd for $C_6H_7N_5O$: C, 43.64; H, 4.27; N, 42.41. Found: C, 43.68; H, 4.37; N, 42.32.

5-Amino-1-benzyloxyimidazole-4-carbonitrile (3, R = H). The reaction was performed in the same manner as above, employing aminomalononitrile *p*-toluenesulfonate (6.34 g, 0.025 mmol) and 30 ml of triethyl orthoformate and warming on a steam bath until TLC indicated the absence of the first starting material. After the excess triethyl orthoformate was removed in vacuo, benzyloxyamine (3 g, 0.025 mmol) in 100 ml of ethanol was added and the mixture was refluxed for approximately 1.5 h. Ethanol was then removed in vacuo and the residue was chromatographed as before for the 2-methyl derivative (**3**, R = CH_3). Recrystallization from ethyl acetate–petroleum ether afforded white crystals of **3** (R = H): 985 mg (19%); mp 140–141 °C; UV λ_{max} (EtOH) 216 nm (ϵ 10.5 × 10^3), 245 (12.0 × 10^3); NMR 6.84 (s, 1, 2C-H), 7.37 (s, 5, $C_6H_5CH_2$), 5.08 (s, 2, $OCH_2C_6H_5$), 5.00 (bs, 2, NH_2).

Anal. Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.74; H, 4.67; N, 26.16.

9-Benzyloxyadenine (5, R = H). **3** (R = H) (4.28 mg, 0.002 mmol) and triethyl orthoformate 10 ml) were warmed on a steam bath until TLC (1:1 petroleum ether–$CHCl_3$) showed absence of the imidazole (45 min). The excess of ortho ester was removed in vacuo. The residual oil was reacted immediately in a sealed bomb with saturated ethanolic ammonia at 120 °C for 3 h. Subsequently the reaction mixture was taken to dryness and chromatographed as for the 8-methyl compound. Recrystallization from ethyl acetate–petroleum ether yielded white crystals of **5** (R = H), 363 mg (75%): mp 165–166 °; UV λ_{max} (pH 1) 210 nm (ϵ 25.4 × 10^3), 258 (15.1 × 10^3); λ_{max} (pH 7) 205 nm (ϵ 23.8 × 10^3), 260 (14.0 × 10^3); NMR δ 8.40 (s, 1, 2-CH), 7.40 (s, 1, 8-CH), 7.33 (s, 5, $C_6H_5CH_2$), 5.37 (s, 2, $OCH_2C_6H_5$), 6.63 (s, 2, NH_2).

Anal. Calcd for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.75; H, 4.53; N, 29.02.

9-Hydroxyadenine (6, R = H). The debenzylation of **5** (R = H) (241 mg, 0.001 mmol) was carried out as above. The free base was obtained from the hydrobromide salt by dissolving in hot dilute ammonia, treatment with charcoal, and precipitating by the addition of glacial acetic acid. The white crystals were collected, washed with water, ethanol, and ether, and dried in vacuo over P_2O_5 at 78 °C: yield 115 mg (78%); UV λ_{max} (pH 1) 215 nm (ϵ 17.4 × 10^3), 261 (13.0 × 10^3); λ_{max} (pH 4.6) 245 nm (ϵ 11.8 × 10^3), 259 (12.1 × 10^3); λ_{max} (pH 10) 234 nm (ϵ 20.8 × 10^3), 262 (9.0 × 10^3); pK_a's 3.59 (±0.05), 5.7 (±0.1).

Anal. Calcd for $C_5H_5N_5O$: C, 39.74; H, 3.33; N, 46.34. Found: C, 39.52; H, 3.42; N, 46.18.

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Registry No.—**1**, 5098-14-6; **3** (R = CH_3), 61193-34-8; **3** (R = H), 61193-35-9; **5** (R = CH_3), 61193-36-0; **5** (R = H), 61193-37-1; **6** (R = CH_3), 61193-38-2; **6** (R = H), 61193-39-3; triethyl orthoacetate, 78-39-7; benzyloxyamine, 622-33-3; triethyl orthoformate, 122-51-0.

References and Notes

(1) This investigation was supported in part by funds from the Public Health Service Research Grants CA-15274 and CA-08748 from the National Cancer Institute, and the NMR experiments were supported in part by PHS Grant CA-17085.
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Studies Directed toward Synthesis of Quassinoids. 2.[1] D-Ring Cleavage of Cholic Acid Derivatives

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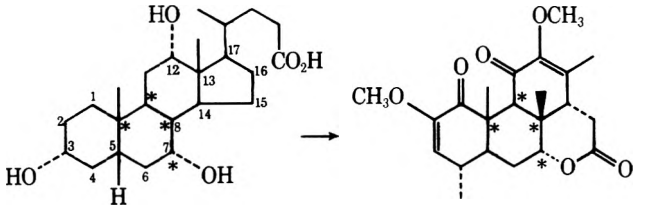
Important results directed toward the conversion of a triterpene derivative, cholic acid, to a diterpene skeleton related to quassin are presented. A useful D-ring cleavage of 17-en-20-one steroids to 16,17-secodioic acids by ozone or permanganate is described, and selective esterification of the least hindered carboxyl group of a glutaric acid anhydride analogue (8) was demonstrated.

A long-term goal of our work is to develop general methods for the eventual synthesis of simaroubaceous lactones[3] related to quassin starting, principally, from cholic acid. The rationale for this approach revolves around the already existing stereochemical attributes common to both cholic acid and quassin (starred positions below). Although positions 5



cholic acid quassin

and 14 will need to be isomerized at some appropriate point in the synthetic sequence, leaving these asymmetric sites unaltered would generate abnormal analogues which would be of interest for biological evaluation. An opposite approach involves building up quassinoids from simpler molecules; this will necessarily require one or more resolution steps involving two or more asymmetric carbons and is under investigation.[4]

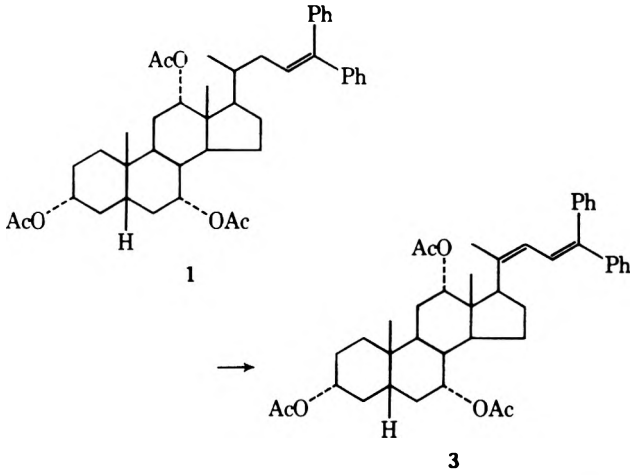
Critical to our approach is 17-side chain degradation and D-ring cleavage. Both transformations are vital areas requiring thorough investigation and development of more improved methods. These developments will have general application beyond our work. This paper describes some of our results in D-ring cleavage.

Results

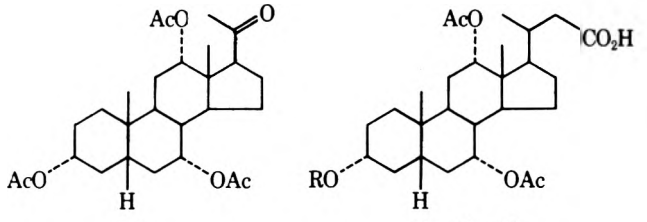
The 17-side chain degradation starts with the Barbier–Wieland sequence.[5] Grignard reaction of methyl cholate with excess phenylmagnesium bromide in THF afforded 3α,7α,12α,24-tetrahydroxy-24,24-diphenyl-5β-cholane, which was acetylated and dehydrated with refluxing acetic anhydride–acetic acid to give monoene **1** (Scheme I); trace amounts of the apo analogue to **1** were observed as a higher R_f component by TLC. Allylic bromination of monoene **1** with NBS followed by dehydrobromination with dimethylaniline[6] resulted in diene **3**. This diene generally contained small amounts of monoene **1** and was used without further purification. Chromium trioxide oxidation of this olefinic mixture yielded mainly ketone **4** and some hydroxy acid **2a** after base extraction and acidification; acetylation of **2a** yielded **2b** which was identical with the acid obtained by oxidation of monoene **1**.

In this work ketone **4** was converted to enone **5** by bromination with 1 equiv of bromine in glacial acetic acid[7] followed by dehydrobromination in hot HMPA[8] or with lithium carbonate in DMF. Ozonolysis of enone **5** and treatment of the ozonide with 30% H_2O_2 in glacial acetic acid afforded a mixture of acids consisting of mainly diacid **7a**; treatment of this

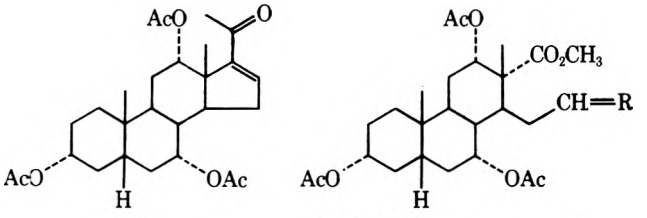
Scheme I



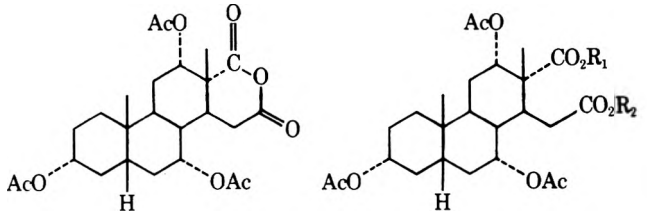
1 **3**



4 **2a**, R = H; **b**, R = Ac



5 **6a**, R = O; **b**, R = H, OH; **c**, R = H, OAc

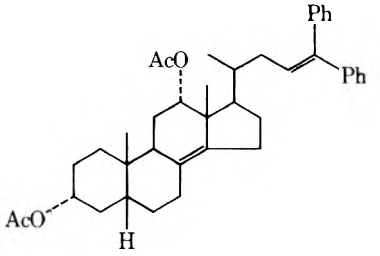


8 **7a**, $R_1 = R_2 = H$; **b**, $R_1 = R_2 = CH_3$; **c**, $R_1 = H$; $R_2 = CH_3$; **d**, $R_1 = H$; $R_2 = Et$; **e**, $R_1 = CH_3$; $R_2 = Et$

acid mixture with diazomethane yielded aldehyde **6a** and dimethyl ester **7b**. If the acid mixture was first treated with acetic anhydride and pyridine, acid anhydride 8 was the principal product. Reaction of acid anhydride **8** with hot absolute methanol generated acid ester **7c**. Alternatively, acid anhydride **8** could be treated with absolute ethanol containing pyridine to yield acid ester **7d** which in turn is converted to diester **7e** by reaction with diazomethane. Aldehyde **6a** can be reduced with sodium borohydride to give alcohol **6b** which may be acetylated to yield **6c**. Oxidation of enone **5** with potassium permanganate followed by esterification produced diester **7b** and an unidentified seco monoester.

Discussion

In the acetylation–dehydration of 3α,7α,12α,24-tetrahydroxy-24,24-diphenyl-5β-cholane minor amounts of a higher R_f by-product were observed, and it was deduced to be the apo analogue of 1 from the NMR, which exhibited only two acetate



apo analogue of monoene 1, 3α,12α-diacetoxy-24,24-diphenyl-5β-chola-8(14),23-diene

peaks around δ 2.0, and the mass spectrum, which gave a molecular ion of *m/e* 594. Formation of this apo analogue of **1** was minimized by thorough removal of trace strong acid from the workup of the precursor diphenylcarbinol or by prior acetylation in acetic anhydride–pyridine before dehydration in acetic anhydride–acetic acid. Other methods for more expeditious degradation of the 17-side chain are currently underway.

Ketone **4** serves as the pivot point in our efforts for D-ring cleavage studies. In bromination and dehydrobromination of ketone **4**, a slight excess of bromine gave 21-bromo-3α,7α,12α-triacetoxy-5β-pregn-16-en-20-one as a by-product, which exhibited a UV bathochromic shift ($\Delta\lambda_{max}$ 9 nm) in the π to π* transition as compared to enone **5**, and it was found more convenient to perform ozonolysis on the unpurified product from the dehydrobromination step. The mass spectrum of enone **5** exhibited an M − 43 base peak which emanates from the migration of the C-18 methyl to position C-17 followed by ejection of the acetyl radical generating an allylic carbonium ion.[9] Formation of aldehyde **6a** was variable, and it may well be that acid-al formation is responsible for its survival in the peracetic acid treatment under the conditions we employed. The alternate structure for aldehyde **6a** where the aldehyde and ester functional groups are interchanged is ruled out by the absence of a significant chemical shift for the C-18 methyl ^{1}H NMR signal upon reduction of **6a** to **6b**. As anticipated the less sterically hindered acid ester **7c** or **7d** can be made by treatment of acid anhydride **8** with either methanol or ethanol, respectively, the bulkier ethanol requiring base catalysis with pyridine. Presence of *m/e* 449 ion peak in the mass spectra of both **7b** and **7e** (Scheme II) substantiates that it is the least sterically hindered carboxyl group that is esterified upon reaction of acid anhydride **8** with either methanol or ethanol.

Experimental Section

General. All melting points were determined with a Fisher-Johns apparatus and are corrected. Infrared data ($\bar{\nu}_{max}$) were obtained on a Perkin-Elmer 710 spectrophotometer; ^{1}H NMR data, reported in parts per million (δ) from internal Me_4Si, were determined in $CDCl_3$ on a Varian A-60 or T-60 NMR; and mass spectra were obtained at an ionization voltage of 70 eV with a Nuclide 12-90-G single focusing instrument having a resolution of 10 000. C, H microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

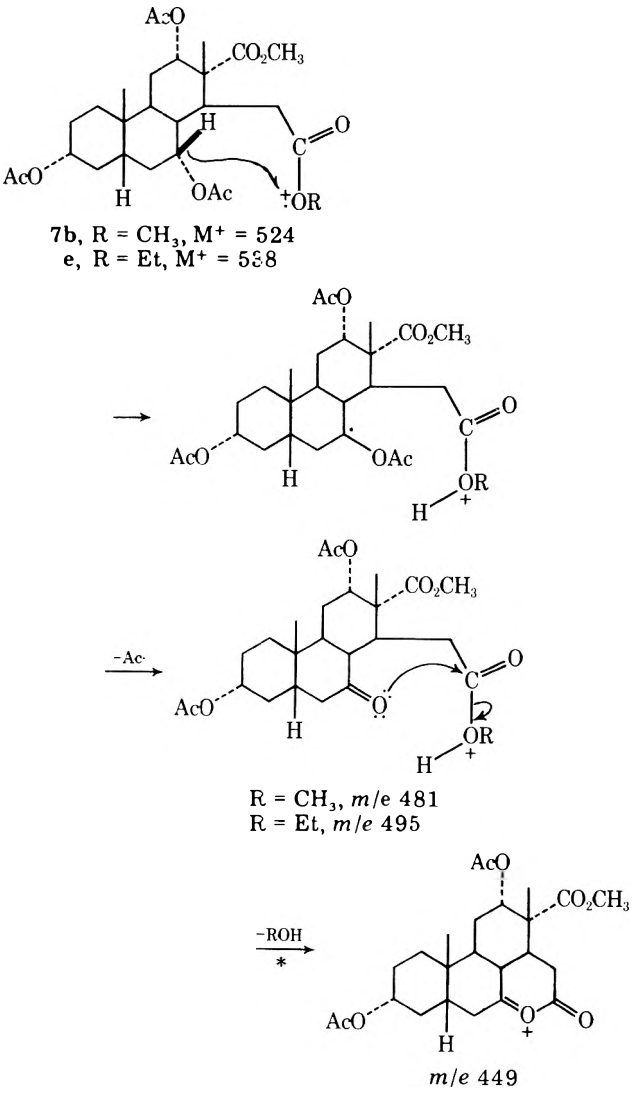
Column chromatography was performed using silica gel (MCB grade 62), and TLC was done on silica gel HF_{254} (E. Merck). Column elution was performed with benzene–EtOAc, and TLC development was done with hexane–EtOAc. Visualization of analytical TLC was achieved by spraying with 2% ceric sulfate in 2 N H_2SO_4 solution followed by brief heating; **4**, **5**, and esters of 7 gave characteristic green colors.

3α,7α,12α-Triacetoxy-24,24-diphenyl-5β-chol-23-ene (1). Methyl cholate (50 g) was reacted with phenylmagnesium bromide in THF to yield 5α,7α,12α,24-tetrahydroxy-24,24-diphenylcholane of mp 225–227 °C (lit.[5a] 220–230 °C). This total product was heated at reflux for 1 h in a mixture of HOAc (300 mL) and acetic anhydride (150 mL). Most of this solvent was removed by distillation, and the residue was poured into H_2O. Column chromatography yielded 65 g of **1**: mp 95–99 °C; $\bar{\nu}_{max}$ 1730, and 1250 (OAc), and 1600 cm^{-1} (C=C); ^{1}H NMR δ 7.22 (s, 10H, C-24 phenyl protons), 6.08 (t, 1H, C-23), 5.08 (peak, 1H, 12β-H), 4.87 (peak, 1H, 7β-H), 4.53 (hump, 1H, 3β-H), 2.10, 2.05, and 2.02 (s, 3H each, 3α,7α,12α-OAc's), 0.92 (s, 3H, C-19), and 0.73 (s, 3H, C-18); λ_{max} 250 nm (log ϵ_{max} 4.3).

A higher R_f product of 3α,12α-diacetoxy-24,24-diphenyl-5β-chola-8(14),23-diene was obtained: $\bar{\nu}_{max}$ 1730 and 1250 (OAc) and 1600 cm^{-1} (C=C); ^{1}H NMR δ 7.20 (s, 10H, phenyl H's), 6.07 (m, 1H, C-23), 5.10 (peak, 1H, 12β-H), 4.60 (hump, 1H, 3β-H), 2.03 (s, 6H, OAc's), 0.87 (s, 3H, C-19), and 0.86 (s, 3H, C-18); *m/e* 594, 534 (M − HOAc), 519 (M − HOAc − CH_3), 474 (M − 2HOAc), 459 (M − 2HOAc − CH_3), 341, 281 (100), and 220.

3α,7α,12α-Triacetoxy-24,24-diphenyl-5β-chola-20(22),23-diene

Scheme II



(3). A mixture of monoene **1** (60 g), CCl_4 (1.2 L), and NBS (23 g) was irradiated with a sun lamp for 25 min while heating at reflux. *N,N*-Dimethylaniline (96 mL) was added to the cool, filtered solution, and CCl_4 was subsequently distilled off. The residue was column chromatographed with benzene to yield 39 g of diene **3** contaminated with some monoene **1**: $\bar{\nu}_{max}$ 1730 (OAc), 1600, 970, 950, 890, and 770 cm^{-1}; ^1H NMR δ 7.25 (s, 10H, C-24 phenyl protons), 6.88 (d, J = 11 Hz, 1H, C-23), 5.90 (d, J = 11 Hz, 1H, C-22), 4.88 (peak, 1H, 7β-H), 4.80 (peak, 1H, 12β-H), 4.56 (hump, 1H, 3β-H), 2.67 (m, 1H, C-17), 2.06 and 2.03 (s, 3H each, 3α,7α-OAc's), 1.94 (s, 3H, 12α-OAc), 1.83 (s, 3H, C-21), 0.92 (s, 3H, C-19), and 0.63 (s, 3H, C-18); λ_{max} 306 nm (log ϵ_{max} 4.4).

3α,7α,12α-Triacetoxy-5β-pregnan-20-one (4). A solution made by dissolving CrO_3 (20 g) in H_2O (20 mL) and adding to glacial HOAc (100 mL) was added to a solution of diene **3** (30 g) in $CHCl_3$ (30 mL) and glacial HOAc (150 mL) while maintaining the temperatures between 45 and 50 °C. After stirring the reaction solution at 50 °C for 1 h, the reaction mixture was cooled and quenched with CH_3OH (20 mL). This mixture was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ layer was concentrated on a rotary evaporator and the residue dissolved in ether which was successively washed with H_2O, dilute HCl, and H_2O again. The ether layer was extracted with 3% KOH solution. Removal of the ether yielded neutral product that was column chromatographed through silica gel. Eluting with benzene–EtOAc (9:1) yielded 11 g of ketone **4**: mp 151–153 °C (crystals from hexane–Et_2O); $\bar{\nu}_{max}$ 1740 (OAc) and 1715 cm^{-1} (ketone); ^1H NMR 5.14 (peak, 1H, 12β-H), 4.93 (peak, 1H, 7β-H), 4.57 (hump, 1H, 3β-H), 3.00 (t, 1H, C-17), 2.18 (s, 3H, C-21), 2.07 (s, 3H, OAc), 2.04 (s, 6H, 2OAc's), 0.93 (s, 3H, C-19), and 0.70 (s, 3H, C-18); m/e 433 (M − 43), 373, 356 (100), 313, 296, 281, and 253.

Anal. Calcd for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 67.71; H, 8.24.

The KOH layer was acidified with dilute HCl and extracted with ether. Removal of the ether and recrystallization of the residue yielded 3 g of acid **2a**: mp 210–211 °C (needles from hexane–acetone); $\bar{\nu}_{max}$ 3475 (OH stretch), 1740 (OAc), and 1710 cm^{-1} (CO_2H); ^1H NMR δ 6.53 (peak, 2H, 3α-OH and CO_2H, exchanges with D_2O), 5.08 (peak, 1H, 12β-H), 4.90 (peak, 1H, 7β-H), 3.47 (hump, 1H, 3β-H), 2.5 (m, 2H, C-22), 2.12 and 2.08 (s, 3H each, 7α,12α-OAc's), 0.92 (s, 3H, C-19), and 0.78 (s, 3H, C-18).

3α,7α,12α-Triacetoxy-5β-cholan-24-oic Acid (2b). Oxidation of monoene **1** or acetylating acid **2a** gave **2b**: mp 105–107 °C (lit.[5] 106–107 °C, needles from hexane–acetone); ^1H NMR δ 9.9 (hump, 1H, CO_2H), 5.11 (peak, 1H, 12β-H), 4.93 (peak, 1H, 7β-H), 4.57 (hump, 1H, 3β-H), 2.5 (m, 2H, C-22), 2.15, 2.10, and 2.06 (s, 3H each, 3α,7α,12α-OAc's), 0.93 (s, 3H, C-19), and 0.78 (s, 3H, C-18).

3α,7α,12α-Triacetoxy-5β-pregn-16-en-20-one (5). To a solution of ketone **4** (6.0 g) in glacial HOAc (120 mL) containing 40% HBr (2 drops) was added Br_2 in glacial HOAc (13 mL of 1.0 M). After this mixture was stirred at room temperature for 10 min, it was poured into ice water which was subsequently extracted with ether. The ether solution was washed successively with H_2O, $NaHCO_3$ solution, and H_2O again. The ether was evaporated on a rotary evaporator, and the residue was dissolved in HMPA (60 mL) and heated at 120 °C with stirring under a N_2 atmosphere for 1 h. The cooled HMPA solution was diluted with H_2O and extracted with EtOAc which was subsequently concentrated. Column chromatography of the residue thus obtained through silica gel afforded 3.6 g of enone **5** upon elution with benzene–EtOAc (95:5): mp 185–187 °C (granular crystals from hexane–Et_2O); $\bar{\nu}_{max}$ 1740 (OAc) and 1670 and 1600 cm^{-1} (C=C–C=O); ^1H NMR δ 6.67 (peak, 1H, C-16), 5.49 (peak, 1H, 12β-H), 5.02 (peak, 1H, 7β-H), 4.56 (hump, 1H, 3β-H), 2.7 (m, 2H, C-15), 2.24 (s, 3H, C-21), 2.10, 2.03, and 1.98 (s, 3H each, 3α,7α,12α-OAc's), and 0.97 (s, 6H, C-18 and C-19); λ_{max} 236 nm (log ϵ_{max} 3.88).

Anal. Calcd for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07; O, 23.60. Found: C, 68.04; H, 8.02; O, 23.94.

Also, a higher R_f product of 21-bromo-3α,7α,12α-triacetoxy-5β-pregn-16-en-20-one was obtained: $\bar{\nu}_{max}$ 1730 and 1250 (OAc) and 1665 and 1595 cm^{-1} (C=C–C=O); ^1H NMR 6.73 δ(peak, 1H, C-16), 5.45 (peak, 1H, 12β-H), 5.00 (peak, 1H, 7β-H), 4.55 (hump, 1H, 3β-H), 4.23 and 3.88 (d, J = 11 Hz, 1H each C-21), 2.10 (s, 3H, OAc), 2.02 (s, 6H, OAc's), and 0.96 (s, 6H, C-18 and C-19); λ_{max} 245 nm (log ϵ_{max} 3.78).

Methyl 3α,7α,12α-Triacetoxy-16,17-seco-5β-androstane-16,17-dioate (7b) and Methyl 3α,7α,12α-Triacetoxy-16,17-seco-16-oxo-5β-androstan-17-oate (6a). Ozone was passed through a solution of enone **5** (0.4 g) in dry EtOAc (40 mL) for 5 min (solution becomes deep blue) at dry ice–acetone temperature. After allowing the solution to warm to room temperature (blue color fades), the solvent was removed in vacuo, the residue was redissolved in glacial HOAc (40 mL) and 30% H_2O_2 (10 mL) was added. After stirring overnight, the HOAc was removed on a rotary evaporator with the aid of a hot water bath. The residue was dissolved in EtOAc which was washed with water (discarded) and then extracted with 5% KOH solution. Acidification of the KOH layer followed by extraction with EtOAc yielded 0.32 g of acidic products. This was dissolved in CH_2Cl_2 and treated with diazomethane prepared from *N*-nitrosomethylurea. Chromatography through silica gel yielded 50 mg of aldehyde **6a** upon elution with benzene–EtOAc (95:5): mp 185–187 °C (needles from hexane–benzene); $\bar{\nu}_{max}$ 1745 (OAc) and 1720 cm^{-1} (aldehyde C=O); ^1H NMR δ 9.88 (m, 1H, C-16), 5.13 (peak, 1H, 12β-H), 4.93 (peak, 1H, 7β-H), 4.56 (hump, 1H, 3β-H), 3.66 (s, 3H, OCH_3), 2.4 (m, 2H, C-15), 2.11, 2.08, and 2.04 (s, 3H, each, 3α,7α,12α-OAc's), 1.24 (s, 3H, C-18), and 0.94 (s, 3H, C-19); m/e 434 (M − HOAc), 392, 360, 332, 300, 272, 257, and 213 (100).

Anal. Calcd for $C_{26}H_{38}O_9$: C, 63.14; H, 7.74; O, 29.12. Found: C, 63.11; H, 7.70; O, 29.19.

Further elution with benzene–EtOAc (9:1) afforded 0.25 g of diester **7b** as a glassy solid: $\bar{\nu}_{max}$ 1730 cm^{-1} (broad); ^1H NMR δ 5.13 (peak, 1H, 12β-H), 4.87 (peak, 1H, 7β-H), 4.57 (hump, 1H, 3β-H), 3.62 (s, 3H, OCH_3), 2.3 (m, 2H, C-15), 2.10, 2.07, and 2.03 (s, 3H each, 3α,7α,12α-OAc's), 1.18 (s, 3H, C-18), and 0.93 (s, 3H, C-19); m/e 524 (M^+), 493 (M − OCH_3), 481 (M − 43), 464 (M − HOAc), 449 (M − 43 − 32), 404 (M − 2HOAc), 344 (M − 3HOAc), and 285 (M − 3HOAc − 59).

Methyl 3α,7α,12α-Triacetoxy-16,17-seco-5β-androstane-16,17-dioate (7b) from Permanganate Oxidation of Enone 5. A solution of enone **5** (400 mg) in benzene (20 mL) containing dicyclohexyl-18-crown-6 (100 mg) and pulverized $KMnO_4$ (600 mg) was stirred at room temperature for 20 h. The brown reaction mixture was treated with $NaHSO_3$ solution (2 g in 10 mL of H_2O), the benzene layer was separated, and the acidified aqueous layer was extracted with EtOAc. The combined organic layers was extracted with 5% NaOH solution. The alkali extract was acidified, concentrated in vacuo, and extracted with EtOAc. Removal of the solvent yielded 150 mg of acid which was treated with diazomethane followed by acetic anhydride–pyridine. Thin layer chromatography yielded 90 mg of diester **7b**. Also, 50 mg of an unidentified lower R_f, secomonoester was obtained, mp 104–106 °C (needles from benzene–hexane).

3α,7α,12α-Triacetoxy-16,17-seco-5β-androstane-16,17-dioic Acid 16-Methyl Ester (7c). The acid (0.30 g) obtained by ozonolysis of enone **5** was heated at reflux with a mixture of pyridine (5 mL) and acetic anhydride (5 mL) for 2 h. This cooled reaction mixture was poured into ice water which was extracted with EtOAc; the EtOAc layer was washed with H_2O, dilute HCl solution, and H_2O again. Removal of the solvent afforded 0.28 g of anhydride **8** containing very little impurity: $\bar{\nu}_{max}$ 1810 and 1770 (anhydride C=O) and 1730 cm^{-1} (OAc); ^1H NMR δ 5.38 (peak, 1H, 12β-H), 5.00 (peak, 1H, 7β-H), 4.57 (hump, 1H, 3β-H), 2.6 (m, 2H, C-15), 2.10 (s, 6H, 7α,12α-OAc's), 2.04 (s, 3H, 3β-OAc), 1.27 (s, 3H, C-18), and 0.94 (s, 3H, C-19). Reaction of this anhydride with dry CH_3OH (10 mL) at 50 °C for 3 h followed by removal of the solvent and chromatography of the residue yielded 0.20 g of acid methyl ester **7c**: mp 106–108 °C (crystal from hexane–EtOAc); $\bar{\nu}_{max}$ 3000 (broad), 1700 (CO_2H), 1745 (OAc), and 1730 cm^{-1} (CO_2CH_3); ^1H NMR δ 8.4 (peak, 1H, CO_2H, exchanges with D_2O), 5.14 (peak, 1H, 12β-H), 4.86 (peak, 1H, 7β-H), 4.53 (hump, 1H, 3β-H), 3.58 (s, 3H, OCH_3), 3.0 (m, 2H, C-15), 2.10 (s, 6H, 7α,12α-OAc's), 2.03 (s, 3H, 3α-OAc), 1.20 (s, 3H, C-18), and 0.93 (s, 3H, C-19).

Anal. Calcd for $C_{26}H_{38}O_{10}$: C, 61.16; H, 7.50. Found: C, 61.26; H, 7.81.

Treatment of this acid ester (**7c**) with diazomethane produced a product which was in every way identical with diester **7b**.

3α,7α,12α-Triacetoxy-16,17-seco-5β-androstane-16,17-dioic Acid 16-Ethyl Ester (7d) and 16-Ethyl-17-methyl 3α,7α,12α-Triacetoxy-16,17-seco-5β-androstane-16,17-dioate (7e). Anhydride **8** (0.30 g) was treated with absolute EtOH (10 mL) and pyridine (2 mL) at 50 °C for 4 h with stirring. The reaction mixture was diluted with H_2O which was extracted with EtOAc. After washing the EtOAc extractrate with dilute HCl and then H_2O, the organic solvent was evaporated off and the residue chromatographed to yield 0.15 g of acid ester **7d**: ^1H NMR δ 8.5 (peak, 1H, CO_2H, exchanges with D_2O), 5.14 (peak, 1H, 12-β-H), 4.86 (peak, 1H, 7β-H), 4.53 (hump, 1H, 3β-H), 4.04 (q, J = 7 Hz, 2H, OEt), 3.0 (m, 2H, C-15), 2.10 (s, 6H, 7α,12α-OAc's), 2.03 (s, 3H, 3α-OAc), 1.22 (t, J = 7 Hz, 3H, OEt), 1.20 (s, 3H, C-18), and 0.93 (s, 3H, C-19). Reaction of this with diazomethane followed by chromatography afforded 0.10 g of diester **7e**: ^1H NMR δ 5.12 (peak, 1H, 12β-H), 4.87 (peak, 1H, 7β-H), 4.53 (hump, 1H, 3β-H), 4.03 (q, J = 7 Hz, 2H, OEt), 3.59 (s, 3H, OCH_3), 3.0 (m, 2H, C-15), 2.09, 2.08, and 2.03 (s, 3H each, 3α,7α,12α-OAc's), 1.23 (t, J = 7 Hz, OEt), 1.17 (s, 3H, C-18), and 0.92 (s, 3H, C-19); m/e 538 (M^+), 507 (M −

OCH_3), 495 (M − 43), 478 (M − HOAc), 449 (M − 43 − 46), 418 (M − 2HOAc), 358 (M − 3HOAc), and 299 (M − 3HOAc − 59).

Methyl 3α,7α,12α-Triacetoxy-16-hydroxy-16,17-seco-5β-androstan-17-oate (6b). A solution of aldehyde **7a** (30 mg) and $NaBH_4$ (20 mg) in CH_3OH (5 mL) was stirred at room temperature for 0.5 h. The reaction mixture was poured into ice water and extracted with EtOAc. After washing the EtOAc layer with dilute HCl solution and then H_2O, the organic solvent was evaporated. Recrystallization of the residue from hexane–EtOAc afforded 20 mg of **6b**: mp 193–195 °C; ^1H NMR δ 5.19 (peak, 2H, 7β,12β-H's), 4.57 (hump, 1H, 3β-H), 3.62 (s, 3H, OCH_3), 3.61 (peak, 2H, C-16), 2.10, 2.07, and 2.03 (s, 3H each 3α,7α,12α-OAc's), 1.25 (s, 3H, C-18), and 0.93 (s, 3H, C-19); *m/e* 436 (M − HOAc), 394, 362, 334, 302, 274 (100), and 213 (100).

Anal. Calcd for $C_{26}H_{40}O_9$: C, 62.89; H, 8.12. Found: C, 62.78; H, 7.88.

Acetylation of **6b** with pyridine–Ac_2O yielded tetraacetate **6c**: ^1H NMR δ 4.97 (peak, 2H, 7β,12β-H's), 4.54 (hump, 1H, 3β-H), 3.93 (peak, 2H, C-16), 3.60 (s, 3H, OCH_3), 2.10, 2.05, 2.02, and 1.96 (s, 3H, each, OAc's), 1.17 (s, 3H, C-18), and 0.93 (s, 3H, C-19).

Acknowledgment. This investigation was supported by Grant 5-R01-CA15824, awarded by the National Cancer Institute, DHEW.

Registry No.—**1**, 51102-05-7; **2a**, 61543-86-0; **2b**, 52840-09-2; **3**, 61543-87-1; **4**, 61543-88-2; **5**, 61543-89-3; **6a**, 61543-90-6; **6b**, 61543-91-7; **6c**, 61543-92-8; **7b**, 61543-93-9; **7c**, 61543-94-0; **7d**, 61543-95-1; **7e**, 61543-96-2; **8**, 61543-97-3; methyl cholate, 1448-36-8; phenyl bromide, 108-86-1; 3α,12α-diacetoxy-24,24-diphenyl-5β-chola-8(14),23-diene, 61543-98-4; NBS, 128-08-5; 21-bromo-3α,7α,12α-triacetoxy-5β-pregn-16-en-20-one, 61543-99-5; ozone, 10028-15-6; diazomethane, 334-88-3.

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Terpenes and Terpenoids. 5. The Four Isomeric Thujanols. Their Preparative Chemistry, Conformation, and Reactivity. A Comprehensive Study

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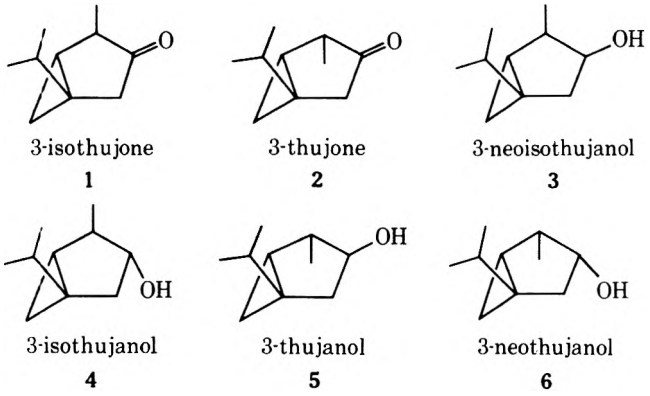
The preparative chemistry (50–100-g scale) of (−)-3-isothujone (**1**), (+)-3-thujone (**2**), (−)-3-neoisothujanol (**3**), (−)-3-isothujanol (**4**), (+)-3-thujanol (**5**), and (+)-3-neothujanol (**6**) was developed. As starting material was utilized western red cedar (*Thuja plicata Don*) leaf oil containing 80–90% of **1**. Conformation and reactivity of alcohols **3–6** were studied by three probes: lanthanide shift reagent (LSR) induced ^1H NMR chemical shifts and their conformational interpretation, rate of chromium trioxide oxidation, and rate of acetic anhydride–pyridine acetylation. Shifts induced by $Eu(thd)_3$ indicated a slightly developed boatlike conformation (**3a–6a**) with a dihedral angle of 14 ± 4° between C2–C3 and/or C3–C4. Positionally analogous protons in *trans*- and *cis*-2-methycyclopentanol (**9, 10**) showed shifts very similar to those in **3–6**. Rates of chromium trioxide oxidation of alcohols **3–6, 9,** and **10** in AcOH at 25.0 ± 0.1 °C follow (alcohol, $k_2 \times 10^2$ L mol^{-1} s^{-1}, relative rate of cyclopentanol = 1): **3**, 36.3, 6.91; **4**, 27.9, 5.31; **5**, 17.7, 3.37; **6**, 55.3, 10.5; **9**, 7.36, 1.40; **10**, 15.4, 2.93. Rates of acetic anhydride–pyridine acetylation follow (alcohol, $k_2 \times 10^5$ L mol^{-1} s^{-1}, relative rate of cyclopentanol = 1): **3**, 14.3, 1.36; **4**, 4.49, 0.42; **5**, 19.4, 1.84; **6**, 0.912, 0.086; **9**, 16.2, 1.54; **10**, 5.22, 0.49. Oxidation and acetylation rates were adequately rationalized by comparison with rates of 2- and 3-substituted cyclopentanols. They supported results observed in the LSR–NMR study. LSR-induced shifts in thujones **1** and **2** indicated a flat, five-membered ring, i.e., an overall L-shaped conformation of these two ketones.

The two isomeric thujones (**1, 2**) and the four isomeric thujanols **3–6** (Scheme I) form a unique group of monoterpenes derived from bicyclo[3.1.0]hexane.[2,3] The ketones are fairly common in nature, whereas the alcohols are relatively rare. The recent review by Whittaker and Banthorpe[4] covering the past 25 years has shown that despite considerable work carried out on various aspects of the chemistry of **1–6** the overall picture remains rather fragmented. In particular, with regard to alcohols **3–6** a systematic study correlating quantitatively their reactivity and exploring their conformation was notably absent. One reason for this may have been the tedious preparation of pure alcohols **3–6** in larger quantities.[5,6,7a]

The present paper deals with two subjects. The first is an extension and conclusion of our work[8,9] concerning the preparation of alcohols **3–6**. Simple procedures have now been developed, which make them easily accessible starting with a single abundant source, viz., western red cedar (*Thuja plicata Don*) leaf oil.[10]

The second subject is the study of conformation and reactivity of these alcohols. As probes we applied the ^1H NMR–LSR technique using $Eu(thd)_3$, rate of chromium trioxide oxidation, and rate of acetylation. The overall conformation of the bicyclohexane skeleton of the thujanols may be boatlike (**3a–6a**), L-shaped with a flat five-membered ring (**3–6**), or chairlike (**3b–6b**). Bergqvist and Norin[6] and Tori[11] proposed on the basis of NMR coupling constants a well-developed boatlike conformation (**1a–6a**) in thujanols as well as in thujones.[12] However, limitations to the conformational interpretation of *J* constants in bicyclo[*n*.1.0] compounds were voiced.[4,13] Later Norin et al.[7b] utilized the $Eu(thd)_3$ LSR reagent to study 3-neoisothujanol (**3**) and 3-thujanol (**5**) and confirmed the suggested boatlike conformation. We found[9] by IR that under conditions of extreme dilution in nonpolar solvents **3** and **5** may exist in a chairlike conformation (**3b, 5b**) due to the intramolecular hydrogen bond between OH and the edge of the cyclopropane ring. As suggested by one referee of

Scheme I. Nomenclature[a] of Thujones (1, 2) and Thujanols (3–6)

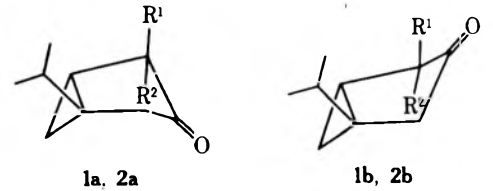


3-isothujone 1 | 3-thujone 2 | 3-neoisothujanol 3

3-isothujanol 4 | 3-thujanol 5 | 3-neothujanol 6

[a] Systematic nomenclature proposed by H. C. Brown et al. [S. P. Acharya, H. C. Brown, A. Suzuki, S. Nozawa, and M. Itoh, *J. Org. Chem.*, 34, 3015 (1969)], based on the utilization of neo and iso prefixes in concert with their utilization in other terpene groups. For details of historic background and rationale of proposal see Brown's paper. In the present paper, as in our previous work, we adopted this systematic nomenclature.

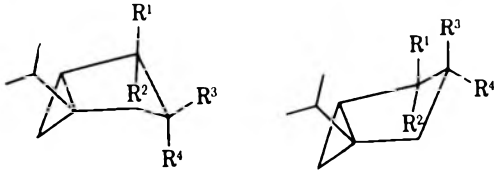
the present paper, the concentrations in NMR measurements were much higher and a preferred intermolecular H bonding with concomitant conformational change to the boat form was possible. With regard to conditions prevailing in preparative work Banthorpe and his group[14] had to consider the possibility of any of the three conformations, depending on specific circumstances, in order to accommodate results of various chemical transformations. Later they concluded[4] that the 2, 3, and 4 positions of the thujane skeleton may be flexible enough to adopt any of the three conformations depending



1a, 2a 1b, 2b

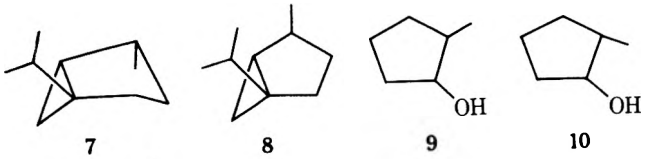
3-isothujone 1a, b $R^1 = CH_3$; $R^2 = H$

3-thujone 2a, b $R^1 = H$; $R^2 = CH_3$

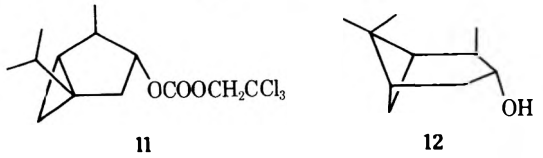


3a–6a 3b–6b

		R^1	R^2	R^3	R^4
3-neoisothujanol	3a, b	CH_3	H	OH	H
3-isothujanol	4a, b	CH_3	H	H	OH
3-thujanol	5a, b	H	CH_3	OH	H
3-neothujanol	6a, b	H	CH_3	H	OH



7 8 9 10



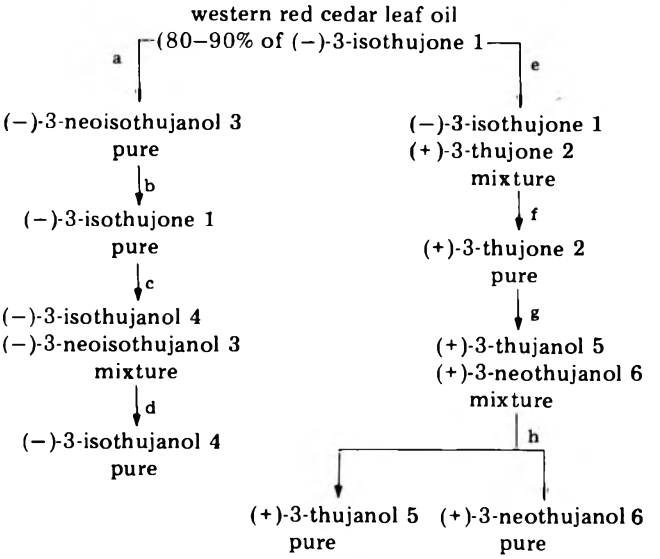
11 12

on specific reaction conditions, solvent, dilution, and reagent. We approached this problem by choosing as models *trans*- and *cis*-2-methylcyclopentanol (**9, 10**) and viewing the thujane skeleton as a methylene bridged cyclopentane. If indeed the assumption of conformational flexibility was warranted (regarding positions 2, 3, and 4) then it could be modeled on the known conformational flexibility (and also uncertainty) of cyclopentane and its derivatives.[15–18] In fact, our present results point clearly in this direction. The two methylcyclopentanols appear to be, in the absence of more suitably substituted compounds, acceptable models providing adequate background for a reasonable, though limited, interpretation of the behavior of thujanols **3–6.**

Results and Discussion

Preparative Chemistry of Thujanols 3–6. As single source for the preparation of thujanols **3–6** we used western red cedar leaf oil which contains 80–90% of (−)-3-isothujone (**1**). The development of its transformation into pure alcohols **3–6** and ketones **1** and **2** is outlined in Scheme II. The indi-

Scheme II. Approach to Pure Thujones (1, 2) and Thujanols (3–6) Starting from Western Red Cedar (*Thuja Plicata Don*) Leaf Oil

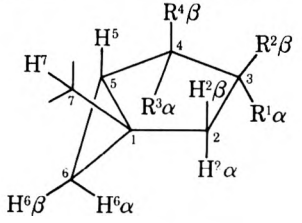


a, Meerwein–Ponndorf–Verley reduction;[19,20] b, oxidation with chromium trioxide;[21] c, reduction with lithium aluminum hydride;[14,23] d, separation with trichloroethyl chloroformate;[22] e, epimerization with sodium hydroxide;[8] f, separation with sodium bisulfite;[8] g, reduction with sodium borohydride;[9,24] h, column chromatography separation on alumina.[9,24]

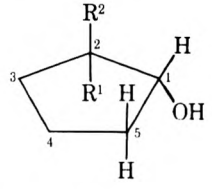
vidual steps outlined therein can be carried out on a 50–100-g scale. This includes steps g and h described by us previously[9,24] for gram quantities only.

Proton Magnetic Resonance Shifts Induced by Eu(thd)$_3$ in Thujanols 3–6 and Thujones 1, 2. The use of lanthanide shift reagents (LSR), most commonly those derived from Eu^{3+}, for the study of stereochemistry and conformation is now a generally accepted technique. From extensive reviews by and work of Cockerill et al., Saunders and Williams, and others[25–27] one may conclude that in relatively simple molecules it is possible to neglect the angular factor of the McConnel–Robertson equation and use a linear correlation between the distance (r and Å) of the donor atom or its lone electron pair from the respective proton and the magnitude of the induced shift G_{LSR} of the latter.[28–30] This assumption was made by Norin et al.[7b] in their study of neoisothujanol (**3**) and thujanol (**5**). In our study we included all

Table Ia. Induced Chemical Shifts $G_{Eu(thd)_3}$ of Protons on C2, C4, C5, C6, C7, and C4 Methyl Group (=C10) in the Four Isomeric Thujanols (3–6) and Protons on C2, C5, and C2 Methyl Group in *trans*- and *cis*-2-Methylcyclopentanol (9, 10)



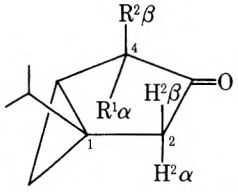
Proton or methyl group	Positional and configurational relationship to 3 OH group	3-Neoisothujanol R¹, R³ = H; R² = OH; R⁴ = CH_3	3-Isothujanol R², R³ = H; R¹ = OH; R⁴ = CH_3	3-Thujanol R¹, R⁴ = H; R² = OH; R³ = CH_3	3-Neothujanol R², R⁴ = H; R¹ = OH; R³ = CH_3
H2α	2 trans	8.69		8.02	
	2 cis		14.10		14.48
H2β	2 trans		7.60		7.35
	2 cis	13.10		13.01	
H4α	2 trans	9.01			
	2 cis		13.81		
H4β	2 trans				7.93
	2 cis			13.35	
$CH_3$4α	2 trans			6.10	
	2 cis				10.00
$CH_3$4β	2 trans		4.87		
	2 cis	9.20			
H5	3 trans		4.85		5.60
	3 cis	4.35		4.25	
H6α		3.13	13.50	4.58	14.47
H6β		2.55	4.95	2.62	5.30
H7		2.93	3.32	2.39	3.19



Proton or methyl group	Positional and configurational relationship to OH group	*trans*-2-Methylcyclopentanol R¹ = H; R² = CH_3	*cis*-2-Methylcyclopentanol R¹ = CH_3; R² = H	Cyclopentanol[a] R¹, R² = H
H2	2 trans		8.31	8.65
	2 cis	13.41		15.30
H5	2 trans	8.10	7.95	8.65
	2 cis	13.60	14.05	15.30
$CH_3$2	2 trans	5.60		
	2 cis		9.61	

[a] Reference 26.

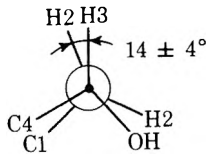
Table Ib. Induced Chemical Shifts $G_{Eu(thd)_3}$ of Protons on C2, C4, and C4 Methyl Group (=C10) in the Two Isomeric Thujones 1 and 2



Proton or methyl group	(3)-Isothujone 1 R¹ = H; R² = CH_3	(3)-Thujone 2 R¹ = CH_3; R² = H
H2α	3.50	3.41
H2β	3.50	3.35
H4α	4.28	
H4β		4.05
$CH_3$4α		2.73
$CH_3$4β	3.20	

four thujanols **3–6** and *trans*- and *cis*-2-methylcyclopentanol (**9, 10**) as models. Additionally, we investigated the two ketones **1** and **2**. Results are summarized in Tables Ia and Ib for the alcohols and ketones, respectively.

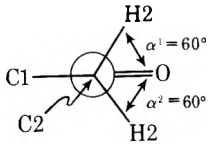
In the alcohols **3–6** the absence of a highly developed chair- or boatlike conformation with a dihedral angle in the 45–60° range between C2–C3 or C3–C4 is immediately apparent. Most fortuitously results obtained with alcohols **4** and **6** (not included in Norins[7b] study) produced rather unambiguous information regarding their conformation. Values of $G_{Eu(thd)_3}$ for protons 2α, 4α, and 6α in isothujanol (**4**) and for protons 2α and 6α in neothujanol (**6**) are practically identical. Therefore, they should be equidistant from oxygen at C3.[31] This will be compatible with only one conformation of C3 relative to C2 and C4 and will in turn depend on the bond angle C4–C5–C6 determining the angle between the planes of the three- and five-membered rings at their juncture. From crystallographic measurements on various bicyclo[3.1.0]-hexane systems[33,34] several values (115.0, 117.4, 118.3, and 123.3°) were assigned to this angle. With a conservative value of 120° and using Dreiding models we found that equidistance of the three protons (at C2, C4, and C6) from oxygen at C3 would be 2.65 ± 0.07 Å and would require only a slight bending of the C3 tip of the five-membered ring toward a boatlike conformation with a dihedral angle estimated at 14 ± 4° between C2 and C3 or C3 and C4[35] as shown:



Striking similarities between *G* values of analogous protons (relative to OH) of the four thujanols **3–6**, of the methylcyclopentanols **9** and **10** and cyclopentanol itself indicate, first, that also alcohols **3** and **5** will have a similar dihedral angle between C2 and C3 and, second, that the conformational behavior of thujanols in the C2–C3–C4 region strongly resembles that of model methylcyclopentanols and cyclopentanol itself.[16–18,36]

Our result is in reasonable agreement with observations made by Norin et al.[7b] on alcohols **3** and **5**. His recorded *G* values were in accord with a projected "flap angle" of 25° (plane delineated by C2, C3, and C4 vs. plane delineated by C1, C2, C4, and C5) for the cyclopentane ring portion of the bicyclohexane system. Since Norins' and our approaches were slightly different in some details (see ref 7b) it may well be that the two results simply represent limits of possible accuracy inherent to the LSR conformational probe when utilized in its primitive form, i.e., with disregard to the angular factors.

Results obtained with thujones **1** and **2** are summarized in Table Ib. Induced shifts of ketonic protons are generally lower than those of alcohols.[25a,b] Therefore only *G* values of protons neighboring the CO group are presented there. It was shown[25a,b] that in cyclic ketones the shift is proportional only to the distance between oxygen of the CO group and the respective proton, the angular vector being negligible. Since shifts of the C2, C4, and C4 Me (= C10) protons are in both ketones very similar, it is fair to conclude that a planar five-membered ring conformation predominates in these two ketones. There is further supporting evidence for this proposition. According to the Barfield–Grant equation[37,38] J_{gem} depends on the angle at which the C=O plane dissects the H–C–H angle of the neighboring CH_2 group. The extremely high $J_{2\alpha,2\beta}$ = 19 Hz in both ketones[6,11] is compatible with only one arrangement, that one in which C=O bisects the H–C–H angle of the neighboring CH_2 group symmetrically, viz.



Any other arrangement would necessitate a lower *J* since 19 Hz is the highest value implied in the Barfield–Grant equation. Extensive data supplied by Cookson et al.[39] leave little doubt in this direction. Cyclopentanone shows *J* = 19.0–19.5 Hz whereas in ketones like cyclohexanone in which α^1 does not equal α^2 *J* = 16.0 Hz or less.[40,41]

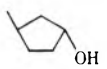
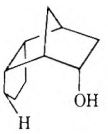
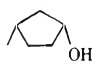
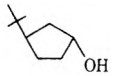
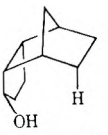
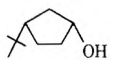
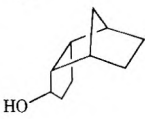
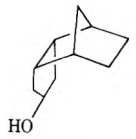
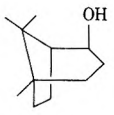
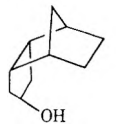
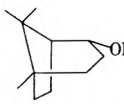
Rate of Chromium Trioxide Oxidation of Thujanols 3–6. It was postulated that the magnitude of ground state steric interactions involving the OH group of alcohols is directly related to their rate of oxidation with chromium trioxide.[18,42–44] However, Pasto and Rao[45] have shown that transition state energy differences, most probably caused by torsional angle effects, may be an important factor, depending on specific stereochemistry in the ground and transition states. Inspection of models of alcohols **3–6** indicated that in the critical C2–C3–C4 region torsional interactions may play an important role. Also, polar (inductive) effects have occasionally been invoked but without a firm quantitative background.[18,46–49] Despite these limitations we had hoped that the rate of chromium trioxide oxidation of alcohols **3–6** could provide reasonable information about their conformation and reactivity. As models we included the two methylcyclopentanols **9** and **10** and isopinocampheol (**12**). Results are summarized in Table II. Oxidation rates of alcohols available from the literature and pertinent to the subsequent discussion are given in Table III.

Thujanol (**5**) (CH_3 and OH trans) shows the lowest rate of oxidation. It is 2.5 times higher than that of *trans*-2-methylcyclopentanol (**9**). This enhancement can be attributed to the influence of the 1,3 relationship between OH and *i*-Pr groups. Richer et al.[50] showed that *cis*-3-*tert*-butylcyclopentanol (**16**) and *cis*-3-methylcyclopentanol (**14**) were oxidized respectively 1.7 and 3.4 times faster than cyclopentanol.[51] Admittedly, no model concerning a 2,4-disubstituted cyclopentanol is available. Comparing thujanol (**5**) (CH_3, OH trans) with neoisothujanol (**3**) (CH_3, OH cis), the oxidation rate is enhanced by a factor of 2.04 paralleling the enhancement (2.09) when going from *trans*- to *cis*-2-methylcyclopentanol (**9** → **10**). The two alcohols (**4** and **6**) with the OH group cis to the methylene bridge of cyclopropane were interesting with regard to the

Table II. Rate Constants of Chromic Acid Oxidation and Acetic Anhydride–Pyridine Acetylation of Thujanols (3–6), 2-Methylcyclopentanols (9, 10), and Isopinocampheol (12)

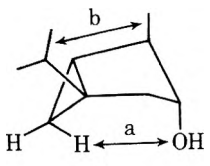
Alcohol		Chromic acid in 90% acetic acid t = 25.0 ± 0.1 °C		Acetic anhydride in pyridine t = 25.0 ± 0.1 °C	
		$k_2 \times 10^2$, L mol^{-} s^{-1}	Relative rate cyclopentanol = 1	$k_2 \times 10^5$, L mol^{-1} s^{-1}	Relative rate cyclopentanol = 1
3-Neoisothujanol	**3**	36.3 ± 2.17	6.91	14.3 ± 0.5	1.36
3-Isothujanol	**4**	27.9 ± 1.46	5.31	4.49 ± 0.27	0.42
3-Thujanol	**5**	17.7 ± 0.39	3.37	19.4 ± 1.0	1.84
3-Neothujanol	**6**	55.3 ± 2.48	10.5	0.912 ± 0.018	0.086
trans-2-Methylcyclopentanol	**9**	7.36 ± 0.42	1.40	16.2 ± 1.2	1.54
cis-2-Methylcyclopentanol	**10**	15.4 ± 0.51	2.93	5.22 ± 0.37	0.49
Isopinocampheol	**12**	85.7 ± 4.81	16.3	30.5 ± 2.6	2.90
Cyclohexanol		3.43 ± 0.19	0.65	8.85 ± 0.55	0.84
Cyclopentanol		5.25 ± 0.24	1.0	10.5 ± 0.48	1.0

Table III. Relative Rates of Chromic Acid Oxidation of Various Alcohols (Cyclopentanol = 1)

13		2.61[a]	**19**		311[b]
14		3.42[a]			
15		1.45[a]	**20**		30.8[b]
16		1.70[a]	**21**		1.22[b]
17		2.31[b]	**22**		81.7[c]
18		1.79[b]	**23**		4.25[c]

[a] Reference 50. [b] I. Rothberg and R. V. Russo, *J. Org. Chem.*, 32, 2003 (1967). [c] H. Favre, M. Lefebvre, and J. C. Richer, *Can. J. Chem.*, 37, 403, 411, 417 (1959).

possibility of assessing the extent of steric interaction along a in **4a**. A pronounced boatlike conformation would manifest



4a

itself by a marked oxidation rate enhancement in comparison with alcohols **3** and **5**. However, alcohol **4** was oxidized only 1.57 times faster than **5**. Thus, the rate-enhancing effect of the CH_2 bridge in **4** is only negligibly higher than the analogous effect of the *i*-Pr group in thujanol (**5**).[52] This is indicative of the absence of any strongly developed boatlike conformation in **4a**, which will be a balance of two nonopposing interactions, viz., a and b. These will depend on slight torsional adjustments along the C2–C3–C4 perimeter.[53] Neothujanol (**6**) (CH_3, OH cis) was oxidized 1.98 times faster than isothujanol (**4**), which is again comparable to the *trans*- to *cis*-2-methylcyclopentanol rate change of 2.09. Isopinocampheol (**12**) was oxidized three times faster than **4** and did not appear to be a good model for the type a interaction in **4a**.[55] In summary, rates of chromium trioxide oxidation observed for thujanols **3–6** indicated absence of a strongly developed and rigid boatlike conformation and were compatible with deductions made on the basis of the NMR–LSR study. These rates were close to those of the model 2-methylcyclopentanols and other cyclopentanols recorded in the literature and confirmed the mobility of the thujane skeleton in the C2–C3–C4 region. However, in the absence of detailed knowledge about ground and transition state energies, the small differences in the observed rates do not permit us to draw any detailed conclusions about conformational differences between the individual alcohols.

Rate of Acetic Anhydride–Pyridine Acetylation of Thujanols 3–6. Acetylation of alcohols with Ac_2O–pyridine is an established method of conformational analysis.[18] Valuable data were acquired by Eliel et al.[57,58] in the cyclohexane series and by Buck et al.[59] on selected cyclohexane derivatives, 1,3-dioxane alcohols, and methoxycyclopentanols. However, there is no background information available in regard to alkyl-substituted cyclopentanols and bicyclic alcohols that could serve as models of **3–6**. Furthermore, the detailed mechanism of the acetylation reaction remains unexplored.[59] This poses limitations to the interpretation of any sets of results. Most probably, the first step is a hydrogen bond association of pyridine with –OH of the alcohol and specific steric requirements are involved since 2-methyl- and 2,6-dimethylpyridine are inactive as catalysts.[60] Results of our measurements on alcohols **3–6, 9, 10,** and **12** are summarized in Table II. Acetylation rates of compounds relevant to the subsequent discussion are shown in Table IV.

Whereas the rates of chromium trioxide oxidation ranged from 3.37 to 10.5 (cyclopentanol = 1), the rates of acetylation, reflecting accessibility of the OH group, varied in a much wider range, viz., 0.086–1.84. The rate of acetylation (1.84) of thujanol (**5**) is close to that of *trans*-2-methylcyclopentanol (**9**), indicating little influence of the *i*-Pr group.[61] A fourfold decrease in the acetylation rate of isothujanol (**4**) when compared with **5** would indicate a more pronounced steric effect of the H6α on the rate of acetylation than on the rate of oxidation. Inspection of models showed that, most probably, the H-bond association of pyridine with the OH group would assume a conformation with the pyridine ring positioned outward and the subsequent approach of anhydride would have

Table IV. Rates of Acetic Anhydride–Pyridine Acetylation of Various Alcohols

Alcohol	Relative rate of oxidation, cyclopentanol = 1
trans-2-Methylcyclohexanol (**24**)	1.09[a]
cis-2-Methylcyclohexanol (**25**)	0.242[a]
trans-2-Methoxycyclopentanol (**26**)	1.44[b]
cis-2-Methoxycyclopentanol (**27**)	0.403[b]
trans-2-Isopropylcyclohexanol (**28**)	1.12[a]
trans-2-Isopropyl-*cis*-5-methylcyclohexanol (**29**)	1.22[a]
trans-4-*tert*-Butylcyclohexanol (**30**)	1.02[a]

[a] Reference 58. [b] Reference 59. In both cases rate values were obtained under conditions identical with those used by us in this work.

to be from the cyclopropane shielded "inside". The high rate of acetylation of isopinocampheol (**12**) shed little light on this subject in contrast to what we hoped for.[62] The relationship between acetylation rates of the two alcohols with OH groups cis to the $-CH_2-$ bridge, viz., isothujanol (**4**) (CH_3, OH trans) and neothujanol (**6**) (CH_3, OH cis), 0.42 and 0.086, respectively, ratio 4.86, approaches the ratio of acetylation rates of *trans*- and *cis*-2-methylcyclopentanol, viz., 3.14. The combined effect of cis-positioned Me group and methylene bridge is larger with respect to acetylation than to chromic acid oxidation. A similar relationship fails for the two alcohols with β-oriented OH groups, viz., thujanol (**5**) and neoisothujanol (**3**) (CH_3, OH cis). The latter is acetylated at a rate only 25% lower than that of alcohol **5**. Apparently, subtle conformational adjustments are compensating for the expected retarding effect of the *cis*-Me group in **3**; its effect is more pronounced in the relative rates of oxidation of **3** and **5**. In summary, as in the case of chromium trioxide oxidations, the four thujanols strongly resemble the behavior of model cyclopentanols. Owing to the size of the Ac_2O–pyridine complex accommodated around the OH group, the boat conformation of alcohols with an α-oriented OH group appears more perceptible through this conformational probe.

Experimental Section

General. Gas–liquid partition chromatography was carried out as described previously.[8,9,19,63,64] A Pye 54 Series instrument with flame ionization detection was used. Elemental analyses were made by Galbraith Laboratories, Knoxville, Tenn., and by Mr. P. Borda, Department of Chemistry, University of British Columbia. Melting points were carried out in capillaries on a Kofler-type microscope hot stage. Solvents, where necessary, were dried with molecular sieve 4a for 72 h. The water content was then less than 0.02% as determined by IR.

(−)-3-Neoisothujanol (3). Small pieces of aluminum foil (9 g) prewashed with carbon tetrachloride were dissolved in 2-propanol (1.5 L). The dissolution was initiated with 40 mg of mercuric chloride.[19] To the solution was added at its boiling point 60 g of cedar leaf oil containing 86% (−)-3-isothujone (**1**). During 1 h 260 mL of *i*-PrOH was distilled off. Then the reaction was stopped by the addition of 90 g of tartaric acid in 200 mL of water. About 700 mL of aqueous *i*-PrOH was distilled off in vacuo and the residue was extracted with 3 × 200 mL of diethyl ether. The extract was washed with 5% aqueous sodium bicarbonate and evaporated. At this stage, four analogous batches were combined to yield 231 g of crude semisolid neoisothujanol. After 4 days standing at 0 °C the crystalline portion was filtered off (160 g). Two recrystallizations (100 mL each) from petroleum ether (bp 30–50 °C) gave 97 g of pure (−)-3-neoisothujanol, mp 66–67 °C, $[\alpha]^{23}_D$ −22.5° (*c* 2, C_2H_5OH) [lit.[5] mp 66–67 °C, $[\alpha]^{18}_D$ −22.5° (*c* 2, C_2H_5OH)] (no detectable impurity by GLC). *p*-Nitrobenzoate, mp 111 °C (lit.[5] 110 °C).

(−)-3-Isothujone (1). The procedure of Brown et al.[21] was applied. (−)-3-Neoisothujanol (**3**, 77 g, 0.5 mol) in diethyl ether (250 mL) was oxidized (25 °C, 2 h) with 250 mL of Brown's mixture. After a standard workup the product was distilled on a spinning band column to yield 71 g (93%) of (−)-3-isothujone, bp 78 °C (12 mm), $[\alpha]^{23}_D$ −20.5° (*c* 2, $CHCl_3$) [lit.[5] bp 74.5 °C (19 mm), $[\alpha]^{18}_D$ −19.95° (neat)]. This material showed on GLC less than 0.5% each of starting (−)-3-neoisothujanol and (+)-3-thujone (**2**) (formed by epimerization of **1**).

Reduction of (−)-3-Isothujone. A slurry of 3.4 g (0.09 mol) of lithium aluminum hydride in 170 mL of diethyl ether was cooled to below −40 °C. A solution of (−)-3-isothujone (20.0 g, 0.13 mol) in 80 mL of ether was added during 1 h at below −40 °C with stirring under a nitrogen blanket. The dropping funnel used was equipped with a small dry ice bath. Stirring was continued for 4 h. The flask was then packed into a dry ice box and left overnight. The reaction mixture was decomposed at room temperature by the addition, successively, of 4 mL of water, 3.5 mL of 15% sodium hydroxide solution, and 10 mL of water. The amorphous precipitate was filtered off and washed with 150 mL of diethyl ether and the washings were combined with the filtered ether phase. This was then distilled to dryness. The crude reduction mixture (19.0 g, 94%) contained 76.0% (−)-3-isothujanol, 16.2% (−)-3-neoisothujanol, 4.4% (+)-3-thujanol, and 2.5% (+)-3-neothujanol as determined by GLC.

(−)-3-Isothujyl 2,2,2-Trichloroethyl Carbonate (11). The preceding mixture (15.4 g, 0.1 mol) in 180 mL of pyridine was treated with 28 g (0.133 mol) of 2,2,2-trichloroethyl chloroformate (30 min, 10–20 °C). A lumpy precipitate formed but later disintegrated. Stirring was continued overnight at 20 °C. The mixture was quenched on ice (400 g) and extracted with 3 × 100 mL of benzene. The extract was washed, successively, with 3% hydrochloric acid, 5% sodium bicarbonate, and water. The residue obtained (32 g) after evaporation of benzene solidified upon cooling. The crude product was dissolved in hot methanol (70 mL) and left overnight at 0 °C. Filtration and washing (5 mL) gave 13.2 g (60% on (−)-3-isothujanol contained in reduction mixture) of pure carbonate **11**, mp 56 °C, single peak on GLC. Anal. Calcd for $C_{13}H_{19}Cl_3O_3$: C, 47.37; H, 5.81; Cl, 32.27. Found: C, 47.22; H, 5.84; Cl, 32.36.

(−)-3-Isothujanol (4). Carbonate **11** (32.9 g, 0.1 mol) dissolved in 600 mL of methanol and 25 mL of acetic acid was treated at reflux during 2 h with 150 g of zinc powder added in small portions. Reflux was continued for another 3 h. After cooling and settling the clear supernatant was decanted and the zinc was washed with methanol (400 mL). The combined methanol was evaporated and the residue was dissolved in 150 mL of methylene chloride. The solution was washed with 100 mL of 5% sodium bicarbonate and water (100 mL) and evaporated to dryness. Distillation gave 14.2 g (92%) of (−)-3-isothujanol, bp 50–52 °C (0.2 mm), mp 22 °C, $[\alpha]^{23}_D$ −9.0° (*c* 2, C_2H_5OH) [lit.[5] mp 22–23 °C, $[\alpha]^{20}_D$ −8.8° (*c* 1.3, C_2H_5OH)]. The alcohol was 99.5%+ by GLC. *p*-Nitrobenzoate mp 92 °C (lit.[6] mp 91–92 °C). This alcohol can be obtained by utilizing western red cedar leaf oil directly in the lithium aluminum hydride reduction. The (−)-3-isothujone (**1**) content should be around 90%. This can be achieved by removing low-boiling fractions by distillation through a short column. The starting material has to be dried, preferably by molecular sieve 4a for several days.

(+)-3-Thujanol (5) and (+)-3-Neothujanol (6). (+)-3-Thujone (**2**, 50 g, 0.33 mol) was reduced with 9.5 g (0.25 mol) of sodium borohybride in 500 mL of 2-propanol and 50 mL of water.[24] The reaction mixture was acidified with acetic acid to pH 6.5 and 350 mL of *i*-PrOH was distilled off in vacuo. The residue was diluted with 800 mL of a saturated sodium sulfate solution and extracted with 3 × 200 mL of methylene chloride. The solvent was evaporated. By GLC the residue contained 60% (+)-3-thujanol (**5**) and 40% (+)-3-neothujanol (**6**). Separation of the two alcohols was carried out on a column of alumina (4 × 130 cm, Woelm activity II). Neothujanol (**6**) was eluted first with cyclohexane–benzene (4:6, respectively). Thujanol (**5**) was eluted with cyclohexane–benzene (2:8, respectively). About 4 L of each solvent mixture was used. The solvents were evaporated and residual alcohols were distilled. (+)-3-Thujanol, bp 98–99 °C (14 mm), $[\alpha]^{23}_D$ +108° (*c* 2, $CHCl_3$) [lit.[5] bp 103 °C (16 mm), $[\alpha]_D$ +106.7° (neat)]. *p*-Nitrobenzoate, mp 78 °C (lit.[5] mp 78 °C). (+)-3-Neothujanol, bp 53–54 °C (0.3 mm), $[\alpha]^{23}_D$ +41.5° (*c* 2, $CHCl_3$) [lit.[7a] $[\alpha]_D$ +42.0° (*c* 1.8, $CHCl_3$)]. *p*-Nitrobenzoate, mp 89 °C (lit.[7a] mp 88–89 °C). Both alcohols were 99.5+% by GLC.

Repurification of Alcohols 3–6. Prior to their utilization in the NMR and kinetic measurement study all four alcohols were repurified by conversion into their *p*-nitrobenzoates;[5–7a] these were recrystallized to a constant melting point and hydrolyzed back to the alcohols, and the alcohols were distilled[5–7a] in vacuo. No impurities could be detected by GLC.

Other Alcohols. Cyclopentanol and cyclohexanol were obtained from commercial sources (Aldrich). *trans*-2-Methylcyclopentanol

(9) and isopinocampheol (12) were prepared by us previously.[65] *cis*-2-Methylcyclopentanol (10) was obtained on separating by column chromatography, in essence using the solvent system described above, a mixture of the cis and trans alcohols 9 and 10 resulting from a sodium borohydride reduction of 2-methylcyclopentanone. This was obtained by oxidizing *cis*-2-methylcyclopentanol using Brown's procedure.[21] All alcohols were repurified as *p*-nitrobenzoates, distilled, and evaluated by GLC. All showed less than 0.1% impurities. Melting and boiling points observed were in accord with the literature.

^{1}H NMR Chemical Shifts Induced by Eu(thd)$_3$ in Thujanols 3–6 and Methylcyclopentanols 9 and 10. In principle, the procedure of Demarco et al.[27] and Cockerill et al.[26] was followed. The alcohols were exactly weighed, about 20 mg (1.0–1.5 × 10^{-4} mol), and dissolved in 0.4 mL of dry deuteriochloroform to yield a solution ca. 0.3 M. A ground glass stoppered microtube was used. The weighed amount of purified (sublimation) Eu(thd)$_3$ was added to obtain molar ratios Eu(thd)$_3$/substrate of about 0.2, 0.4, and 0.55. This represents a range of 20–50 mg of reagent added. For each ratio studied a separate alcohol solution was used and duplicate runs were made for each ratio. After dissolution of the Eu complex the generally clear solution was filtered through a glass sinter filter into a NMR tube using nitrogen pressure. Spectra were measured on a Varian HA-100 instrument. The observed induced shifts for all protons were identified and plotted against the molar ratio Eu(thd)$_3$/substrate. For all protons there was very good linear relationship between the molar ratio and induced shift in the measured range. The gradient $G_{Eu(thd)_3}$ was established in the usual manner.[25a,b] Agreement between duplicate runs was ±5% or better.

Chromium Trioxide Oxidation of Alcohols. Oxidation rates were measured as described by Roček et al.[47] The thermostated cell holder of a Cary 15 recording spectrophotometer was kept at 25 ± 0.1 °C. Cells, 1 cm path, were placed in the holder about 30 min before measurement. All solutions to be used were kept in a thermostated bath at the same temperature. The substrate alcohol solutions were transfered into the cells about 15 min before reaction start. Chromic acid solution was introduced into the cell using a syringe which had been kept at 25 °C. The mixture in the cell was then gently stirred with the syringe to assure rapid homogenization. Subsequently, the time vs. absorption (350 nm) recording system was started and the absorption was recorded automatically. Acetic acid (90%) was prepared by diluting acetic acid (analytical grade, 900 mL) with distilled water to 1000 mL at 25 °C. Chromic acid (analytical grade, British Drug Houses) solutions were prepared no later than 3 h before each measurement. During this time the loss of chromic acid as determined spectrophotometrically was negligible. Concentration of substrate alcohols was in the 2–5 × 10^{-3} M range. Concentration of chromium trioxide stock solutions was in the same range. Since only 0.2 mL was used for 4 mL of the alcohol substrate solution the alcohol excess was in the 15–30 times range. Excellent straight line plots were obtained for the log *A* vs. time relationship over the first 60–70% of the reaction. These were used for calculating the first-order rate constant k_1. Second-order rate constants were obtained from k_1 and the initial alcohol concentration. Each measurement was duplicated using the same stock solutions. A total of three stock solutions was made up for each alcohol with corresponding fresh chromium trioxide solutions. Thus, values in Table II represent an average of six measurements on three independently prepared solutions.

Acetic Anhydride–Pyridine Acetylation of Alcohols. Acetylation rates of alcohols **3–6, 9, 10,** and **12** were determined exactly as discribed by Eliel and Lukach.[57] Equimolar quantities of acetic anhydride and alcohol were used. Concentrations were about 1 × 10^{-1} mol/L. Second-order rate constants were evaluated from slopes of best fit lines obtained by plotting reciprocal of acetic anhydride concentration vs. time following the approach of Buck et al.[59] Generally good linearity was observed to 80–90% of reaction completion. All reactions proceeded to at least 95% completion. Examination of products by GLC and ^{1}H NMR indicated that alcohol acetates were the only reaction products. Values in Table II are averages of three runs. The value obtained for cyclohexanol is in excellent agreement with that obtained by Eliel et al.[57] and Buck et al.[59] for the same compound.

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Registry No.—**1,** 546-80-5; **2,** 471-15-8; **3,** 21653-20-3; **4,** 21653-18-9; **5,** 7712-79-0; **6,** 21653-19-0; **9,** 25144-04-1; **10,** 25144-05-2; **11,** 61558-19-8; **12,** 27779-29-9; 2,2,2-trichloroethyl chloroformate, 17341-93-4; cyclohexanol, 108-93-0; cyclopentanol, 96-41-3.

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(52) We may use the same approach that we applied in estimating the effect of the *i*-Pr group in thujanol (**5**) and view the $-CH_2-$ bridge as remotely comparable to $-CH_3$. Then, *cis*-3-methylcyclopentanol (**14**) is oxidized 3.42 times faster than cyclopentanol.[50] This comes very close to the observed rate (5.31) for isothujanol (**4**), in which an additional effect of the neighboring methyl group will be present.
(53) An –OH group located at a conformationally mobile section of a five-membered ring, which itself is a part of a bicyclic system, can escape severe steric interactions through slight torsional adjustments when compared to an –OH group located at a rigid position of such a bicyclic system. A good example is the pair of alcohols **19** and **20**. The size of the molecule itself appears unimportant as shown by the rate of oxidation of alcohol **21**. Displacement of an OH group by only 0.3 Å is sufficient to reduce ground state interactions to ⅓ of their original magnitude.[43,44,54] This corresponds to about 12° in angular rotation, a value close to the 14° indicated for the torsional angle between C2–C3 (and C3–C4) by our LSR study.
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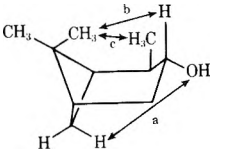

Dreiding models reveal strong steric interaction along b and c. Extent of the boatlike conformation is given by the balance of these two interactions. Oxidation will relieve b and (depending on the conformation of the resulting ketone) possibly c. Relief of the latter type is, to a degree, illustrated by comparing alcohols **22** and **23**.
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Synthetic Studies on Terpenoids. 5.[1] Syntheses of γ- and δ-Lactones from β-(2,7-Dimethyl-1,2-dihydroxycycloheptyl)propionic Acid[2]

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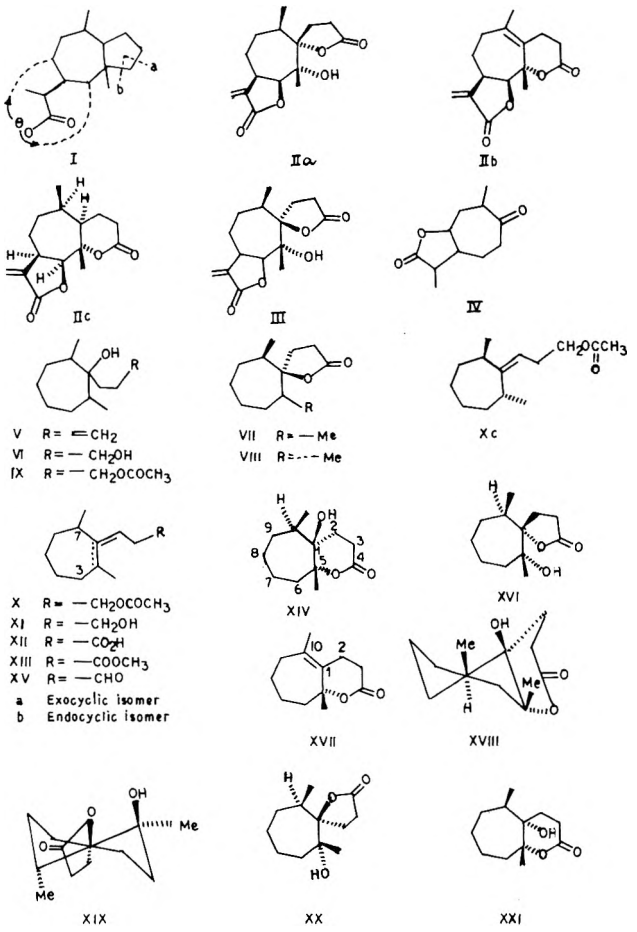
Starting from 2,7-dimethylcycloheptanone, the lactones VII, VIII, XIV, XVI, XX, and XXI have been synthesized and their conformation and stereochemistry studied. XVI represents the partial structure of IIa. VII and XXI represent the partial structures of III and IIc, respectively. Isomerization of δ-lactone to γ-lactone in the presence of acid has been discussed.

The γ-lactone moiety associated with sesquiterpene monolactones involves the isopropyl group. The other lactonic moiety in the recently discovered sesquiterpene dilactones,[3] which are again related to pseudoguaianolides (I), is formed through fission of the cyclopentane ring at a, viz., vermecrin[4] and greenein,[5] or at b, viz., psilostachyins[6] (IIa–c) and canambrin[7] (III). Experiments have been initiated in this laboratory and reported earlier[2] with a view to developing methods for building up stereospecifically different types of the lactonic functions associated with the cycloheptane ring. The compounds so formed may represent partial structures of IIa–c and III with defined stereochemical assignments at each of the three asymmetric centers present in some of these model compounds. Another aspect of interest is to study the relative rate of formation of different types of lactones, γ- and/or δ-, consistent with conformational stability of the highly mobile cycloheptane ring.

In a previous publication,[8] the lactone IV has been synthesized, its identity with one of the degradation products from xanthumin has been established, and its conformation has been discussed.

2,7-Dimethylcycloheptanone required for these studies was synthesized by two different methods. The condensation product from ethyl 6-bromohexanoate[9] and diethyl methylmalonate on hydrolysis and subsequent esterification afforded diethyl α-methylsuberate. This was also prepared through the fission of ethyl 2-methylcycloheptanone-2-carboxylate in the presence of a catalytic amount of sodium ethoxide.[10] The diester was subjected to cyclization according to modified high-dilution technique.[11] The cyclized product was methylated in situ to afford 2-ethoxycarbonyl-2-7-dimethylcycloheptanone and this on hydrolysis gave 2,7-dimethylcycloheptanone. The ketone was found by GC analysis to be a mixture (4:1) of two components. These were separated by



preparative GC (see Experimental Section). The NMR and mass spectra of both the components are superimposable, but their IR spectra show some distinct difference in the 920–1060-cm^{-1} region. The major component is the *cis*-2,7-dimethylcycloheptanone because, the two methyl groups being situated α to the carbonyl function, it will readily epimerize and assume mainly the equatorial conformation representing the cis stereochemistry. This is further supported by the behavior[12] of 2,6-dimethylcyclohexanone, which is present (85:15, cis:trans).

The ketones were treated with allylmagnesium bromide to afford V in an excellent yield. The crude product obtained by passing diborane gas through V was oxidized[13] with chromic acid to afford the spirolactones VII and VIII. Again, hydroboration of V followed by treatment with alkaline hydrogen peroxide[14] furnished the diols VI. Oxidation of VI with alkaline potassium permanganate solution afforded the same mixture of spirolactones as evident from comparative IR and GC studies. Analytical GC of the lactonic mixture showed two peaks with retention times of 12 and 13 min, and the ratio of peak heights was ca. 15:78 with minor components (~6%). The lactonic mixture was separated into two components by preparative GC (see Experimental Section). One component (A) is a colorless oil (15%), and another (B), colorless prisms (78%). However, it was very difficult to separate the mixture into pure components by preparative GC because retention times of two components were close to each other. Therefore, two components were not obtained in a pure state, and their purities were shown to be 95% by analytical GC. The major component B should possess the stereoformula VII because allylmagnesium bromide attacked mainly from the opposite side of the two cis-oriented methyl groups in dimethylcycloheptanone. The minor component A should be depicted by VIII as it has arisen from the minor constituent of dimethylcycloheptanone. Both the components absorbed in the IR at 1760 cm^{-1} in the carbonyl region, but showed some significant difference in the 800–1300-cm^{-1} region. The NMR spectra of VII showed two distinct doublet of the two secondary methyl groups centered at δ 1.0 (J = 6 Hz) and 0.904 (J = 7 Hz). The two secondary methyl groups of compound VIII appeared as two distinct doublets centered at δ 1.0 (J = 6 Hz) and 0.89 (J = 7 Hz).

The diols VI were treated with acetic anhydride and pyridine to give the hydroxyacetates IX, which on dehydration with phosphorus oxychloride and pyridine afforded the unsaturated acetates Xa,b. Analytical GC showed it to be a mixture of two components (80:15) with a minor constituent (~5%). The NMR spectra of the unsaturated acetates confirm the structure Xa for the major constituent. The presence of a low-intensity singlet at δ 1.75 can be assigned to the vinylic methyl group, suggesting thereby that the isomeric acetate Xb is also present in a lesser amount. The minor constituent mentioned above may be Xc, which is the only other possibility in the acetate mixture and may arise from the minor constituent (~20%) originally present in dimethylcycloheptanone. However, its presence could not be detected through NMR studies. For further confirmation, the isomeric acetates were separated into pure constituents Xa and Xb through preparative GC and their structures confirmed by NMR studies (see Experimental Section). The IR and mass spectra of Xa and Xb showed slight but significant differences. The same mixture of unsaturated acetates (Xa,b) was also prepared by treatment of VI with acetic anhydride in the presence of anhydrous acetate. Their identity was established through comparative IR, NMR, and GC studies.

Xa,b were saponified to XIa,b, which on oxidation with Jones reagent furnished XIIa,b, and the pure crystalline acid XIIa was isolated as the major fraction (vide infra). The corresponding methyl ester mixtures (XIIIa,b) could not be separated into pure components by using different columns in preparative GC. The mixture was treated with an excess of an ethereal solution of monoperphthalic acid. The crude epoxide, arising mainly from attack of the oxidizing agent from the opposite side of the secondary methyl group due to steric reasons, was boiled with aqueous sodium hydroxide solution to effect opening of the epoxide ring through the carboxylate ion. The products were separated into a neutral and an acidic fraction and the latter corresponds to about 80% of the mixture. The neutral material was chromatographed and a solid compound having a δ-lactone moiety was isolated from the benzene–ether fraction (50:1) and it showed a single peak it GC. The diaxial opening[15] of the epoxide, irrespective of the stereochemistry of the oxide ring, should give rise to the cis lactone. The methyl group at C-5 is already in the equatorial position and hence β oriented. Therefore, the hydroxylactone may be given the stereochemical assignment as depicted in XIV. Elution with benzene–ether (1:1) afforded a hydroxylactone as a liquid with a γ-lactonic moiety as revealed in the IR. Its purity was tested through TLC in different solvent systems. Elemental analyses, various spectral data, and the well-appreciated diaxial opening of the epoxide ring again suggested that XX should be the stereoformula of the hydroxy-γ-lactone. XIV with C-1 hydroxyl and C-10 hydrogen in trans disposition was anticipated to be easily dehydrated to XVII. When subjected to dehydration with phosphorus oxychloride and pyridine or thionyl chloride and pyridine at low temperature it yielded a complex mixture[16] of unsaturated compounds, as revealed in the NMR. The presence of XVII, the partial structure of IIb, in the product is indicated by an ill-defined triplet at δ 1.72.

The crystalline acidic fraction was found to be XIIa and is characterized by one olefinic proton at δ 5.45, coupled to two protons at δ 3.15 (J = 7.5 Hz). A decoupling experiment confirmed this. There is a hydroxyl proton appearing at δ 11.47 arising from the carboxylic acid function. Both the methyl

groups are split into doublets at δ 0.94 and 1.04 (J = 7.5 Hz). It is interesting to note that the β,γ-unsaturated acid (XIIa) resisted epoxidation with monoperphthalic acid under these conditions and epoxidation is most likely stereospecific.

With a view to studying the possibility of the formation of a γ- and/or δ-lactone from a vicinally situated cis-hydroxylated acid from XIIIb, experiments had been designed accordingly. As the desired unsaturated acid is present as a minor constituent, attempts have been made to force the double bond to migrate inside the ring leading to the formation of the tetrasubstituted double bond as is found in XIIb. Xa,b was treated with *N*-lithioethylenediamine[17] and the product did not exhibit any IR absorption for the acetate group, indicating thereby that this had been knocked off. The material was reacetylated and from the NMR it was found that about 50% of conversion to the endocyclic isomer had taken place. Estimation was possible through comparison with the methylene protons of the acetate function and the vinyl proton of the exocyclic isomer. This types of isomerization was next studied with XIa,b. In this case also only 50% of conversion had taken place. Increase of the reaction period had virtually no effect on the extent of isomerization (beyond 50%) and this was evidently an equilibrium mixture. This arises due to severe 3,7-interaction, present in the endocyclic bond isomer, and this is a characteristic property of cycloheptene derivatives.[18] Next it was decided to oxidize the isomerized XIIa,b. Oxidation with Jones reagent having been found unsatisfactory, oxidation with ruthenium tetroxide was next attempted. The oxidation product in this case was found to be a mixture of neutral and acidic parts and from the nature of the products it was evident that ruthenium tetroxide had affected the double bond. The isomerized XIa,b were next oxidized with chromium trioxide and pyridine to the corresponding aldehydes (XVa,b). These were again oxidized with silver oxide to afford the unsaturated acids (XIIa,b). The corresponding methyl esters (XIIIa,b) were oxidized with osmium tetroxide giving rise to cis disposition of the two vicinal groups. The resulting product was characterized in the IR by two distinct bands corresponding to a broad band in the hydroxyl region and a single band at 1735 cm^{-1} characteristic of the ester function. This was hydrolyzed under mild alkaline conditions and the free hydroxy acid was subjected to lactonization under mild acidic conditions. The acidic material was removed and the neutral material thus obtained exhibited two distinct bands at 1760 and 1740 cm^{-1} in the IR indicating the presence of a γ-lactone and a δ-lactone. On chromatography over neutral alumina, hydroxy-γ-lactone XVI was isolated as a liquid on elution with benzene–ether (1:1). Its purity was tested through TLC in different solvent systems and sharp NMR signals. The molecular ion peak in the mass spectrum appears at m/e 212 and the base peak is at m/e 194, indicating removal of the elements of water. The presence of tertiary Me at δ 1.3 as a sharp singlet in the NMR of XVI completely ruled out the possibility of the formation of an isomeric hydroxy-γ-lactone from XIIa. XVI represents the partial structure of psilostachyin (IIa). Elution with benzene–ether (50:1) afforded a crystalline material (mp 150 °C). It exhibited a sharp band at 1740 cm^{-1} in the IR indicating the presence of a δ-lactonic moiety. The elemental analyses and other spectral data suggest that XXI is the structure for the δ-lactone. It is likely that the oxidation to the endocyclic double bond has again taken place[19] mostly from the back side of the secondary methyl group in XIIIb because two products could only be isolated. Evidently the trans-lactone ring has been formed and this is present in IIc.

From the conformational analysis of the seven-membered ring, the δ-lactone XIV is represented by the stereoformula XVIII and the spirolactone XVI by XIX on the basis of calculations previously detailed out from this laboratory.[8]

One interesting point should be mentioned here: opening of the epoxide through the carboxylate ion leading to the formation of the δ-lactone XIV is kinetically controlled. Isomerization takes place on treatment with acids resulting in a mixture of γ- and δ-lactones. If the lactonic mixture is warmed (60–70 °C) on a water bath for a prolonged period (4–6 h), the product isolated is the γ-lactone XX; evidently the equilibrium of δ- and γ-lactones shifts to the γ-lactone, thereby affording the thermodynamically more stable γ-lactone XX as the major, if not the only, product. Similar experiments with the mixture of XXI and XVI lead to the same conclusion that the thermodynamically stable γ-lactone XVI is formed as a major product. These results are quite comparable to those with lactonic functions attached to cyclohexane rings.

Experimental Section

Boiling and melting points are uncorrected. The IR spectra were taken on a Perkin-Elmer Model 21 double beam recording spectrophotometer in chloroform solution. UV absorption spectra were measured for 95% ethanol solution with a Beckman DU 2 spectrophotometer (manually operated). The NMR spectra were determined with a Varian A-60 spectrometer for solutions in CCl_4 and peak positions are reported in parts per million from Me_4Si serving as internal reference. Light petroleum refers to the fraction of bp 60–80 °C. All solvent extracts were dried over Na_2SO_4.

2,7-Dimethylcycloheptanone. 2-Methyl-2-ethoxycarbonylcycloheptanone (120 g) was subjected to cleavage in presence of Na (1 g) in EtOH (60 mL) by heating on a water bath for 6 h. The product was worked up to afford diethyl α-methylsuberate (105 g), bp 140 °C (7 mmHg). This was subjected to cyclization according to high-dilution technique and methylated in situ with methyl iodide to afford **2-ethoxycarbonyl-2-7-dimethylcycloheptanone.** The crude keto ester (50 g) was heated under reflux with concentrated HCl (300 mL) for 30 h to afford **2,7-dimethylcycloheptanone** (25 g), bp 105 °C (40 mmHg). Anal. Calcd for $C_9H_{16}O$: C, 77.1; H, 11.5. Found: C, 76.9; H, 11.4. It yielded an orange 2,4-dinitrophenylhydrazone. 99 °C (ethanol). Anal. Calcd for $C_{15}H_{20}O_4N_4$: C, 56.2; H, 6.2. Found: C, 56.1; H, 6.2. The ketones were separated into two components a and b by using a column 6 m in length with 15 mm i.d., and consisting of 5% Carbowax 20M. It was operated at 100 °C with a flow rate of 200 mL/min of He. Compound a and b had retention times of 31.4 and 35.4 min, respectively.

1-Allyl-2,7-dimethyl-1-hydroxycycloheptanes (V). A solution of 2,7-dimethylcycloheptanone (7.5 g) in ether (30 mL) was added under N_2 during 1 h with stirring to a cold (0 °C) slurry of allylmagnesium bromide from allyl bromide (22.5 g) and Mg (12 g) in ether (100 mL). The reaction mixture was left overnight and the excess Grignard reagent decomposed with dilute aqueous NH_4Cl. The organic phase was worked up and distilled to afford V (9 g), bp 98–100 °C (7 mmHg). Anal. Calcd for $C_{12}H_{22}O$: C, 79.0; H, 12.1. Found: C, 79.1; H, 12.1.

2,7-Dimethyl-1-hydroxy-1-(3′-hydroxypropyl)cycloheptane (VI). B_2H_6 generated from the addition of $NaBH_4$ (1 g) in diglyme (25 mL) to boron trifluoride etherate (10 mL) in diglyme (8 mL) was passed through a solution of the unsaturated alcohol V (4 g) in dry THF (50 mL) below 30 °C. After 2 h the solution was flushed with dry N_2 for 20 min and finally with dry air for 6 h. The residual thick mass was diluted with acetone (40 mL) and stirred overnight with a mixture of NaOH solution (10 mL, 10%) and H_2O_2 (16 mL, 30%) at room temperature and next day with an additional amount of H_2O_2 (8 mL) for 2 h. The reaction mixture was partitioned between ether and brine and the organic layer afforded the diols VI (4 g), bp 136 °C (0.8 mmHg), ν_{max} 3500 cm^{-1}. Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.9; H, 12.1. Found: C, 71.6; H, 11.9.

Lactones of 3-(2′,7′-Dimethylhydroxycycloheptyl)propionic Acid (VII, VIII). A. The diol VI (1 g) in H_2O (60 mL), containing KOH (0.3 g), was oxidized by gradual addition of $KMnO_4$ (3 g) during 4 h with stirring at room temperature. The reaction mixture was filtered and the filtrate extracted with ether to remove the neutral material. The alkaline aqueous layer was acidified and extracted with ether. The ethereal extract was washed with aqueous Na_2CO_3 solution (2%) and H_2O and dried. On distillation it afforded VII and VIII (0.6 g), bp 140–142 °C (5 mmHg), ν_{max} 1765 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.4; H, 10.3. Found: C, 73.3; H, 10.2.

B. A solution of the unsaturated alcohol V (4.5 g) in THF (50 mL) was saturated with excess B_2H_6 at a temperature below 30 °C. The

excess reagent was decomposed as described earlier. The residual thick mass was diluted with acetone (40 mL) and Jones reagent (120 mL) added dropwise at 15 °C with stirring over a period of 8 h. After usual workup the concentrated extract (ca. 4 g) was mixed with methanolic NaOH solution (30 mL, 15%) and heated on a steam bath for 30 min. The cooled reaction mixture was diluted with NaOH solution (50 mL, 5%) and the neutral material taken up with ether. The alkaline solution was acidified with dilute HCl and extracted with ether. The ethereal solution was washed with H_2O, dried, and distilled to afford VII and VIII (3 g), bp 140–142 °C (5 mmHg). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.4; H, 10.3. Found: C, 73.2; H, 10.2. The IR and GC spectra of the lactones obtained through different methods were superimposable.

Separation of the Lactonic Mixture (VII and VIII). Before preparative GC the sample was examined in various columns [5% Carbowax 20M, 5% CHDMS, 5% OV-101 (SE-30), 5% XE-60, 2% polyphenyl ether, 5% QF-1]. Of the various columns, 5% XE-60 and 5% QF-1 were found to be suitable and for the present purposes. 5% XE-60 was employed for separation of the lactonic mixture. For analytical GC a glass column 3 mm × 3.0 m consisting of 5% XE-60 on Chromosorb W (80–100 mesh) was operated at 200 °C with a flow rate of 50 ml/min of nitrogen. For preparative GC a column 15 mm × 1.5 m consisting of 5% XE-60 on Chromosorb W (80–100 mesh) was operated at 170 °C with a flow rate of 300 ml/min of He. As the GC of the sample showed a broad peak, it was separated into different fractions. By repeated preparative GC of each fraction the lactone VII was obtained as colorless prisms, mp 34–36 °C, and VIII as a colorless oil.

2,7-Dimethyl-1-hydroxy-1-(3′-acetoxypropyl)cycloheptanes (IX). Ac_2O (15 mL) was added to a solution of the diols VI (3 g) in pyridine (15 mL). After 18 h at room temperature the mixture was poured into H_2O and worked up to afford IX (3.0 g): bp 132 °C (2 mmHg); ν_{max} 3500 and 1730 cm^{-1}. Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.4; H, 10.8. Found: C, 69.3; H, 10.9.

2,7-Dimethyl-1-(3′-acetoxypropyl)cycloheptene (Xb) and Bond Isomer (Xa). A. $POCl_3$ (5 mL) was added to a solution of the monoacetate IX (3 g) in pyridine (12 mL) and allowed to stand overnight. The contents were heated on a steam bath for 1 h and after cooling, the dark reaction mixture was cautiously poured into crushed ice (300 g) and the mixture thoroughly stirred. The organic material was distilled to afford the acetates Xa,b (2.3 g), bp 94–95 °C (0.6 mmHg), ν_{max} 1730 cm^{-1}. Anal. Calcd for $C_{14}H_{24}O_2$: C, 75.0: H, 10.8. Found: C, 74.9; H, 10.6. The isomerized acetate mixture was separated by preparative GC using a column 6 m in length with 15 mm i.d. consisting of 5% diethylene glycol succinate polyester at 150 °C with a flow rate of 200 mL/min of He. The exocyclic isomer had a retention time of 17.1 min and the endocyclic isomer had a retention time of 24.0 min. Endocyclic isomer: NMR δ 1.1 (3 H, d, J = 7 Hz), 1.65 (3 H, s), 2.05 (3 H, s), 4.1 (2 H, t, J = 6 Hz); M^+ m/e 224; ν_{max} 1730 cm^{-1}. Exocyclic isomer: NMR two methyls split into two doublets, δ 0.93, 1.03 (J = 7 Hz), 2.05 (3 H, s), 2.45 (2 H, t, J = 8 Hz), 4.1 (2 H, t, J = 6 Hz), and 3.15 (1 H, t); M^+ m/e 224: ν_{max} 1730 cm^{-1}.

B. A mixture of the diols VI (3.2 g), anhydrous NaOAc (4 g), and Ac_2O (20 mL) was refluxed in an oil bath for 5 h. The reaction mixture was cooled and excess of Ac_2O decomposed by adding H_2O and warming it on a water bath for 15 min. The organic material was taken up in ether and the ethereal solution washed with Na_2CO_3 solution (5%) and H_2O and dried. On distillation it afforded the unsaturated acetates (Xa,b, 3.5 g), bp 100–102 °C (1 mmHg). Anal. Calcd for $C_{14}H_{24}O_2$: C, 75.0; H, 10.8. Found: C, 74.8; H, 10.8. The IR spectra of the two samples prepared through different methods were superimposable.

2,7-Dimethyl-1-(3′-hydroxypropyl)cycloheptene (XIb) and Bond Isomer (XIa). The unsaturated acetate mixture (Xa,b, 3 g) was heated under reflux for 3 h with alcoholic KOH solution (40 mL, 2 N). Workup afforded the unsaturated alcohols (XIa,b, 2.2 g), bp 92–93 °C (0.6 mmHg). Anal. Calcd for $C_{12}H_{22}O$: C, 79.0; H, 12.1. Found: C, 79.0; H, 12.0.

3-(2′,7′-Dimethylcycloheptylidene)propionic Acid (XIIa). Jones reagent (5.5 mL) was slowly added to a cooled (0 °C) solution of the unsaturated alcohols (XIa,b, 3 g) in acetone (60 mL) with occasional shaking during 10 min. The reaction mixture was kept at 0 °C for a further 15 min. Usual workup yielded XIIa,b (1 g), bp 135–137 °C (8 mmHg). Fractional crystallization afforded XIIa (700 mg), mp 86 °C (light petroleum), ν_{max} 1715 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.4; H, 10.3. Found: C, 73.3; H, 10.1.

Methyl 3-(2′,7′-Dimethylcycloheptenyl)propionate (XIIIb) and Bond Isomer (XIIIa). Unsaturated acids (XIIa,b, 2 g) were esterified with an ethereal solution of CH_2N_2 and after usual workup and distillation, afforded XIIIa,b (1.8 g), bp 110 °C (0.2 mmHg). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.2; H, 10.5. Found: C, 74.1; H, 10.3.

δ-Lactone of 3-(2′,7′-Dimethyl-*trans*-1′,2′-dihydroxycycloheptyl)propionic Acid (XIV) and γ-Lactone of 3-(2′,7′-Dimethyl-*trans*-1′,2′-dihydroxycycloheptyl)propionic Acid (XX). An ethereal solution of monoperphthalic acid (90 mL, 4%) was added to the unsaturated esters (XIIIa,b, 1.7 g) in ether (20 mL) at 0 °C and the residue left after removal of the solvent was heated under reflux with NaOH solution (25 mL, 5%). The alkaline aqueous solution, after removing neutral material with ether, was acidified with dilute HCl and warmed on a water bath (50 °C) for 30 min. The organic material was taken up in ether and the ethereal extract washed with Na_2CO_3 solution (2%). The residue obtained after removal of the solvent was chromatographed over neutral alumina. The fraction eluted with benzene and ether (50:1) afforded the solid δ-lactone XIV (60 mg): mp 68 °C (light petroleum); ν_{max} 3620 and 1740 cm^{-1}; NMR δ 1.04 (3 H, d, J = 7 Hz, 2-Me), 1.34 (3 H, s, 7-Me), and 2.0 (1 H, s, exchangeable). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.9; H, 9.5. Found: C, 67.8; H, 9.4. Elution with benzene–ether (1:1) afforded the γ-lactone XX (240 mg) as a liquid which was evaporatively distilled at 120–122 °C (0.1 mmHg): ν_{max} 1760 cm^{-1}; NMR δ 0.9 (3 H, d, J = 7 Hz), 1.4 (3 H, s), and 2.1 (1 H, s, exchangeable). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.9; H, 9.5. Found: C, 67.5; H, 9.4.

The Na_2CO_3 washings were acidified with dilute HCl and yielded XIIa (1.25 g). It melted at 86 °C alone or on admixture with the sample described above.

Isomerization of the Unsaturated Acetates (Xa,b). Ethylenediamine (ca. 120 mL), dried with KOH and distilled over Na, was heated to 120 °C (oil bath temperature) under N_2. Freshly cut Li (1.5 g) was added in small bits with vigorous stirring. The liquid turned blue and after some time the color disappeared. When whole Li was added, the liquid acquired a pale yellow color with a small amount of a white suspended solid. The solution was further heated for 45 min to ensure complete dissolution . The unsaturated acetate mixture (2.5 g) was added in three installments whereupon the mixture turned light green. It was heated for 10 h at 115–120 °C. The contents were cooled in an ice bath and cold water gradually added till the initially formed white solid just dissolved. The organic material was extracted with ether and the ethereal extract washed with dilute HCl (6 N). The resulting product was distilled at 100 °C (1 mmHg) to afford a colorless material (1.5 g) which was reacetylated with Ac_2O (5 mL) and pyridine (5 mL). Distillation afforded the isomerized acetates (1.5 g): bp 100 °C (1 mmHg); ν_{max} 1730 cm^{-1}; NMR δ 2.0 (3 H, s), 4.1 (2 H, t, J = 7 Hz), 5.2 (½ vinylic proton).

Isomerization of the Unsaturated Alcohols (XIa,b). Unsaturated alcohols (5 g) were isomerized as described above, using *N*-lithioethylenediamine prepared from Li (2 g) and ethylenediamine (150 mL), at 115–120 °C for 15 h. It was worked up in the usual way to afford the isomerized unsaturated alcohols (2 g): bp 100 °C (1 mmHg); NMR δ 3.6 (2 H, t, J = 7 Hz), 5.2 (½ vinylic proton).

3-(2′,7′-Dimethylcycloheptenyl)propionaldehyde (XVb) and Bond Isomer (XVa). To dry CrO_3–pyridine complex from CrO_3 (12 g, 120 mmol) in CH_2Cl_2 (300 mL) was added at 10 °C the isomerized unsaturated alcohol mixture (3.6 g, 20 mmol) in CH_2Cl_2 (5 mL). After stirring for an additional 30 min at room temperature, the solution was decanted from the black residue and washed with NaOH solution (5%) and HCl (5%), and distillation of the residue afforded the aldehydes (XVa,b, 2.8 g), bp 115 °C (1 mmHg); ν_{max} 1724 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O$: C, 79.9; H, 11.2. Found: C, 79.7; H, 11.1.

Methyl 3-(2′,7′-Dimethylcycloheptenyl)propionate (XIIIb) and Bond Isomer (XIIIa). The unsaturated aldehydes (XVa,b, 2.6 g, 14.2 mmol) were added with shaking to a suspension of Ag_2O in H_2O prepared from $AgNO_3$ (4.9 g, 18.3 mmol). After the solution was allowed to stand for 30 min, a black deposit was filtered off and the filtrate acidified with HCl (6 N). Workup afforded the crude acid mixture (2.4 g) and this was esterified with an excess of ethereal CH_2N_2 solution. Distillation afforded the unsaturated esters XIIIa,b: 2.2 g; bp 110 °C (0.2 mmHg); ν_{max} 1730 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.2; H, 10.5. Found: C, 74.3; H, 10.5.

γ-Lactone of 3-(2′,7′-Dimethyl-*cis*-1′,2′-dihydroxycycloheptyl)propionic Acid (XVI) and δ-Lactone of 3-(2′,7′-Dimethyl-*cis*-1′,2′-dihydroxycycloheptyl)propionic Acid (XXI). To the unsaturated esters (XIIIa,b, 1.2 g) in ether (25 mL) was added OsO_4 (1 g) with stirring and the solution was left as such for 48 h. The residue, after removal of ether, was taken up in dry dioxane (25 mL) and H_2S passed for 10 min. Precipitated osmium sulfide was removed by filtration and from the filtrate dioxane was removed under suction. The residue was treated with NaOH (0.7 g) and MeOH (14 mL) and left overnight. Next day it was warmed at 60 °C for 2 h and cooled and the neutral fraction removed with ether. The aqueous alkaline solution was acidified with HCl and warmed on a steam bath for 30 min.

The acidic part was removed with dilute Na_2CO_3 solution (2%). The neutral part (500 mg) showed IR absorptions at 1760 and 1740 cm^{-1}. It was chromatographed over neutral alumina (18 g). Benzene–ether (50:1) eluted the γ-lactone XVI (360 mg) as a liquid, which was evaporatively distilled at 130 °C (0.1 mmHg): ν_{max} 3620, 1760 cm^{-1}; NMR δ 0.9 (3 H, d, J = 7 Hz), 1.3 (3 H, s), and 2.2 (1 H, s, exchangeable); M^+ m/e 212. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.9; H, 9.5. Found: C, 67.5; H, 9.4. Elution with benzene–ether (1:1) afforded the solid δ-lactone XXI (20 mg): mp 150 °C (EtOAc–light petroleum); ν_{max} 3620, 1740 cm^{-1}; NMR δ 0.95 (3 H, d, J = 7 Hz), 1.34 (3 H, s), and 2.2 (1 H, s, exchangeable). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.9; H, 9.4. Found: C, 67.6; H, 9.4.

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Registry No.—V, 61426-32-2; VI, 61426-33-3; VII, 61426-34-4; VIII, 61475-98-7; IX, 61426-35-5; Xa, 19923-89-8; Xb, 61426-36-6; XIa, 61426-37-7; XIb, 61426-38-8; XIIa, 61426-39-9; XIIb, 61426-40-2; XIIIa, 61426-41-3; XIIIb, 61426-42-4; XIV, 19946-75-9; XVa, 61426-43-5; IVb, 61426-44-6; XVI, 61426-45-7; XX, 61475-99-8; XXI, 61527-74-0; 2,7-dimethylcycloheptanone isomer a, 21631-95-8; 2,7-dimethylcycloheptanone isomer b, 21631-93-6; *cis*-2,7-dimethylcycloheptanone 2,4-dinitrophenylhydrazone, 21631-96-9; *trans*-2,7-dimethylcycloheptanone 2,4-dinitrophenylhydrazone, 21631-94-7; 2-methyl-2-ethoxycarbonylcycloheptanone, 20043-64-5; diethyl α-methylsuberate, 61426-46-8; 2-ethoxycarbonyl-2,7-dimethylcycloheptanone, 7272-18-6; allyl bromide, 106-95-6; Ac_2O, 108-24-7; CH_2N_2, 624-90-8.

References and Notes

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The Structure of Benulin, a New Pentacyclic Triterpene Hemiketal Isolated from *Bursera arida* (Burseraceae)

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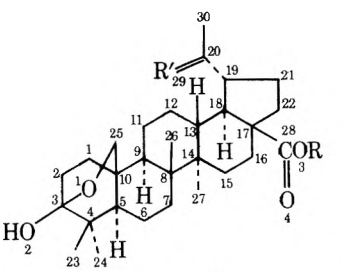
Investigation of the chloroform extract of *Bursera arida* (Burseraceae) resulted in the isolation of a new pentacyclic triterpene hemiketal which was named benulin. On the basis of biogenetic considerations and physical and chemical data, benulin was postulated to be 3α-hydroxy-3,25-epoxylup-20(29)-en-28-oic acid. This structure was confirmed by an x-ray study of benulin.

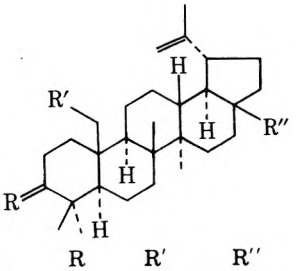
Fractionation of the chloroform extract of the stems, leaves, twigs, and bark of *Bursera arida* (Rose) Standl (Burseraceae)[2] yielded, in addition to β-sitosterol, naringenin, betulonic acid, and four new lignans, benulin, a new pentacyclic triterpene hemiketal. Benulin (I) is 3α-hydroxy-3,25-epoxylup-20(29)-en-28-oic acid.

Results and Discussion

Elemental analysis and molecular weight determination suggested the molecular formula $C_{30}H_{46}O_4$ for benulin. The general appearance of the IR and NMR spectra and the fragmentation pattern in the mass spectrum suggested a triterpene with a lupane skeleton. Spectral data (IR, NMR, mass) indicated the presence of a carboxyl and an isopropenyl group in benulin. Confirmation was established by the preparation of the methyl ester (Ia) and the dihydro (Ib) derivatives and their spectral data.



	R	R′
I	H	CH_2
Ia	Me	CH_2
Ib	H	Me



	R	R′	R″
II	O	H	COOH
IIa	O	OAc	COOH
IIb	H_2	OH	COOH
IIc	β-OH	OH	CH_2OH
IId	β-OAc	OAc	CH_2OAc

The presence of a hydroxyl group and hemiketal linkage was established by the acetylation of benulin, leading to keto

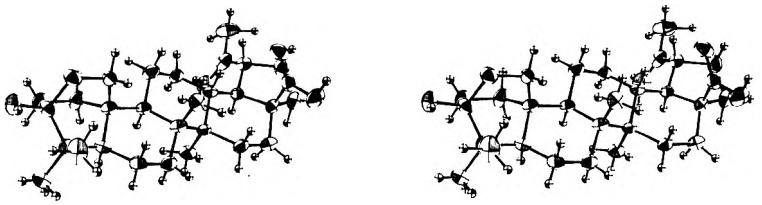


Figure 1. Stereoscopic view of a single molecule. Hydrogen atoms are shown as spheres, and other atoms as 50% probability ellipsoids.

monoacetate IIa. The IR spectrum displayed, in addition to a carboxyl carbonyl band (1690 cm^{-1}) and an acetate carbonyl band (1740 cm^{-1}), a third band at 1710 cm^{-1} (cyclohexanone). This evidence indicated the presence of a hemiketal linkage which, under acetylating conditions, cleaved to generate a cyclohexanone system with a hydroxymethylene group which was subsequently acetylated. Spectral data (mass, NMR) confirmed the presence of a $-CH_2OAc$ group in IIa. The mass spectrum of its Huang-Minlon reduction product IIb (loss of 14 + 42 mass units) and a deuterated product (gain of 2 mass units) indicated clearly the presence of a carbonyl group in the acetylated product. Basic hydrolysis of the acetate produced the parent compound. In view of its resistance toward acetylation, the hydroxyl group involved in the hemiketal linkage of I is presumably tertiary. Lithium aluminum hydride reduction of methyl benulinate (Ia) not only reduced the ester group but also ruptured the hemiketal linkage to give a triol (IIc) which on acetylation furnished a triacetate (IId).

The possible site for the hemiketal linkage was established by the mass spectrum fragmentation pattern of benulin and its derivatives. The most noteworthy peak in the mass spectrum of benulin is at *m/e* 313. Esterification or hydrogenation of benulin exerted no influence on this peak, nor on the general fragmentation pattern. Acetylation, however, which disturbed the hemiketal linkage, not only wiped out the peak at *m/e* 313 but also altered the fragmentation pattern. The pronounced loss of M − AcOH and M − CH_2OH in the mass spectrum of monoacetate IIa and its Huang-Minlon reduction product (IIb), respectively, indicated that the hemiketal linkage originated at an angular position. The co-occurrence of benulin with betulonic acid, a triterpene known to have structure II, in the same plant led to I as the most biogenetically satisfactory structure for benulin.

An x-ray study was successfully carried out on crystalline benulin. As can be seen from the resulting ORTEP[3] plot in Figure 1, the structure is indeed I. Rings B, C, and D have chair conformations, as in 3β-acetoxy-20-hydroxylupane,[4] the other lupane type triterpenoid whose structure has been studied by x-ray diffraction. Ring A and the other rings of the oxabicyclo[2.2.2]octane system have boat conformations. Ring E has the envelope conformation as evidenced by torsion angles, starting from C17–C18–C19–C21 and going clockwise, of 21.5, 4.2, −28.7, 41.3, and −38.9°. The torsion angles C18–C19–C20–C29 and C18–C19–C20–C30 are −71.1 and −11.1°, respectively. The torsion angles around C17–C28 are C18–C17–C28–O3 (162.9°), C18–C17–C28–O4 (−16.8°), C22–C17–C28–O3 (−86.5°), and C22–C17–C28–O4 (93.6°).

The average C–C distances in rings A, B, C, D, and E are 1.554, 1.557, 1.558, 1.560, and 1.554 Å, and the corresponding bond angle values are 109.5, 111.9, 110.0, 110.7, and 104.4°, respectively. Only C9–C10 (1.598 Å) and C8–C14 (1.599 Å), between highly substituted carbons, are significantly longer. The molecular packing is governed partly by intermolecular hydrogen bonds between O2–O4 (2.727 Å) and O3–O1 (2.717 Å), which bind molecules infinitely in the *a* direction. The only other intermolecular distances less than 3.5 Å are O1–O4 (3.414 Å) and O2–C28 (3.467 Å).

Benulin (I) has not previously been synthesized, nor isolated from a natural source. Therefore it is the first triterpene with a lupane skeleton for which a hemiketal linkage terminating at a C-3 bearing hydroxyl group has been established. Biosynthetically, it may arise from betulonic acid (II), which accompanies it in *Bursera arida*, by hydroxylation at C25 followed by hemiketal formation.

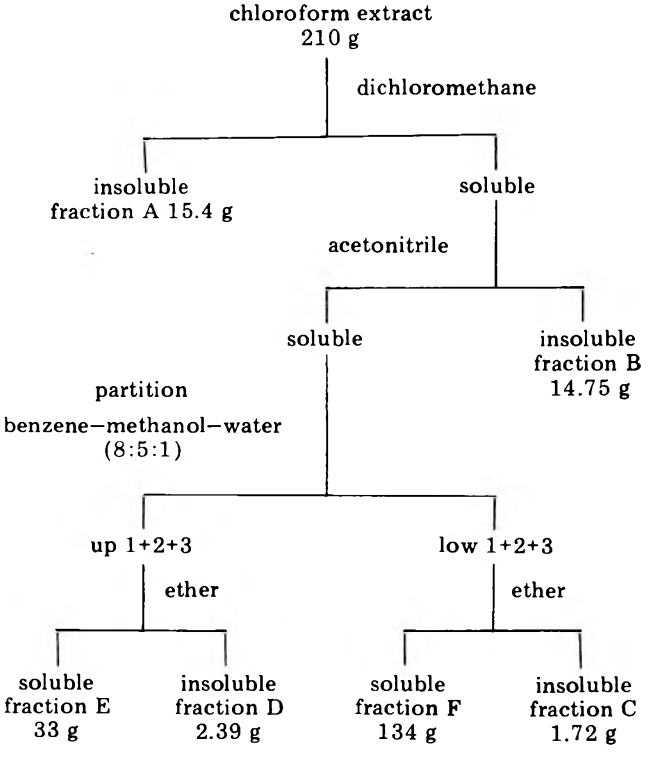
Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Carbon and hydrogen analyses were carried out by Chemalytics, Inc., Tempe, Ariz. Infrared (IR) spectra were run on a Beckman IR-33 spectrophotometer. Unless otherwise mentioned all nuclear magnetic resonance (NMR) spectra were run in $CDCl_3$ using Varian T-60 and HA-100 instruments and peak positions are given in δ values, using tetramethylsilane as an internal standard. Mass spectra were recorded on a Hitachi Perkin-Elmer Model RMU-6E mass spectrometer.

Benulin (I). The stems, leaves, twigs, and bark of *Bursera arida*, collected in Tehuacan, Puebla, Mexico, during the month of June 1971, were ground in a Wiley Mill and stored at −10 °C prior to extraction.

The ground material (8 kg) was extracted exhaustively in a Lloyd-type extractor with chloroform. A 210-g portion of the air-dried chloroform extract was fractionated as outlined in Scheme I. Fraction

Scheme I. Fractionation of Chloroform Extract of *Bursera arida*



F, which on TLC showed the presence of benulin as one of the major spots, was then subjected to silica gel 60 column chromatography. Elution with 1% methanolic dichloromethane yielded fractions containing nearly pure benulin which were further purified by crystallization, giving benulin (I), mp 281–283 °C, as cubelets from benzene–methanol. The IR [(KBr) 3380, 1690, 1645, and 880 cm^{-1}], NMR [($CDCl_3$–CD_3COOD) 4.66–4.7 (d, 2 H, $H_2C{=}CCH_3$), 1.68 (s, 3 H, $H_2C{=}CCH_3$), 0.87 (s, 3 H, CH_3), 0.97 (s, 6 H, 2 CH_3), and 1.02 (s, 3 H, CH_3)], and mass [*m/e* 470 (M^+), 455, 452, 440, 313, 234, 205, 203, 189, and 187] spectra were in accord with structure I.

Anal. Calcd for $C_{30}H_{46}O_4$: C, 76.55; H, 9.85. Found: C, 76.42; H, 9.96.

Colorless crystals of benulin (I, $C_{30}H_{46}O_4$) were grown from chloroform–benzene for an x-ray study. A prism of dimension 0.3 × 0.2 × 0.4 mm was mounted with the c axis parallel to the goniostat ϕ axis. The space group was determined by film methods to be $P2_12_12_1$. The cell parameters were found by least-squares fitting of the settings for the four angles of seven reflections on a Picker-FACS-I diffractometer (Cu Kα, λ = 1.54178 Å, graphite monochromator) to be a = 19.2710 (8), b = 19.1091 (8), and c = 7.1356 (3) Å. The crystal density was measured by flotation as 1.179 g/mL, agreeing well with a calculated density of 1.188 g/mL assuming four molecules in the unit cell. Intensity data were collected using a scintillation counter with pulse-height analyzer, θ–2θ scan technique, maximum $\sin\theta/\lambda$ 0.562, 2°/min scan rate, 10-s background counts, attenuators when the count rate exceeded 10^4 counts/s, and 2° scan range with a dispersion factor allowing for α_1–α_2 splitting at large 2θ values. Of 2314 independent reflections measured, 1979 > 3α (I) were considered observed. Three standard reflections were monitored every 50 measurements to check the crystal alignment and the stability; no decrease in the intensity of standards was observed. Lorentz and polarization corrections were applied to the data, but no correction was made for absorption.

Phases for reflections with normalized structure factor $E > 1.4$ were generated using the direct method program MULTAN.[5] All nonhydrogen atoms were located on an E map using calculated phases as coefficients. Full matrix least-squares refinement in which positional and isotropic thermal parameters were varied reduced R to 0.117. Two more cycles of least-squares refinement using anisotropic thermal parameters reduced R to 0.096. A difference map at this stage revealed all the hydrogen atoms. One more cycle of least-squares refinement using anisotropic temperature factors for nonhydrogen atoms and isotropic temperature factors (of nonhydrogen atoms to which they were attached) for hydrogen atoms brought R to 0.061. Refinement was terminated at this stage since the ratios of shifts in parameters to estimated standard deviations were all less than 0.3. The refinement was based on F_o, the quantity minimized being $\Sigma w(F_o - F_c)^2$. The weighting scheme used was based on counter statistics as defined by Corfield et al.,[6] the value of p being 0.04. The scattering factors used were those of Hanson et al.[7] No correction was applied for extinction.

Methyl Benulinate (Ia). Esterification of I with diazomethane in the usual manner afforded Ia, mp 210.5–211.5 °C. The IR [(KBr) 1730 and 1210 cm^{-1}], NMR [3.63 (s, 3 H, $COOCH_3$)], and mass [m/e 484 (M^+)] spectra were in accord with structure Ia.

Dihydrobenulin (Ib). Catalytic hydrogenation of benulin with platinum oxide in methanol gave dihydrobenulin, showing a negative tetranitromethane test. The IR [(KBr) 1380, 1360, and no absorption at 1645 and 880 cm^{-1}] and mass [m/e 472 (M^+)] spectra were in accord with structure Ib.

3-Keto-10-acetoxymethylbenulin (IIa). Acetylation of benulin with acetic anhydride–pyridine on a steam bath afforded IIa, mp 120 °C (MeOH). The IR [(CCl_4) 1740, 1710, and 1690 cm^{-1}], NMR [1.93 (s, 3 H, CH_2OCOCH_3)], and mass [m/e 512 (M^+), 452, and no peak at 313] spectra were in accord with structure IIa.

The deuterated product of IIa, prepared according to the procedure of Djerassi et al.,[8] displayed a molecular ion peak at m/e 514 in the mass spectrum.

10-Hydroxymethyl-3-deoxybenulin (IIb). Huang-Minlon reduction of IIa with hydrazine hydrate and potassium hydroxide in ethylene glycol afforded IIb, mp 151–153 °C. The IR [(KBr) no absorption at 1740 and 1710 cm^{-1}] and mass [m/e 456 (M^+) and 425 (base)] spectra were in accord with structure IIb.

Benulintriol (IIc). Reduction of Ia with $LiAlH_4$ in the usual way yielded a triol, mp 160–162 °C. The IR [(KBr) 3700–3100 cm^{-1} and no carbonyl absorption], NMR [0.83 (s, 3 H, CH_3), 1.08 (s, 6 H, 2 CH_3), 1.23 (s, 3 H, CH_3), and 1.73 (s, 3 H, CH_3)], and mass [m/e 458 (M^+), 428, 427, 410, 409, 189, and 187] spectra were in accord with structure IIc.

Benulinitriol Triacetate (IId). The triol IIc, on acetylation under conditions as described for IIa, yielded IId, mp 160–162 °C. The IR [(KBr) 1730, 1225 cm^{-1} and no hydroxyl absorption], NMR [two acetyl methyl peaks (1 Hz apart) integrating for 9 protons], and mass [m/e 524, 424, and 452; molecular ion peak at m/e 584 was not observed] spectra were in accord with structure IId.

Anal. Calcd for $C_{36}H_{56}O_6$: C, 73.93; H, 9.65. Found: C, 74.19; H, 9.17.

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Registry No.—I, 59157-84-5; Ia, 59157-88-9; Ib, 61426-07-1; IIa, 61426-08-2; IIb, 61426-09-3; IIc, 61426-10-6; IId, 61426-11-7.

Supplementary Material Available. Tables of atomic coordinates, temperature factors, bond distances, bond angles, and torsion angles (6 pages). Ordering information is given on any current masthead page.

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A Total Synthesis of Biotin Based on Derivatives of 2,5-Dihydrothiophene[1a]

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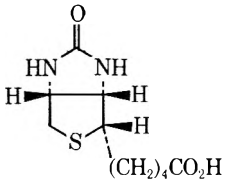
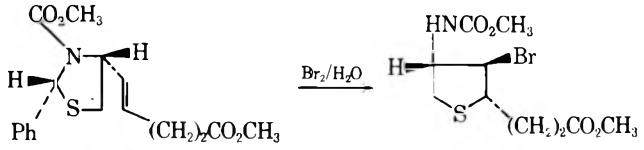
A stereospecific total synthesis of biotin (1) from the ketone **10** has been achieved. The approach features the use of stable derivatives of 2,5-dihydrothiophene (**6**), which allows functional group manipulations at C(3) and C(4) and generation of the all-cis stereochemistry of biotin. The terminal carbomethoxy group of the enamine **11** is selectively hydrolyzed, setting up a modified Curtius reaction of the key acid **16**. The reduction of the mixed diurethane **23** proceeds stereospecifically to afford the all-cis tetrahydrothiophene **24**. Finally, aqueous base simultaneously removes the piperidide protecting group and cyclizes the diurethane substituents directly to the imidazolidone moiety of biotin, which is obtained directly, uncontaminated by any stereoisomers.

A resurgence of interest in the development of new syntheses of the growth promotant *d*-biotin (1) has been sparked by recent disclosures[1b] in the areas of animal health and nutrition. Recently, we reported[2a,b] two total syntheses of this natural product originating from L(+)-cysteine and pimelic acid, respectively. The former approach featured a novel oxidative cyclization of the olefinic thiazolidine **2** to the tetrahydrothiophene **3** and proceeded stereospecifically. The

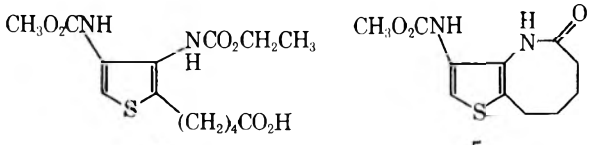


1



2 3

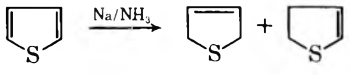
latter effort relied upon catalytic hydrogenation of thiophene substrates such as **4** and **5** in order to generate the required all-cis configuration of the three asymmetric centers of biotin.



4 5

One practical difficulty of this last approach rested in the well-precedented[3] resistance of thiophenes toward reduction, a fact which necessitated the use of rather harsh conditions in this step. We speculated that a synthesis based upon derivatives of a dihydrothiophene might obviate this problem.

Birch first reported[4] the dissolving metal reduction of thiophene to 2,5-dihydrothiophene (**6**), which was isolated but tended to disproportionate, and 2,3-dihydrothiophene (**7**), which readily polymerized.



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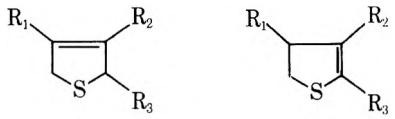
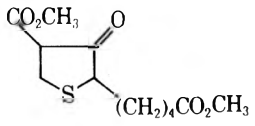
Such ominous precedent augured poorly for the stability of our potential intermediates. However, we planned to elaborate trisubstituted dihydrothiophenes such as **8** or **9**. The substituents must, of course, be capable of transformation into



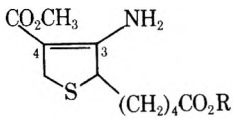
8 9

the biotin framework. The additional constraint of requiring that R_1–R_3 stabilize the intervening double bond would greatly increase our ability to carry out the necessary chemistry in this series.[5] We elected to work with derivatives of 2,5-dihydrophene (compounds related to **8**) in light of the greater stability of the parent **6**.

A simple entry into this class of compounds was achieved by the reaction of the ketone **10**[6] with ammonium formate to



10

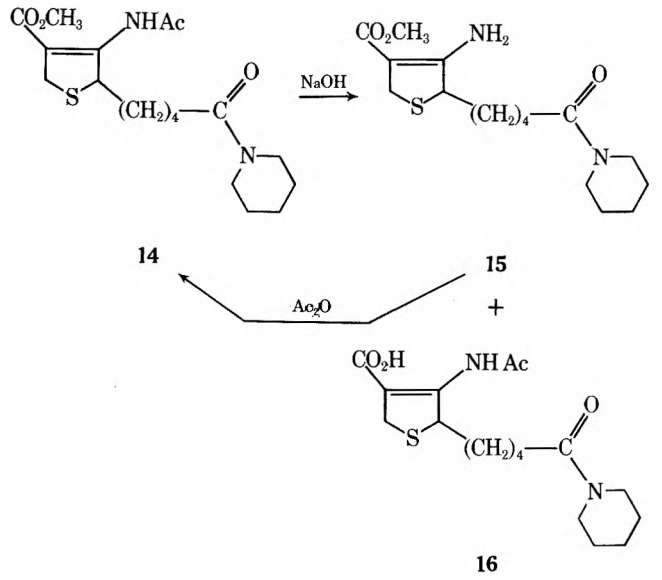


11, R = CH_3
12, R = H
13, R = CO_2Et

yield the enamine diester **11**. This particular substitution pattern afforded a nicely stable dihydrothiophene. Since our plans called for a Curtius reaction[7] at C(4), a differentiation of the redundant ester functionality present in the diester **11** had to be accomplished. Although hydrazine did not distinguish between these esters, methanolic potassium hydroxide selectively hydrolyzed the terminal carbomethoxy group to afford the crystalline monoacid **12**. The ester at C(4) is presumably less susceptible to hydrolysis by virtue of its stabilizing electronic interaction with the C(3) amine.

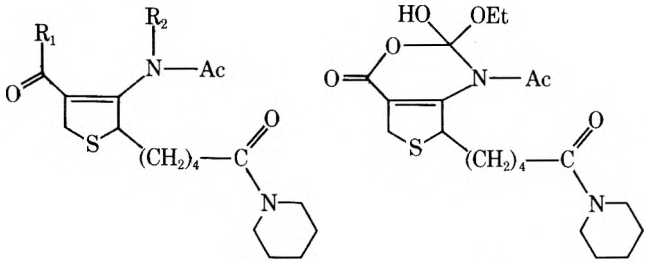
The acid group of **12** was protected as its piperidide **15** by reaction of piperidine with the corresponding mixed anhydride **13**. Acylation of the relatively unreactive amino group of **15** was carried out by acetic anhydride/perchloric acid to yield the acetamide **14** in 92% overall yield based on the ketone **10**. Hydrolysis of the acetamide **14**, which contains four reactive sites, afforded a mixture of the desired acid **16** and the amino ester **15**. These compounds were readily separated during workup by a bicarbonate extraction and the compound **15** was then recycled. In this manner, yields of the acid **16** approached 90%.

The stage was now set for the introduction of the C–N bond at C(4) via a modified Curtius reaction[8] on the acid **16**. This would afford the first dihydrothiophene in our series lacking the electronic stabilization through the C(3)–C(4) double bond that had been relied upon to this point. Treatment of the acid



14 15 16

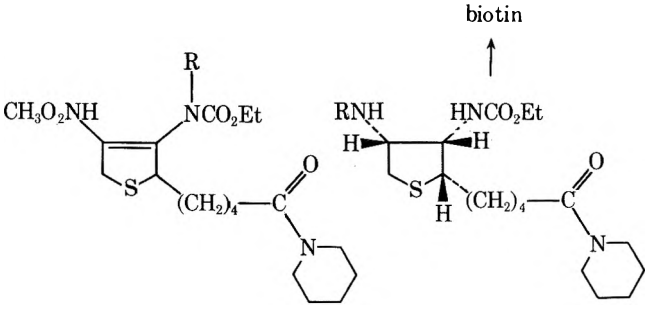
16 with 2 equiv of ethyl chloroformate yielded ultimately the imido mixed anhydride **20**, a result of the initial formation[9]



18

17, $R_1 = OCO_2Et$; $R_2 = H$
19, $R_1 = OH$; $R_2 = CO_2Et$
20, $R_1 = OCO_2Et$; $R_2 = CO_2Et$
21, $R_1 = N_3$; $R_2 = CO_2Et$

of the amido mixed anhydride **17**, intramolecular acyl transfer presumably via **18** to yield the imido acid **19**, and further reaction to the observed product **20**.[10] Addition of sodium azide, which readily selected the most reactive of the five carbonyl groups present in **20**, yielded the desired acyl azide **21** as a colorless oil. The acyl azide **21** underwent a smooth Curtius reaction upon heating in methanol under reflux and yielded the desired imido urethane **22**, containing the required ni-



22, R = Ac
23, R = H
24, R = CO_2CH_3
25, R = H

trogen atom attached to C(4). Mild hydrolysis of **22** with 1 N sodium hydroxide in tetrahydrofuran selectively deacetylated the compound and afforded the crystalline diurethane **23** in an overall yield of 75% from the acid **16**. The product **23** is a stable substance showing no tendency to disproportionate, which was in marked contrast to the properties of 2,5-dihydrothiophene itself.[4]

As had been hoped, catalytic hydrogenation of **23** occurred smoothly under conditions which had no effect upon similarly substituted thiophenes.[11] This reflects the absence of the resonance energy barrier to reduction characteristic of the aromatics.[12] The reduction proceeds stereospecifically, and only the desired all-cis tetrahydrothiophene **24** is produced in 91% yield. Basic hydrolysis of the product **24** led directly to *dl*-biotin (**1**) in 60% yield. Presumably, the less hindered urethane at C(4) is hydrolyzed to the corresponding amine **25**, which then cyclizes onto the C(3) urethane before the latter suffers hydrolysis.[13] This use of a C(3)–C(4) diurethane as a precursor to the imidazolidone moiety of biotin is a convenient and expeditious use of these amine protecting groups which are then partially incorporated into the target molecule.

Thus, the use of suitably chosen derivatives of 2,5-dihydrothiophene as intermediates for a stereospecific total synthesis of biotin has been demonstrated. These compounds are stable representatives of the class and allow the required manipulations to be carried out on the system before they perform the final task of generating the all-cis stereochemistry of biotin.

The resolution of *dl*-biotin to the biologically active *d* enantiomer has been accomplished in excellent yield by Harris and co-workers.[14] Therefore, this work constitutes a total synthesis of *d*-biotin itself.

Experimental Section

Melting points were determined on a Rinco Model M-50 melting point apparatus and are uncorrected. IR spectra were obtained using a Beckman IR-9 spectrophotometer. A Cary 14 recording spectrophotometer was used for UV absorption spectra. NMR spectra were determined with Varian T-60 and HA-100 spectrometers using tetramethylsilane as the internal reference. Mass spectra were recorded on a CEC 21-110B mass spectrometer at 70 eV using a direct insertion probe. Thin layer chromatography was carried out using Merck F-254 silica gel plates.

3-Amino-4-carbomethoxy-2,5-dihydro-2-thiophenevaleric Acid Methyl Ester (11). A solution of 50.0 g (0.182 mol) of 4-carbomethoxy-2-[4,5-dihydrothiophen-3(2*H*)-one]valeric acid methyl ester (**10**) in 550 mL of absolute ethanol was treated with 91.6 g (1.45 mol) of ammonium formate. The reaction mixture was heated under reflux for 5.0 h, cooled, and concentrated. The residue was partitioned between methylene chloride and water. The aqueous phase was further extracted with three 50-mL portions of methylene chloride. The organic extracts were pooled, dried over sodium sulfate, and evaporated, leaving 50 g of enamino diester **11** as a colorless oil, suitable for use in the next step: IR ($CHCl_3$) 3500, 3350 (NH_2), 1735 (ester), 1680 (Ar ester), 1620 (enamine), 1290 cm^{-1}; UV max (CH_3OH) 282 nm (ϵ 10 100); NMR ($CDCl_3$) δ 5.93 (b, 2 H, NH_2), 4.11 (b, 1 H, CH), 4.00–3.60 (m, 2 H, CH_2S), 3.69 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3), 2,32 (t, 2 H, CH_2), 2.0–1.3 (m, 6 H); mass spectrum *m/e* 273 (M^+), 241 (base), 210, 208, 158, 99. For analysis, a sample of **11** was chromatographed on silica, eluting with ethyl acetate/hexane (1:1).

Anal. Calcd for $C_{12}H_{19}NO_4S$ (273.35): C, 52.73; H, 7.01; N, 5.12; S, 11.73; Found: C, 52.53; H, 7.07; N, 4.81; S, 11.43.

3-Amino-4-carbomethoxy-2,5-dihydro-2-thiophenevaleric Acid (12) To a solution of 27.3 g (0.1 mol) of the enamino diester **11** in 250 mL of absolute methanol was added 4.0 g (0.1 mol) of sodium hydroxide. The reaction was heated under reflux for 4.0 h, cooled, and concentrated. The residue was partitioned between methylene chloride and 10% sodium bicarbonate. The aqueous layer was further extracted with methylene chloride. The organic extracts were pooled, dried over sodium sulfate, and evaporated to yield 6.4 g (23%) of unreacted starting material. The aqueous phase was acidified and extracted thrice with methylene chloride. These extracts were dried and evaporated to yield 18.3 g (0.071 mol, 71%) of the monoacid **12** as a tan solid. The recovered enamino diester was recycled using the above procedure to yield an additional 5.3 g of product, bringing the total yield of the monoacid **12** to 23.6 g (0.092 mol, 92%). For analysis, the product was recrystallized from ethyl acetate/petroleum ether to give white cubes: mp 102–103 °C, IR (KBr) 3425, 3300 (NH_2), 2800–2600 (OH), 1740 (ester), 1690 (acid), 1640 (enamine), 1560 cm^{-1}; UV max (CH_3OH) 283 nm (ϵ 13 300); NMR (ME_2SO) δ 11.78 (b, 1 H, acid), 7.00 (b, 2 H, NH_2), 4.01 (b, 1 H, CH), 3.56 (s, 3 H, OCH_3), 3.55 (s, 2 H, CH_2S), 2.30 (t, 2 H, CH_2), 2.0–1.2 (m, 6 H); mass spectrum *m/e* 259 (M^+), 227 (base), 158, 126.

Anal. Calcd for $C_{11}H_{17}NO_4S$ (259.32): C, 50.95; H, 6.61; N, 5.40; S,

12.36. Found: C, 50.96; H, 6.68; N, 5.31; S, 12.29.

3-Amino-4-carbomethoxy-2,5-dihydro-2-thiophenevaleric Acid Piperidide (15). To a solution of 5.18 g (0.02 mol) of the monoacid **12** in 60 mL of tetrahydrofuran at 25 °C was added 2.8 mL (0.02 mol) of triethylamine, followed by 1.98 mL (0.02 mol) of ethyl chloroformate. The reaction was allowed to proceed for 1.5 h and the mixture treated dropwise at 25 °C with 2.0 mL (0.20 mol) of piperidine. After an additional 2.0 h the mixture was concentrated and taken up in 100 mL of methylene chloride. The solution was washed with 10% sodium bicarbonate and 1 N hydrochloric acid and the organic phase was dried and evaporated to afford 6.50 g of the amino ester **15** as a pale yellow oil. This product is used directly in the next step: IR ($CHCl_3$) 3500, 3350 (NH_2), 1680, 1660 (amide, vinylogous urethane), 1440, 1290 cm^{-1}; UV max (CH_3OH) 283 nm (ϵ 10 620); NMR ($CHCl_3$) δ 6.25 (b, 2 H, NH_2), 4.15 (b, 1 H, CH), 3.68 (s, 3 H, OCH_3), 3.8–3.3 (bm, 6 H), 2.3 (t, 2 H, CH_2), 2.0–1.3 (b, 12 H); mass spectrum *m/e* 326 (M^+), 295, 267, 241, 140, 127, 112, 86 (base), 84.

3-Acetamido-4-carbomethoxy-2,5-dihydro-2-thiophenevaleric Acid Piperidide (14). To a solution of 7.4 g (0.0226 mol) of the amino ester **15** in 50 mL of acetic anhydride was added dropwise 1 mL of perchloric acid. The reaction was allowed to proceed for 1.5 h at 25 °C and the mixture concentrated in vacuo. The residue was partitioned between 10% sodium bicarbonate and methylene chloride. The aqueous phase was further extracted with three 30-mL portions of methylene chloride. The organic phases were pooled, dried over sodium sulfate, and evaporated to yield 8.2 g of the acetamide **14** as a colorless oil. Owing to its instability, the product was immediately hydrolyzed to the acid: NMR ($CDCl_3$) δ 6.80 (bs, 1 H, NH), 4.20 (m, 1 H, CH), 3.70 (s, 3 H, OCH_3), 3.8–3.1 (m, 7 H), 2.2 (t, 2 H, CH_2CO), 2.1 (s, 3 H, Ac), 1.8–1.2 (b, 12 H).

3-Acetamido-4-carboxy-2,5-dihydro-2-thiophenevaleric Acid Piperidide (16). A solution of 8.2 g (0.022 mol) of the acetamide **14** in 80 mL of methanol was treated with 40 mL of 1 N sodium hydroxide. The reaction mixture was stirred at 25 °C for 3.0 h and concentrated. The residue was partitioned between methylene chloride and water. The aqueous phase was further extracted with methylene chloride. The organic extracts were combined, dried over sodium sulfate, and evaporated to yield 2.45 g (34%) of the amino ester **15** which was saved for recycling. This aqueous layer was acidified with 50 mL of 1 N hydrochloric acid and extracted with three 75-mL portions of methylene chloride. These organic extracts were pooled, dried, and evaporated to afford 4.8 g [0.0136 mol, 61% (94% corrected)] of the acid **16** as a colorless oil which was used directly in the next step: IR ($CHCl_3$) 3500 (NH), 2800–2500 (acid), 1700, 1620, 1260 cm^{-1}; UV max 268 nm (ϵ 9825); NMR ($CDCl_3$) δ 9.0 (b, 1 H, CO_2H), 5.1 (b, 1 H, NH), 4.0–3.2 (m, 7 H), 2.30 (t, 2 H, CH_2), 2.10 (s, 3 H, NAc), 1.9–1.3 (b, 12 H); mass spectrum *m/e* 354 (M^+), 336, 310 (base), 277, 140.

4-Azidocarbonyl-3-(*N*-carbethoxyacetamido)-2,5-dihydro-2-thiophenevaleric Acid Piperidide (21). A solution of 2.12 g (0.006 mol) of the acid **16** in 25 mL of acetone to which 1.3 mL of water had been added was cooled in an ice bath for 15 min and treated with 1.8 mL (0.0129 mol) of triethylamine in 25 mL of acetone. To this mixture was added dropwise 1.23 mL (0.0129 mol) of ethyl chloroformate in 2.7 mL of acetone. The reaction was allowed to proceed at 0 °C for 1 h. At this point a solution of 0.8 g (0.0063 mol) of sodium azide in 5 mL of water was added dropwise over 5 min. The mixture was stirred at 0 °C for an additional 2 h and then partitioned between ice water and methylene chloride. The aqueous phase was further extracted with methylene chloride. The organic extracts were combined, dried over sodium sulfate, and evaporated to afford 2.8 g of the acyl azide **21** as a colorless oil: IR (CH_2Cl_2) 2100 (N_3), 1740 (acyl azide), 1690 (piperidide), 1680 (CO_2Et), 1620, 1200 cm^{-1}.

3-(*N*-Carbethoxyacetamido)-4-carbomethoxyamino-2,5-dihydro-2-thiophenevaleric Acid Piperidide (22). A solution of 2.8 g (0.066 mol) of the acyl azide **21** in 50 mL of methanol was slowly brought up to reflux temperature over a 15-min period. The reaction mixture was maintained at that temperature for 5.0 h, cooled, and evaporated to yield 2.33 g (0.0056 mol, 85%) of the imido urethane **22** as a colorless oil. The product can be used in the next step without further purification: IR ($CHCl_3$) 3410 (NH), 1740 (urethanes), 1710, 1690 (amides), 1620, 1500, 1260 cm^{-1}; UV max (CH_3OH) 230 (infl) (ϵ 12 040), 275 nm (sh) (ϵ 720); NMR ($CDCl_3$) δ 6.4 (b, 1 H, NH), 4.20 (q, 2 H, OCH_2), 4.10 (bs, 1 H, CH), 4.0–3.2 (m, 7 H), 3.8 (s, 3 H, OCH_3), 2.53 (s, 3 H, NAc), 2.30 (t, 2 H, CH_2), 1.8–1.3 (b, 12 H), 1.3 (t, 3 H, CH_3); mass spectrum *m/e* 455 (M^+), 423, 380, 292 (base), 276.

3-Carbethoxyamino-4-carbomethoxyamino-2,5-dihydro-2-thiophenevaleric Acid Piperidide (23). A solution of 100 mg (0.219 mol) of the imido urethane **22** in 10 mL of tetrahydrofuran was treated with 2 mL of 1 N sodium hydroxide, stirred at 25 °C for 2.0 h, and concentrated in vacuo. The residue was partitioned between water and methylene chloride. The aqueous phase was further extracted with methylene chloride. The organic extracts were pooled, dried over sodium sulfate, and evaporated to give 80 mg (90%) of the diurethane **23** as a white solid. For analysis, the product was recrystallized from ethyl acetate to give white needles: mp 121–122 °C; IR (KBr) 3550, 3400 (NH), 1730 (urethanes), 1690 (amide), 1520, 1300, 1240 cm^{-1}; UV max (CH_3OH) 205 nm (ϵ 15 200), 232 (sh) (9700); NMR ($CDCl_3$) δ 7.35 (bd, 1 H, NH), 7.12 (bd, 1 H, NH), 4.20 (q, 2 H, OCH_2), 4.0 (b, 1 H, CH), 3.80 (s, 3 H, OCH_3), 4.0–3.2 (m, 6 H), 2.4 (t, 2 H, CH_2), 2.0–1.4 (m, 12 H), 1.3 (t, 3 H, CH_3); mass spectrum *m/e* 413 (M^+), 381, 367, 338, 324, 292 (base).

Anal. Calcd for $C_{19}H_{31}N_3O_5S$ (413.54): C, 55.19; H, 7.56; N, 10.16; S, 7.75. Found: C, 54.97; H, 7.63; N, 10.24; S, 7.95.

***all-cis*-3-Carbethoxyamino-4-carbomethoxyamino-2-tetrahydrothiophenevaleric Acid Piperidide (24).** A solution of 347 mg (0.840 mmol) of the diurethane **23** in 200 mL of acetic acid was hydrogenated at 50 °C for 10.0 h at a pressure of 1800 psi in the presence of 2.0 g of 10% Pd/C catalyst. The autoclave was cooled and vented, and the catalyst was filtered and washed with acetic acid. The filtrate was evaporated to dryness and the residue dried under high vacuum to give 320 mg (91%) of the all-cis tetrahydrothiophene **24**, which traveled as one spot in several TLC systems. The product was obtained as a colorless oil and was suitable as such for direct conversion to *dl*-biotin: IR (CH_2Cl_2) 3320 (NH), 1730 (urethanes), 1640 (amide), 1540, 1240 cm^{-1}; NMR ($CDCl_3$) δ 6.3 (b, 1 H, NH), 5.8 (b, 1 H, NH), 4.8–4.0 (bm, 5 H), 3.8 (s, 3 H, OCH_3), 3.8–3.0 (m, 6 H), 2.2 (t, 2 H, CH_2CO), 2.0–1.3 (b, 12 H), 1.2 (t, 3 H, CH_3).

***dl*-Biotin (1).** A sample of 320 mg (0.77 mmol) of the all-cis tetrahydrothiophene **24** in 5 mL of 1 N sodium hydroxide was heated under reflux for 4.0 h, cooled, and acidified to pH 1 with 1 N hydrochloric acid. Pure *dl*-biotin separated from the solution as a white solid which was collected by filtration. The yield after drying was 113 mg (60%). The product was recrystallized from water to yield an analytical sample, mp 232–233 °C, identical in all respects with an authentic sample of *dl*-biotin: IR (KBr) 3300, 3250 (NH), 2700–2500 (acid), 1705 (urea), 1690 cm^{-1} (acid); NMR (Me_2SO) δ 6.7 (bs, 1 H, NH), 6.5 (bs, 1 H, NH), 4.30 (m, 2 H, NCHCHN), 3.15 (b, 1 H, CHS), 2.75 (m, 2 H, CH_2S), 2.22 (t, 2 H, CH_2), 1.5 (bm, 6 H); mass spectrum *m/e* 244 (M^+), 184, 112, 97 (base), 85. No biotin stereoisomers were detected in this reaction.

Anal. Calcd for $C_{10}H_{16}N_2O_3S$ (244.29): C, 49.16; H, 6.60; N, 11.47; S, 13.12. Found: C, 49.12; H, 6.52; N, 11.50; S, 13.40.

Acknowledgment. We wish to thank the staff of the Physical Chemistry Department of Hoffmann-La Roche for the determination of spectral and analytical data.

Registry No.—**1**, 22377-59-9; **10**, 59851-05-7; **11**, 61617-88-7; **12**, 61617-89-8; **14**, 61617-90-1; **15**, 61617-91-2; **16**, 61617-92-3; **21**, 61617-93-4; **22**, 61617-94-5; **23**, 61617-95-6; **24**, 61617-96-7; ammonium formate, 540-69-2; piperidine, 110-89-4.

References and Notes

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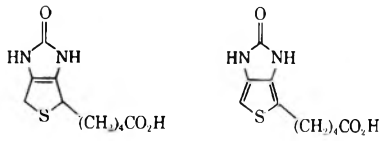
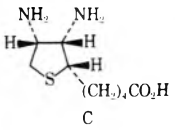


A B



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of the American Chemical Society, San Francisco, Calif., Aug 29–Sept 3, 1976.

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Mesoionic Compounds. 39. Synthesis of Some Functionally Substituted Five-Membered Systems Using 1,2-Bielectrophiles as Cyclization Agents[1a]

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α-Bromoacyl chlorides, functioning as 1,2-bielectrophiles, undergo ready reaction in the presence of Et_3N with several monoprotonic 1,3-binucleophiles to provide an especially convenient synthesis of some five-membered mesoionic ring systems containing diverse functional substituents. The *anhydro*-4-hydroxythiazolium hydroxide system results from N-monosubstituted thioamide derivatives, the *anhydro*-4-hydroxy-1,3-dithiolium hydroxide system from dithiobenzoic acids, and the *anhydro*-5-hydroxy-1,3-oxathiolium hydroxide system from thiobenzoic *S*-acids. These ring systems all undergo ready cycloaddition with dimethyl acetylenedicarboxylate to provide a convenient synthetic procedure for thiophenes containing a variety of substituents in the 2 position.

The majority of five-membered mesoionic ring systems can generally be synthesized[2] by one of five synthetic routes involving either (1) a cyclodehydration; (2) a cyclization via an intermediate isocyanate or isothiocyanate; (3) cyclizations involving nitriles; (4) interconversion of other mesoionic systems; or (5) dealkylation of suitable quaternary heterocycles. The cyclodehydrative process has been widely applied and, as would be anticipated, an extensive variety of cyclodehydration agents has been utilized. The synthesis of the appropriately substituted carboxylic acid precursor often presents difficulties, and in this report we describe a simple and effective route to several of these ring systems that not only overcomes the above disadvantages but also enables functional groups other than the usual alkyl and aryl groups to be introduced into the ring system. These syntheses are now readily accomplished by using a suitable monoprotonic 1,3-binucleophile with a 1,2-bielectrophile such as an α-haloacyl halide, and the following applications illustrate this synthetic approach.

***anhydro*-4-Hydroxythiazolium Hydroxide System.** The usual method of preparation[3a–c] of this system involves the S-alkylation of N-monosubstituted thioamides with an α-halo acid, followed by cyclodehydration of the resulting acid with Ac_2O/Et_3N. This method was often unsuccessful with thioamides containing a variety of substituents attached to the thioxo carbon atom; e.g., attempted alkylation of the thiourea **1** [R = $N(CH_3)_2$] or the dithiocarbamate **1** (R = SR) with α-bromophenylacetic acid (**2**, R^1 = Ph; X = Br; Y = OH) led to hydrolysis products, while the use of ethyl α-bromomalonate (**2**, R^1 = COOEt; X = Br; Y = OH) as an alkylating agent for thiobenzanilide was complicated by concomitant decarboxylation. However, the use of an α-bromoacyl chloride derivative **2** (R^1 = Ph, COOEt; X = Br; Y = Cl) allows the initial alkylation and subsequent ring closure to be accomplished in one step. The intermediate **3** (Y = Cl) is most likely involved, although the ketene derived from it by loss of HCl cannot be definitely excluded. The various substituted derivatives of **4** prepared by this procedure are described in Table I. In this instance the thioamide behaves as a 1,3-binucleophile, resulting in the formation of a five-membered ring on reaction with the 1,2-bielectrophile. In an earlier publication[3d] the reaction of the thioamide with a 1,3-bielectrophile, chlorocarbonylphenylketene, resulted in the ready formation of the six-membered mesoionic system, *anhydro*-6-hydroxy-4-oxo-2,3,5-trisubstituted-4*H*-1,3-thiazinium hydroxide, in excellent yields.

It is possible for four different intermediates to be involved, depending on the site of the initial condensation, but only two isomeric reaction products are possible. If reaction had occurred initially at the acid chloride function to give the intermediate **5**, then ring closure would result in formation of the isomeric *anhydro*-5-hydroxythiazolium hydroxide system **6**. The formation of **6** was excluded in two ways. The intermediate acid **3** (R = *S*-alkyl; R^1 = Ph; Y = OH) was prepared and cyclized with dicyclohexylcarbodiimide to **4** (R = *S*-alkyl;

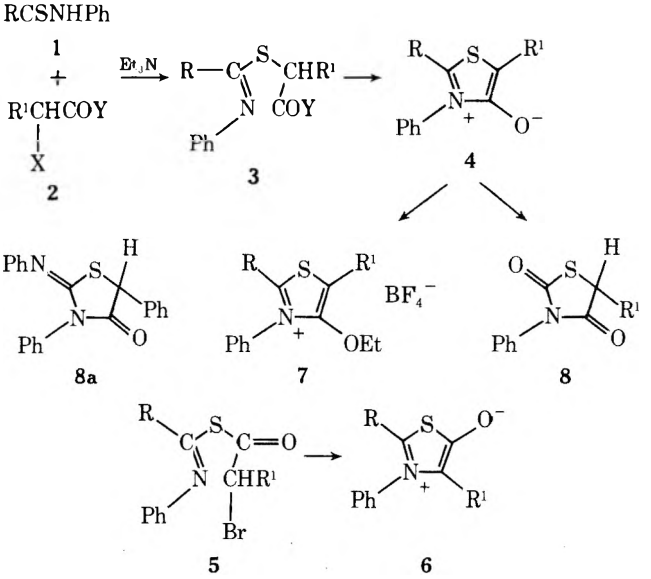
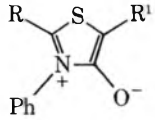
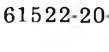


Table I. *anhydro*-4-Hydroxythiazolium Hydroxide Derivatives[j]



Registry no.	Substituents R	Substituents R¹	Mp, °C	Yield, %	Crystal habit	Mol formula	M⁺· (rel int)	λ_{max} (CH_3OH), nm (log ε)	ν_{CO}, cm^{-1}	$\nu_{C=N}$, cm^{-1}	NMR, δ ($CDCl_3$)
61522-15-4	CH_3S	Ph	158–160	78	Golden prisms[a]	$C_{16}H_{13}NOS_2$	299 (30)	243 (4.02), 273 (3.99), 417 (4.04)	1620	1585	7.95–7.00 (m, 10, aromatic), 2.55 (s, 3, SCH_3)
61522-16-5	EtS	Ph	131–133	75	Orange prisms[b]	$C_{17}H_{15}NOS_2$	313 (32)	251 (4.03), 273 (4.01), 421 (4.04)	1630	1590	8.00–7.05 (m, 10, aromatic), 3.00 (q, 2, SCH_2CH_3), 1.37 (t, 3, SCH_2CH_3)
61522-17-6	*n*-PrS	Ph	131–133	76	Orange prisms[b]	$C_{18}H_{17}NOS_2$	327 (38)	241[c] (3.68), 276[c] (3.71), 422 (3.77)	1630	1595	8.00–7.00 (m, 10, aromatic), 2.98 (t, 2, $SCH_2CH_2CH_3$), 1.75 (h, 2, $SCH_2CH_2CH_3$), 1.00 (t, 3, $SCH_2CH_2CH_3$)
61522-18-7	PhS	Ph	166–168	61	Orange prisms[b]	$C_{21}H_{15}NOS_2$	361 (48)	252 (4.05), 270[c] (4.01), 430 (4.00)	1640	1600	7.90–7.10 (m, aromatic)
61522-19-8	EtS	COOEt	168–169.5	57	Yellow prisms[d]	$C_{14}H_{15}NO_3S_2$	309 (29)	247 (4.12), 373 (3.99)	1675 1645	1595	7.65–7.18 (m, 5, aromatic), 4.30 (q, 2, $CO_2CH_2CH_3$), 3.20 (q, 2, SCH_2CH_3), 1.45 (t, 3, $CO_2CH_2CH_3$), 1.35 (t, 3, SCH_2CH_3)
61522-20-1		Ph	156.6–158.5 dec	64	Golden-yellow prisms[e]	$C_{19}H_{18}N_2O_2S$	338 (31)	237[c] (4.10), 292 (3.96), 392 (3.71)	1640	1590	7.80–6.85 (m, 10, aromatic), 3.60–3.25 (m, 4, OCH_2CH_2N), 3.10–2.78 (m, 4, OCH_2CH_2N)
61522-21-2	$(CH_3)_2N$	Ph	150 dec	58	Gold needles[f]	$C_{17}H_{16}N_2OS$	296 (33)	238 (4.09), 304 (4.04), 408 (3.84)[g]	1640	1630	7.80–7.00 (m, 10, aromatic), 2.70 [s, 6, $(CH_3)_2N$]
61522-22-3	$(CH_3)_2N$	COOEt	198–199.5	25	Cream plates[f]	$C_{14}H_{16}N_2O_3S$	292 (10)	258 (4.00), 345 (3.90)	1680	1620	7.53–7.13 (m, 5, aromatic), 4.22 (q, 2, $CO_2CH_2CH_3$), 2.88 [s, 6, $(CH_3)_2N$], 1.30 (t, 3, $CO_2CH_2CH_3$)
61522-23-4	CN	Ph	188–190 dec	30	Red needles[a]	$C_{16}H_{10}N_2OS$	278 (50)	272 (4.05), 310[c] (3.52), 489 (4.24)[g]	1630	2190 ($\nu_{C\equiv N}$)	8.25–7.25 (m, 10, aromatic)
18100-80-6	Ph	Ph	253–256[h]	76	Red-orange needles[f]	$C_{21}H_{15}NOS$					
61522-24-5	Ph	COOEt	160–161	54	Brilliant yellow needles[i]	$C_{18}H_{15}NO_3S$	325 (12)		1680 1660		
52730-98-0	*p*-ClC_6H_4	Ph	197–199 dec	71	Red needles[b]	$C_{21}H_{14}ClNOS$	363 (3)	268 (4.31), 449 (4.19)	1625	1590	7.02–6.90 (m, aromatic)
61522-25-6	*p*-ClC_6H_4	COOEt	154–154.5	23	Golden-yellow prisms[e]	$C_{18}H_{14}ClNO_3S$	359 (9)	226[c] (4.23), 247[c] (4.12), 396 (3.76)	1680 1665	1595	7.57–7.00 (m, 9, aromatic), 4.34 (q, 2, $CO_2CH_2CH_3$), 1.37 (t, 3, $CO_2CH_2CH_3$)
61522-26-7	*p*-$CH_3OC_6H_4$	Ph	187.5–189.5	65	Orange prisms[b]	$C_{22}H_{17}NO_2S$	359 (0.5)	277 (4.12), 297[c] (4.03), 443 (4.12)	1630	1600	7.15–6.65 (m, 14, aromatic), 3.75 (s, 3, OCH_3)
61522-27-8	*p*-$CH_3OC_6H_4$	COOEt	194–195	33	Golden-yellow prisms[e]	$C_{19}H_{17}NO_4S$	355 (13)	227 (4.19), 302 (3.88), 398 (3.06)	1655	1600	7.6–6.7 (m, 9, aromatic), 4.37 (q, 2, $CO_2CH_2CH_3$), 3.8 (s, 3, OCH_3), 1.37 (t, 3, $CO_2CH_2CH_3$)

[a] Crystallized from benzene. [b] Crystallized from benzene–petroleum ether F. [c] Shoulder. [d] Crystallized from $CHCl_3$–petroleum ether F. [e] Crystallized from $CHCl_3$–ether. [f] Crystallized from acetone. [g] $CHCl_3$ solvent. [h] Lit.[3c] mp 251–252 °C. [i] Crystallized from benzene–ether. [j] Satisfactory analytical values (±0.4% for C, H, N) were reported for all compounds in table.

Table II. Thiophenes Obtained from 4 and Acetylenic Dipolarophiles[f]

Registry no.	Substituent R	Substituent R^1	Substituent R^2	Mp, °C	Yield, %	Crystal habit	Mol formula	M^+. (rel int)	λ_{max} (CH_3OH), nm (log ϵ)	ν_{CO},[e] cm^{-1}	NMR, δ ($CDCl_3$)
61522-09-6	CH_3S	Ph	$COOCH_3$	130–131	67	Cream prisms[d]	$C_{15}H_{14}O_4S_2$	322 (100)	236 (4.37), 313 (4.16)	1730 1700	7.40 (s, 5, aromatic), 3.85 (s, 3, CO_2CH_3), 3.80 (s, 3, CO_2CH_3), 2.60 (s, 3, SCH_3)
61522-10-9	CH_3S	Ph	COOH	235–237	100	Colorless prisms[b]	$C_{13}H_{10}O_4S_2$	294 (19)	227 (4.16), 309 (3.92)	1730 1675	7.55 (s, 5, aromatic), 2.62 (s, 3, SCH_3)
61522-11-0	EtS	Ph	$COOCH_3$	117–119	63	Colorless prisms[d]	$C_{16}H_{16}O_4S_2$	336 (100)	235 (4.26), 313 (4.02)	1730 1700	7.42 (s, 5, aromatic), 3.90 (s, 3, CO_2CH_3), 3.80 (s, 3, CO_2CH_3), 3.05 (q, 2, SCH_2CH_3), 1.41 (t, 3, SCH_2CH_3)
61522-12-1	*n*-PrS	Ph	$COOCH_3$	74–76	46	Cream prisms[d]	$C_{17}H_{18}O_4S_2$	350 (100)	236 (4.35), 315 (4.11)	1730 1700	7.45 (s, 5, aromatic), 3.90 (s, 3, CO_2CH_3), 3.80 (s, 3, CO_2CH_3), 3.01 (t, 2, $SCH_2CH_2CH_3$), 1.80 (h, 2, $SCH_2CH_2CH_3$), 1.08 (t, 3, $SCH_2CH_2CH_3$)
61522-13-2	$(CH_3)_2N$	Ph	$COOCH_3$	108–109	69	Cream plates[c]	$C_{16}H_{17}NO_4S$	319 (100)	203 (4.33), 227 (4.27), 319 (4.08)	1740 1700	7.24 (m, 5, aromatic), 3.68 (s, 3, CO_2CH_3), 3.63 (s, 3, CO_2CH_3), 2.88 (s, 6, $(CH_3)_2N$)
61522-14-3	$(CH_3)_2N$	COOEt	$COOCH_3$	89–91	16	Colorless needles[c]	$C_{13}H_{17}NO_6S$	315 (100)	215 (4.05), 238 (3.96), 305[d] (3.91), 335 (4.20)	1740 1710 1680	4.28 (q, 2, $CO_2CH_2CH_3$), 3.93 (s, 3, CO_2CH_3), 3.78 (s, 3, CO_2CH_3), 3.07 [s, 6, $(CH_3)_2N$], 1.32 (t, 3, $CO_2CH_2CH_3$)

[a] From benzene–petroleum ether F. [b] From aqueous ethanol. [c] From CH_3OH. [d] Shoulder. [e] KBr. [f] Satisfactory analytical values (±0.4% for C, H, N) were reported for all compounds in table.

R^1 = Ph) giving products identical with those obtained in the direct condensation above. Also on reaction with dimethyl acetylenedicarboxylate substituted thiophenes rather than pyrrole derivatives were obtained, the latter resulting from reaction of the ring system **6** with acetylenic dipolarophiles.[3e] These thiophenes are described in Table II, and, in one instance, hydrolysis to the corresponding dicarboxylic acid was utilized to characterize further the product obtained from the cycloaddition.

The introduction of an alkyl- or arylthio group into the 2 position of **4** was achieved by using the appropriate alkyl or aryl phenyldithiocarbamate **1** (R = SCH_3, SC_2H_5, S-*n*-C_3H_7, and SPh) prepared by treatment of ammonium phenyldithiocarbamate with excess of the appropriate alkyl (or aryl) halide in aqueous solution at room temperature. Modification of the original procedure,[4] as described in the Experimental Section, results in improved yields of products. Addition of α-bromophenylacetyl chloride[5] in an inert solvent such as benzene, ether, or tetrahydrofuran to the alkyl (or aryl) phenyldithiocarbamate in benzene followed by the slow addition of Et_3N resulted in the separation of triethylamine HCl/HBr, and the mesoionic system **4** was obtained by concentration of the filtrate. 2-Bromo-2-ethoxycarbonylacetyl chloride[6] (**2**, R^1 = COOEt; X = Br; Y = Cl) also reacted readily, allowing the introduction of an ethoxycarbonyl substituent into the 5 position of **4**.

The structures of these *anhydro*-4-hydroxythiazolium hydroxides **4** follow from their spectral characteristics (Table I) and their conversion with Meerwein's reagent into the 4-ethoxythiazolium salts **7**. They also underwent ready hydrolysis[7] to the appropriate thiazolidine-2,4-diones **8**. Thus the *anhydro*-2-alkylthio-3,5-diphenyl-4-hydroxythiazolium hydroxides (**4**, R = CH_3S, C_2H_5S, *n*-C_3H_7S; R^1 = Ph) were hydrolyzed in boiling aqueous ethanol (1:2) over 3–4 h giving 3,5-diphenylthiazolidine-2,4-dione[8] (**8**, R^1 = Ph), characterized by two carbonyl absorptions at 171.3 and 169.4 ppm in its ^{13}C NMR spectrum. However, the *anhydro*-2-alkylthio-5-ethoxycarbonyl-4-hydroxy-3-phenylthiazolium hydroxides (**4**, R = *S*-alkyl; R^1 = COOEt) required a 7-h reflux in dilute HCl to effect hydrolysis and in this case hydrolysis of the ester substituent and subsequent decarboxylation occurred as 3-phenylthiazolidine-2,4-dione[9] (**8**, R^1 = H) was obtained.

In the *anhydro*-2-alkylthio-3,5-diphenyl-4-hydroxythiazolium hydroxides (**4**, R = *S*-alkyl; R^1 = Ph) the exocyclic sulfur atom no doubt contributes to the stability of the system by reducing the positive charge on the thioamide portion of the nucleus. This was reflected to some degree by the reduced yields of the thiophenes obtained from their cycloadditions with dimethyl acetylenedicarboxylate. It was also of interest to study the effect of a 2-alkoxyl substituent on the stability of the ring system and use of an *O*-alkyl phenylthiocarbamate (**1**, R = OCH_3, OC_2H_5) in the above reactions should lead to the desired product. Reaction with the acid chloride **2** (R^1 = Ph; X = Br; Y = Cl) always led to an oil from which only the thiazolidine-2,4-dione **8** (R^1 = Ph) could be isolated, indicating a marked susceptibility of the ring system to hydrolysis at the 2 position when a 2-alkoxy substituent is at that position.

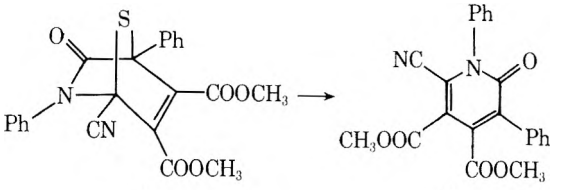
Use of substituted thioureas in the initial condensation provides a convenient method for the introduction of a 2-disubstituted amino substituent. Thus *N*-(*N*-phenylthiocarbamoyl)morpholine (**1**, R = *N*-morpholino) and α-bromophenylacetyl chloride in the presence of Et_3N gave in good yield *anhydro*-3,5-diphenyl-4-hydroxy-2-morpholinothiazolium hydroxide (**4**, R = *N*-morpholino; R^1 = Ph). In addition to its spectral characteristics (Table I), it was characterized by hydrolysis with hot dilute HCl to 3,5-diphenylthiazolidine-2,4-dione (**8**, R^1 = Ph). Other representatives of **4** with 2-amino substituents prepared by this procedure are also described in Table I and the substituted thiophenes obtained

from their cycloaddition with dimethyl acetylenedicarboxylate are reported in Table II.

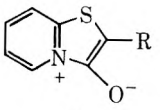
2-Alkylthiothiazoles undergo reaction with primary and secondary amines such as methylamine, morpholine, and piperidine and the 2-alkylthio substituent is replaced by the amino group.[9] However, in this present study replacement of the 2-alkylthio substituent in **4** with a 2-morpholino group could not be effected under a variety of conditions. It should also be mentioned that reaction of *N*-(*N*-phenylthiocarbamoyl)morpholine (**1**, R = *N*-morpholino) with α-bromophenylacetic acid did not give the expected intermediate acid **3** (R = *N*-morpholino; R^1 = Ph; Y = OH). Rather ring closure to **4** and concomitant hydrolysis occurred under the reaction conditions so that 3,5-diphenylthiazolidine-2,4-dione (**8**, R^1 = Ph) was obtained. Similar results were observed with *N,N*-dimethyl-*N'*-phenylthiourea and α-bromophenylacetic acid.

N,N'-Diphenylthiourea (**1**, R = PhNH) and α-bromophenylacetyl chloride also underwent ready reaction and in this case, as the substituent pattern in **1** precluded formation of the mesoionic system, 3,5-diphenyl-2-phenylimino-4-thiazolidone (**8a**) was obtained. This was hydrolyzed to 3,5-diphenylthiazolidine-2,4-dione (**8**, R^1 = Ph) with hot, 40% aqueous H_2SO_4, and its formation provides additional evidence in support of the general reaction pathway described above.

This present procedure allows considerable diversity in the substituents to be introduced into **4**. Thus using a variety of thiobenzanilides (**1**, R = aryl) with α-bromophenylacetyl chloride or 2-bromo-2-ethoxycarbonylacetyl chloride resulted in ready formation of *anhydro*-4-hydroxythiazolium hydroxide derivatives **4** with additional 2 substituents as described in Table I. All these underwent ready cycloaddition with dimethyl acetylenedicarboxylate to form the corresponding thiophene except *anhydro*-2-cyano-3,5-diphenyl-4-hydroxythiazolium hydroxide (**4**, R = CN; R^1 = Ph), formed from 1-cyanothioformanilide[11] (**1**, R = CN) and α-bromophenylacetyl chloride. In this case, instead of elimination of phenyl isocyanate from the intermediate **9**, sulfur was lost and dimethyl 6-cyano-1,3-diphenyl-2-oxopyridine-4,5-dicarboxylate (**10**) was formed, although trace amounts of the



9 **10**

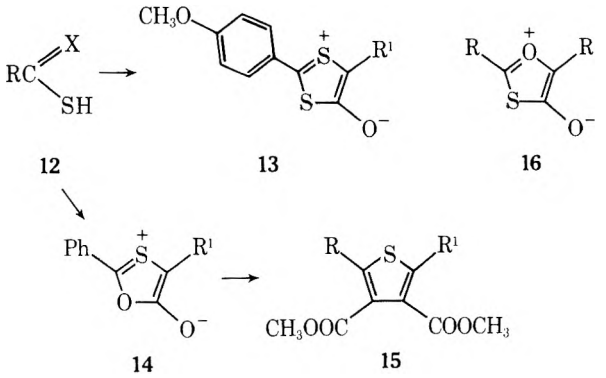


11

corresponding thiophene were apparently present (TLC) in the crude reaction mixture. This is not unexpected as the reaction of **4** (R = R^1 = Ph) with dicyanoacetylene resulted in a mixture of the corresponding thiophene and pyridone.[3a] The 5-ethoxycarbonyl group apparently reduces the dipolar characteristics of the ring system as **4** (R = Ph; R^1 = COOEt) was recovered in practically quantitative amount from prolonged reflux in xylene in the presence of 2-pyridylacetylene.

This procedure is as equally readily applicable to fused thiazole systems.[12] Thus 2-mercaptopyridine reacted readily with α-bromophenylacetyl chloride in the presence of Et_3N to give *anhydro*-3-hydroxy-2-phenylthiazolo[3,2-*a*]pyridinium hydroxide (**11**, R = Ph) and the corresponding 2-ethoxycarbonyl derivative (**11**, R = COOEt) was obtained using 2-bromo-2-ethoxycarbonylacetyl chloride. The ring system **11** did not undergo cycloaddition with dimethyl acetylenedicarboxylate.

***anhydro*-4-Hydroxy-1,3-dithiolium Hydroxide System.** This ring system has been prepared[13] by cyclodehydration of thioaroylthioglycollic acids with Ac_2O/Et_3N and, like the thiazolium system above, is an attractive precursor to substituted thiophenes. Reaction of *p*-methoxydithiobenzoic acid (**12**, R = *p*-$CH_3OC_6H_4$; X = S) with the above 1,2-bielectrophiles now provides an extremely ready entry into the 1,3-dithiolium system as the dithiobenzoic acids themselves are conveniently prepared[14] from aryl Grignard reagents and CS_2. Thus from **12** (R = *p*-$CH_3OC_6H_4$; X = S) and α-bromophenylacetyl chloride, *anhydro*-4-hydroxy-2-*p*-methoxyphenyl-5-phenyl-1,3-dithiolium hydroxide (**13**, R^1 = Ph) was obtained



12 **13** **16**

14 **15**

in satisfactory yield and the corresponding 5-ethoxycarbonyl derivative **13** (R^1 = COOEt) was prepared using 2-bromo-2-ethoxycarbonylacetyl chloride. Although **13** (R^1 = Ph) underwent cycloadditions with dimethyl acetylenedicarboxylate, **13** (R^1 = COOEt) did not, no doubt owing to delocalization of the negative charge over the 5-ethoxycarbonyl substituent which was reflected in the infrared absorptions of the carbonyl groups at 1660 and 1650 cm^{-1}. It also did not form a cycloadduct with 2-pyridylacetylene, a reactive dipolarophile.

***anhydro*-5-Hydroxy-1,3-oxathiolium Hydroxide System.** This ring system has been found to be extremely unstable, with a strong electron-withdrawing substituent in the 4 position of the nucleus being necessary for isolation of the ring system. *anhydro*-2-*p*-Chlorophenyl-5-hydroxy-4-trifluoroacetyl-1,3-oxathiolium hydroxide has been prepared[15] by cyclodehydration of *p*-chlorobenzoylthioglycollic acid with trifluoroacetic anhydride and it was very susceptible to hydrolysis. Reaction of thiobenzoic *S*-acid (**12**, R = Ph; X = O) with α-bromophenylacetyl chloride/Et_3N gave *anhydro*-5-hydroxy-2,4-diphenyl-1,3-oxathiolium hydroxide (**14**, R^1 = Ph) which was not isolated but reacted with dimethyl acetylenedicarboxylate to form the thiophene **15** (R = R^1 = Ph). Reaction of **12** (R = Ph; X = O) with 2-bromo-2-ethoxycarbonyl chloride, however, did not result in formation of the ring system. The product obtained was identified as dibenzoyl disulfide, apparently formed by oxidation of **12** (R = Ph; X = O) by the 2-bromo-2-ethoxycarbonylacetyl chloride, similar oxidations having been observed by other reactive bromo compounds.[16] A recent communication[17] describes the preparation of the isomeric system, *anhydro*-4-hydroxy-1,3-oxathiolium hydroxide system **16**, by ring closure of a thiocarbonyloxyacetic acid with Ac_2O. Like **14**, the isomeric system **16** was too unstable for isolation but could be trapped with acetylenic dipolarophiles, in this case affording a convenient entry into substituted furan systems.

Experimental Section[18]

Reaction of *N,N*-Dimethyl-*N'*-phenylthiourea and α-Bromophenylacetic Acid. Attempted Preparation of *anhydro*-2-

Dimethylamino-3,5-diphenyl-4-hydroxythiazolium Hydroxide. *N,N*-Dimethyl-*N'*-phenylthiourea [**1**, R = $(CH_3)_2N$] (0.54 g, 0.003 mol), α-bromophenylacetic acid (**2**, R^1 = Ph; X = Br; Y = OH) (0.65 g, 0.003 mol), and Et_3N (0.31 g, 0.003 mol) were refluxed in dry benzene (25 mL) for 2 h. Filtration of the Et_3N·HBr and evaporation of the benzene gave 3,5-diphenylthiazolidine-2,4-dione (**8**, R^1 = Ph) as a yellow solid which crystallized from EtOH as colorless, matted needles: 0.18 g (22%); mp 173–175 °C (lit.[8] mp 172.5–173 °C); IR (KBr) 3050 (CH), 1750 (CO), 1680 cm^{-1} (CO); NMR ($CDCl_3$) δ 5.42 (s, 1, H_5), 7.47 (s, 10, aromatic); mass spectrum *m/e* (rel intensity) M^+· 269 (90).

Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66,89; H, 4.12; N, 5.20. Found: C, 66.52; H, 4.02; N, 5.17.

Similarly 1-morpholinothioformanilide (**1**, R = C_4H_8NO) (0.67 g, 0.003 mol), α-bromophenylacetic acid (0.65 g, 0.003 mol), and Et_3N (0.31 g, 0.003 mol) were refluxed in dry benzene (30 mL) for 2 h. Filtration of the Et_3N·HBr and evaporation of the solvent gave a yellow solid which crystallized from ethanol as colorless, matted needles identical with 3,5-diphenylthiazolidine-2,4-dione: 0.4 g (49%); mp 173–175 °C; mmp 173–175 °C. The dione was also obtained in the reaction of *O*-methyl (or *O*-ethyl) phenylthiocarbamate and α-bromophenylacetic acid.

General Procedure for the Reaction of N-Monosubstituted Thioamides with 1,2-Bielectrophiles. Preparation of *anhydro*-2-Dimethylamino-3,5-diphenyl-4-hydroxythiazolium Hydroxide [4, R = $(CH_3)_2N$; R^1 = Ph]. α-Bromophenylacetyl chloride (**2**, R^1 = Ph; X = Br; Y = Cl) (0.7 g, 0.003 mol) in $CHCl_3$ (10 mL) was added dropwise to a stirred solution of *N,N*-dimethyl-*N'*-phenylthiourea [**1**, R = $(CH_3)_2N$] (0.54 g, 0.003 mol) in dry $CHCl_3$ (10 mL). After 5 min, Et_3N (0.61 g, 0.006 mol) in dry $CHCl_3$ (5 mL) was added dropwise and the resulting yellow solution stirred for 5 min before being washed with two equal portions of H_2O. After separation and drying over Na_2SO_4, the $CHCl_3$ solution was reduced in volume to 2–3 mL and addition of Et_2O and scratching induced a yellow solid to crystallize. Filtration and washing with Et_2O gave yellow, irregular prisms which crystallized from acetone as gold needles, 0.52 g (58%), mp 150 °C dec (Table I). THF or benzene may also be used as the solvent in the above reaction.

General Procedure for the Reaction of *anhydro*-4-Hydroxythiazolium Hydroxides with Acetylenic Dipolarophiles. Preparation of Dimethyl 2-Dimethylamino-5-phenylthiophene-3,4-dicarboxylate [15, R = $(CH_3)_2N$; R^1 = PH]. *anhydro*-2-Dimethylamino-3,5-diphenyl-4-hydroxythiazolium hydroxide (0.12 g, 4×10^{-4} mol) and dimethyl acetylenedicarboxylate (0.1 g, 7×10^{-4} mol) were refluxed in dry benzene (10 mL) under N_2 for 6 h. Evaporation of the solvent gave a yellow oil which when triturated with CH_3OH (~1 mL) deposited a cream solid which was isolated by filtration. Crystallization from CH_3OH gave cream plates, 0.09 g (69%), mp 108–109 °C (Table II).

In the preparation of dimethyl 5-ethoxycarbonyl-2-dimethylaminothiophene-3,4-dicarboxylate the residue after evaporation of the solvent was purified by PLC (1.0 mm, $CHCl_3$/EtOAc, 90:10).

Dimethyl 6-Cyano-1,3-diphenyl-2-oxopyridine-4,5-dicarboxylate (10). *anhydro*-2-Cyano-3,5-diphenyl-4-hydroxythiazolium hydroxide (**4**, R = CN; R^1 = Ph) (0.28 g, 0.001 mol) and dimethyl acetylenedicarboxylate (0.21 g, 0.0015 mol) were refluxed in dry benzene (18 mL) under N_2 for 24 h. Evaporation of the solvent gave an orange oil which upon cooling began to crystallize. Trituration with CH_3OH (~1 mL) and scratching induced further crystllization. Filtration and washing with a small portion of cold CH_3OH gave cream, irregular prisms which, after washing with a small portion of CS_2 to remove elemental sulfur, crystallized from ethanol as tiny, colorless needles: 0.21 g (53%); mp 168–169 °C; IR (KBr) 2950 (CH), 2230 (C≡N), 1740, 1730, 1670 cm^{-1} (CO); λ_{max} (CH_3OH) 345 nm (log ε 4.04), 268 (4.01), 204 (4.54); NMR ($CDCl_3$) δ 3.62 (s, 3, CH_3), 3.96 (s, 3, CH_3), 7.45 (m, 10, aromatic); mass spectrum *m/e* (rel intensity) M^+· 388 (68).

Anal. Calcd for $C_{22}H_{16}N_2O_5$: C, 68.03; H, 4.15; N, 7.21. Found: C, 67.57; H, 4.21; N, 7.21.

Alkyl (or Aryl) Phenyldithiocarbamate.[4] A stirred suspension of ammonium phenyldithiocarbamate in water was treated with an excess of alkyl or aryl halide (CH_3I, EtBr, *n*-PrBr, or C_6H_5Br) and the mixture stirred at room temperature for 6 h. On cooling in a dry ice/acetone bath, crystallization was induced by scratching and the resulting precipitate was separated and washed with H_2O. Recrystallization from benzene or ligroin gave the phenyldithiocarbamate as colorless prisms.

Alternative Preparation of *anhydro*-3,5-Diphenyl-4-hydroxy-2-methylthiothiazolium Hydroxide (4, R = CH_3S; R^1 = Ph). Methyl phenyldithiocarbamate (**1**, R = CH_3S) (18.3 g, 0.1 mol) in benzene (150 mL) was treated with α-bromophenylacetic acid (21.5 g, 0.1 mol) and Et_3N (13.0 g, 0.13 mol). After stirring overnight at room temperature, the precipitate of Et_3N·HBr was separated and the solvent removed in vacuo. The oily residue, dissolved in anhydrous CH_2Cl_2, was treated with an equimolar amount of *N,N'*-dicyclohexylcarbodiimide with stirring at room temperature. The precipitated *N,N'*-dicyclohexylurea was filtered after 12 h and washed with CH_2Cl_2, the combined filtrates concentrated in vacuo, and crystallization induced by triturating the chilled residue with a small amount of anhydrous ether. The orange solid crystallized from benzene forming golden prisms, 17.5 g (50%), mp 158–160 °C (Table I).

Alkylation of *anhydro*-2-Alkylthio-3,5-diphenyl-4-hydroxythiazolium Hydroxide with Meerwein's Reagent. A stirred solution of *anhydro*-3,5-diphenyl-4-hydroxy-2-methylthiothiazolium hydroxide (**4**, R = CH_3S; R^1 = Ph) (0.73 g, 0.0024 mol) in CH_2Cl_2 (10 mL) was treated with a 10% excess of triethyloxonium tetrafluoroborate[19] (0.532 g, 0.0028 mol) and the reaction mixture kept at room temperature for 24 h. On diluting the chilled solution with anhydrous ether the solid that separated was collected and recrystallized from CH_2Cl_2/Et_2O giving 3,5-diphenyl-4-ethoxy-2-methylthiothiazolium tetrafluoroborate (**7**, R = CH_3S; R^1 = Ph) as colorless prisms: 955 mg (92%); mp 199–201 °C; IR (KBr) 3065, 2985, 2910 (CH), 1600 (C=N), 1120–1010 cm^{-1} (BF_4^-); λ_{max} (CH_3OH) 329 nm (log ε 4.16), 263 sh (3.89), 241 sh (4.02); NMR ($CDCl_3$) δ 7.90–7.25 (m, 10, aromatic), 3.98 (q, 2, OCH_2CH_3), 2.83 (s, 3, SCH_3), 0.93 (t, 3, OCH_2CH_3).

Anal. Calcd for $C_{18}H_{18}BF_4NOS_2$: C, 52.05; H, 4.37; N, 3.38. Found: C, 52.06; H, 4.34; N, 3.46.

Similarly 3,5-diphenyl-4-ethoxy-2-ethylthiothiazolium tetrafluoroborate (**7**, R = EtS; R^1 = Ph) crystallized from CH_2Cl_2 as colorless prisms (87%): mp 204–206 °C; IR (KBr) 3065, 2980, 2935 (CH), 1600 (C=N), 1110–1010 cm^{-1} (BF_4^-); λ_{max} (CH_3OH) 330 nm (log ε 4.17), 260 sh (3.91), 240 sh (3.99); NMR ($CDCl_3$) δ 7.85–7.30 (m, 10, aromatic), 3.95 (q, 2, OCH_2CH_3), 3.40 (q, 2, SCH_2CH_3), 1.50 (t, 3, SCH_2CH_3), 0.95 (t, 3, OCH_2CH_3).

Anal. Calcd for $C_{19}H_{20}BF_4NOS_2$: C, 53.14; H, 4.70; N, 3.26. Found: C, 53.09; H, 4.74; N, 3.30.

3,5-Diphenyl-4-ethoxy-2-*n*-propylthiothiazolium tetrafluoroborate (**7**, R = *n*-C_3H_7S; R^1 = Ph) also crystallized from CH_2Cl_2 as cream prisms (77%): mp 133–134.5 °C; IR (KBr) 3070, 2970, 2935 (CH), 1600 (C=N), 1115–1010 cm^{-1} (BF_4^-); λ_{max} (CH_3OH) 330 nm (log ε 4.29), 260 sh (4.04), 240 sh (4.11); NMR ($CDCl_3$) δ 7.90–7.25 (m, 10, aromatic),3.98 (q, 2, OCH_2CH_3), 3.36 (t, 3, $SCH_2CH_2CH_3$), 1.95 (h, 2, $SCH_2CH_2CH_3$), 1.05 (t, 3, $SCH_2CH_2CH_3$), 0.95 (t, 3, OCH_2CH_3).

Anal. Calcd for $C_{20}H_{22}BF_4NOS_2$: C, 54.18; H, 5.00; N, 3.16. Found: C, 54.35; H, 5.05; N, 3.14.

Alkaline Hydrolysis of Dimethyl 2-Methylthio-5-phenylthiophene-3,4-dicarboxylate (15, R = CH_3S; r^1 = Ph). Dimethyl 2-methylthio-5-phenylthiophene-3,4-dicarboxylate (1.5 g, 0.0015 mol) in a 10% NaOH solution of aqueous methanol (1:1) (14 mL) was heated under reflux for 4 h. The methanol was removed in vacuo and the aqueous solution was acidified with 2 N HCl. Filtration of the precipitate and recrystallization from aqueous ethanol gave the corresponding 2-methylthio-5-phenylthiophene-3,4-dicarboxylic acid as colorless prisms, 0.46 g (100%), mp 235–237 °C (Table II).

3,5-Diphenyl-2-phenyliminothiazolidin-4-one (8a). A solution of α-bromophenylacetyl chloride (0.7 g, 0.003 mol) in benzene (10 mL) was added dropwise to a stirred solution of *N,N'*-diphenylthiourea (**1**, R = PhNH) (0.7 g, 0.003 mol). After 5 min at room temperature Et_3N (0.61 g, 0.006 mol) in benzene (5 mL) was added dropwise, the colorless reaction mixture changing to a red color, and stirring was continued for an additional 10 min. After removal of Et_3N·HX, the solvent was removed under reduced pressure and the oily residue triturated with ethanol giving cream prisms which crystallized from ethanol as colorless prisms of **8a**: 0.63 g (61%); mp 131–132 °C (lit.[8] mp 131–132.5 °C); IR (KBr) 3050 (CH), 1725, 1650 (CO), 1600 cm^{-1} (C=N); NMR (Me_2SO-d_6) δ 7.80–6.90 (m, 15, aromatic), 5.82 (s, 1, CH).

***anhydro*-3-Hydroxy-2-phenylthiazolo[3,2-*a*]pyridinium hydroxide (11, R = C_6H_5)** was obtained from the reaction of 2-mercaptopyridine and α-bromophenylacetyl chloride as described above. It crystallized from chloroform/ether as reddish-yellow prisms: mp 182–184 °C (lit.[12] mp 183–185 °C); IR (KBr) 3100–2950 (CH), 1620 (CO), 1590 cm^{-1} (C=N).

Similarly *anhydro*-2-ethoxycarbonyl-3-hydroxythiazolo[3,2-*a*]pyridinium hydroxide (**11**, R = $COOC_2H_5$) was obtained from the reaction of 2-mercaptopyridine and 2-bromo-2-ethoxycarbonylacetyl chloride. It also crystallized from chloroform/ether as golden prisms (30%): mp 166.5–168 °C; IR (KBr) 3110, 3080, 2975, 2935, 2900 (CH), 1725, 1650 (CO), 1610 cm^{-1} (C=N); λ_{max} (CH_3OH) 249 nm (3.90), 270 (3.76), 401 (4.05); NMR ($CDCl_3$) δ 8.15–7.35 (m, 4, aromatic), 4.40 (q,

2, $CO_2CH_2CH_3$), 1.39 (t, 3, $CO_2CH_2CH_3$); mass spectrum *m/e* (rel intensity) M^+· 223 (79).

Anal. Calcd for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06; N, 6.27. Found: C, 53.79; H, 3.97; N, 6.22.

Hydrolysis of *anhydro*-2-Alkylthio-3,5-diphenyl-4-hydroxythiazolium Hydroxides (4, R = CH_3S, C_2H_5S, *n*-C_3H_7S; R^1 = Ph). The mesoionic thiazole derivative (200 mg) in ethanol/H_2O (1:2) (15 mL) was refluxed for 3–4 h. Upon cooling, the solid precipitate was separated by filtration, washed with water, and recrystallized from ethanol giving colorless prisms of 3,5-diphenylthiazolidine-2,4-dione (8, R^1 = Ph) in 58–61% yields.

Hydrolysis of *anhydro*-5-Ethoxycarbonyl-2-ethylthio-4-hydroxy-3-phenylthiazolium Hydroxide (4, R = SC_2H_5; R^1 = COOEt). The mesoionic compound 4 (R = C_2H_5S; R^1 = COOEt) (0.15 g, 0.0005 mol) in H_2O (10 mL) was treated with about 3 drops of concentrated HCl solution and then the reaction mixture was refluxed for 7 h. Upon cooling a precipitate separated and it was recrystallized from aqueous ethanol giving 3-phenylthiazolidine-2,4-dione (8, R^1 = H) as colorless prisms with physical constants corresponding to those reported:[9,10b] 0.5 g (56%); mp 146–148 °C; IR (KBr) 3070, 2980, 2930, 1695, 1675, 1600 cm^{-1}; λ_{max} (CH_3OH) 218 nm sh (log ϵ 3.99); NMR ($CDCl_3$) δ 7.65–7.03 (m, 5, aromatic), 4.05 (s, 2, CH_2); mass spectrum *m/e* (rel intensity) M^+· 193 (68) [M − CO], 165 (3) [M − CO, COS], 105 (5).

Hydrolysis of *anhydro*-3,5-Diphenyl-4-hydroxy-2-morpholinothiazolium Hydroxide (4, R = *N*-Morpholino; R^1 = Ph). The mesoionic compound (0.15 g, 0.0004 mol) in ethanol/H_2O (1:3) (8 mL) containing 3 drops of concentrated HCl solution was refluxed for 3 h. Upon cooling, a solid separated and was washed with water. Recrystallization from ethanol gave 3,5-diphenylthiazolidine-2,4-dione as colorless prisms, 70 mg (59%), mp 172–174 °C (lit.[8] mp 172.5–173 °C).

***anhydro*-4-Hydroxy-2-*p*-methoxyphenyl-5-phenyl-1,3-dithiolium Hydroxide.** α-Bromophenylacetyl chloride (0.7 g, 0.003 mol) in benzene (10 mL) was added dropwise to a stirred solution of *p*-methoxydithiobenzoic acid (0.552 g, 0.003 mol) in benzene (10 mL). After 5 min, Et_3N (0.61 g, 0.006 mol) in benzene (5 mL) was added dropwise and the resulting purple solution stirred at room temperature for 10 min. After the separation of the precipitated solid, the filtrate was concentrated in vacuo and the oily residue triturated with ether/petroleum ether F. The crystals which separated were recrystallized from $CHCl_3$/petroleum ether F giving purple prisms: 0.55 g (61%); mp 124–126 °C (lit.[13] mp 125–126 °C); IR (KBr) 1575 cm^{-1} (CO); NMR ($CDCl_3$) δ 3.8 (s, 3, CH_3O), 7.93–6.97 (m, 9, aromatic).

***anhydro*-5-Carboethoxy-4-hydroxy-2-*p*-methoxyphenyl-5-phenyl-1,3-dithiolium Hydroxide.** 2-Bromo-2-ethoxycarbonylacetyl chloride (4.6 g, 0.02 mol) in benzene (30 mL) was added dropwise to a solution of *p*-methoxydithiobenzoic acid (3.7 g, 0.02 mol) in benzene (30 mL) and the reaction mixture was then stirred at room temperature for 10 min. To this stirred mixture was added dropwise a solution of Et_3N (4.1 g, 0.04 mol) in benzene (20 mL). After 10 min, the precipitated Et_3N·HX was filtered and the filtrate concentrated in vacuo. Trituration of the oily residue with petroleum ether F induced a red solid which was separated by filtration. Washing with a small amount of H_2O and crystallization from benzene/petroleum ether F gave red prisms: 2.7 g (45%); mp ca. 148 °C dec; IR (KBr) 1660, 1650 cm^{-1} (CO); λ_{max} (CH_3OH) 495 nm (log ϵ 3.29), 352 (4.50), 252 (4.11); NMR ($CDCl_3$) δ 8.26–6.80 (m, 4, aromatic), 4.36 (q, 2, $CO_2CH_2CH_3$), 3.90 (s, 3, CH_3), 1.35 (t, 3, $CO_2CH_2CH_3$); mass spectrum *m/e* (rel intensity) M^+· 296 (9).

Anal. Calcd for $C_{13}H_{12}O_4S_2$: C, 52.68; H, 4.08. Found: C, 52.48; H, 3.99.

Trapping of *anhydro*-2,4-Diphenyl-5-hydroxy-1,3-oxathiolium Hydroxide with Dimethyl Acetylenedicarboxylate. A solution of thiobenzoic acid (1.38 g, 0.01 mol) and triethylamine (2.02 g, 0.02 mol) in benzene (20 mL) was added dropwise to a stirred solution of α-bromophenylacetyl chloride (2.34 g, 0.01 mol) and benzene (20 mL) over N_2. Dimethyl acetylenedicarboxylate (1.42 g, 0.01 mol) was added and then the reaction mixture was refluxed for 24 h. After cooling, the Et_3N·HX was removed by filtration and the filtrate concentrated in vacuo. Trituration of the oily residue with methanol induced a colorless solid to crystallize. Filtration and crystallization from methanol gave colorless prisms which were identical with authentic dimethyl 2,5-diphenylthiophene-3,4-dicarboxylate, 0.4 g (11%), mp 166–168 °C (lit.[13b] 167–168 °C).

Registry No.—1 (R = CH_3S), 701-73-5; 1 (R = EtS), 13037-20-2; 1 (R = PrS), 14594-43-0; 1 (R = PhS), 27063-57-6; 1 (R = morpholino), 15093-54-6; 1 (R = $(CH_3)_2N$), 705-62-4; 1 (R = CN), 4955-82-2; 1 (R = Ph), 636-04-4; 1 (R = *p*-ClC_6H_4), 6244-75-3; 1 (R = *p*-$CH_3OC_6H_4$), 26060-23-1; 2 (R′ = Ph; X = Br; Y = OH), 4870-65-9; 2 (R′ = Ph; X = Br; Y = Cl), 19078-72-9; 2 (R′ = COOEt; X = Br; Y = Cl), 41141-81-5; 7 (R = CH_3S; R′ = Ph), 61522-29-0; 7 (R = EtS; R′ = Ph), 61522-31-4; 7 (R = *n*-C_3H_7S; R′ = Ph), 61522-33-6; 8 (R′ = Ph), 4695-03-8; 8 (R′ = H), 1010-53-3; **8a**, 4694-99-9; **10**, 61522-34-7; **11** (R = Ph), 32044-03-4; **11** (R = COOEt), 61522-35-8; **12** (R = *p*-$CH_3OC_6H_4$; X = S), 2168-77-6; **12** (R = Ph; X = O), 98-91-9; 13 (R′ = Ph), 21132-27-4; 13 (R′ = COOEt), 61522-36-9; dimethyl acetylenedicarboxylate, 762-42-5; triethyloxonium tetrafluoroborate, 368-39-8; 2-mercaptopyridine, 2637-34-5.

References and Notes

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Mesoionic Compounds. 40. A Convenient Route to the *anhydro*-4-Hydroxyimidazolium Hydroxide System[1]

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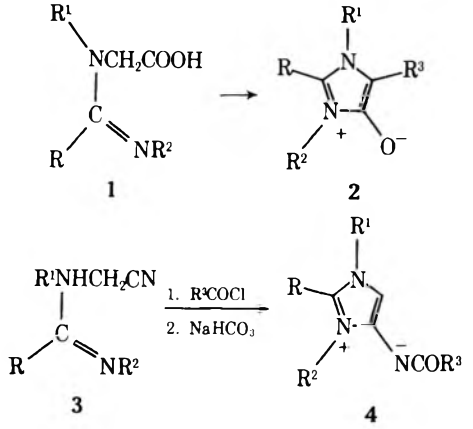
N,N'-Disubstituted amidines and α-bromoacetyl chlorides underwent ready condensation in the presence of triethylamine to form a variety of functionally substituted derivatives of the title mesoionic system. These underwent ready 1,3-dipolar cycloaddition with acetylenic dipolarophiles forming, in turn, functionally substituted pyrroles. This mesoionic system also underwent ready hydrolysis with water to the corresponding imidazolidine-2,4-diones.

In the previous paper[2] in this series, the condensation of a suitable 1,3-binucleophile containing at least one hydrogen atom with a reactive 1,2-bielectrophile incorporating an α-bromoacyl chloride function was shown to be a particularly convenient route to several mesoionic ring systems. In addition to the ease of reaction, it enabled a variety of functional groups to be incorporated into the mesoionic system, greatly extending their potential use as precursors to other heterocycles. We now describe an extension of this synthetic route to the preparation of the *anhydro*-4-hydroxyimidazolium hydroxide system, which is difficult to prepare by other procedures.

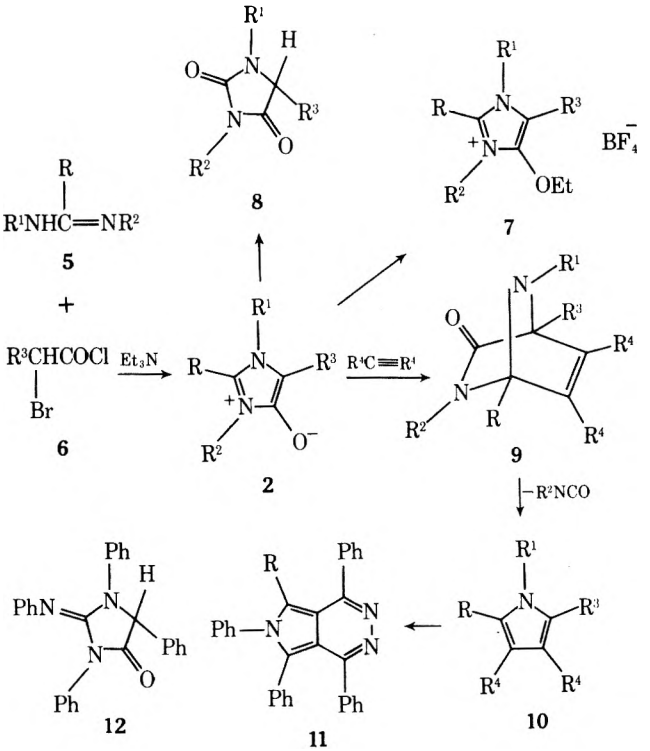
Previous attempts to prepare derivatives of this ring system have centered around the dehydrative cyclization of glycine derivatives **1** with acid anhydrides[3] to form the 4-hydroxy derivative **2**, or ring closure[4] of the corresponding nitrile **3** to the acylimino derivative **4**. However, in the cyclization of **1** to



2, an acyl substituent, R^3, corresponding to the acyl group of the acid anhydride used for the cyclization was always introduced into the 5 position of the nucleus. Representatives of this ring system with an exocyclic sulfur atom have also been prepared, in this instance the route involving reaction of *anhydro*-2,4-diphenyl-5-hydroxy-3-methyloxazolium hydroxide[5] or *anhydro*-2-aryl-5-hydroxy-3-methylthiazolium hydroxides[6] with phenyl isothiocyanate to give the appropriately substituted derivatives. Reaction of the former mesoionic ring system with phenyl isocyanate has also been reported[7] to give the corresponding *anhydro*-4-hydroxyimidazolium hydroxide system.

The 5-acetyl derivative **2** ($R^3 = COCH_3$) did not react with acetylenic or olefinic dipolarophiles,[4] and also was relatively stable to hot acids, alkali, and benzylamine,[3b] this stability being attributed to delocalization of the exocyclic negative charge over the 5-acyl substituent. MO calculations predict[3b] appreciable dipolar activity for this ring system and considerable effort has been expended to obtain derivatives without the 5-acyl substituent as well as other representatives of this ring system. Reaction of benzoylformic acid anil with trifluoroacetic anhydride in dry pyridine at 0 °C results[8] in dimerization and evolution of CO_2 with the ultimate formation of *anhydro*-4-hydroxy-1,2,3,5-tetraphenylimidazolium hydroxide (**2**, R = R^1 = R^2 = R^3 = Ph). More recently the reaction of symmetrically substituted amidines with α-bromophenylacetyl chloride or α-bromopropionyl chloride, followed by reaction with dimethyl acetylenedicarboxylate, was found to give substituted pyrroles,[9] a reaction which must have involved an intermediate *anhydro*-4-hydroxyimidazolium hydroxide system though this ring system was not isolated in this study.

1,3-Diphenyl-2-methyl-2-pseudothiourea (**5**, R = CH_3S;



R^1 = R^2 = Ph) and α-bromophenylacetyl chloride[10a] (**6**, R^3 = Ph) in the presence of 2 mol of Et_3N underwent an extremely facile condensation to give *anhydro*-4-hydroxy-2-methylthio-1,3,5-triphenylimidazolium hydroxide (**2**, R = SCH_3; R^1 = R^2 = R^3 = Ph) (Table I). An equally ready reaction with 2-bromo-2-ethoxycarbonylacetyl chloride[10b] (**6**, R^3 = COOEt) gave *anhydo*-5-ethoxycarbonyl-1,3-diphenyl-4-hydroxy-2-methylthioimidazolium hydroxide (**2**, R = SCH_3; R^1 = R^2 Ph; R^3 = COOEt). The analytical and spectral data described in Table I leave no doubt that ring closure had occurred to the desired system, and this was confirmed by further chemical transformations described below. Most of these imidazolium hydroxide derivatives could be stored for relatively long periods of time at ca. 0 °C; at room temperature decomposition occurred after several days.

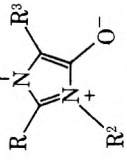
Alkylation of **2** (R = SCH_3; $R^1 = R^2$ = Ph; R^3 = Ph and COOEt) with Meerwein's reagent[11] occurred readily in methylene chloride giving the corresponding ethyl ethers **7**, readily characterized by analytical and spectral data (Experimental Section). Hydrolysis of **2** (R = SCH_3; $R^1 = R^2 = R^3$ = Ph) in refluxing ethanol/water (1:3) occurred over 3 h yielding 1,3,5-triphenylimidazolidine-2,4-dione[12] (**8**, $R^1 = R^2 = R^3$ = Ph). Similarly, the corresponding 5-ethoxycarbonyl derivative of **2** underwent ready hydrolysis. In refluxing dilute HCl, 5-ethoxycarbonyl-1,3-diphenylimidazolidine-2,4-dione[13] (**8**, $R^1 = R^2$ = Ph; R^3 = COOEt) was readily obtained, the ester function being stable under these conditions. However, further hydrolysis of **8** ($R^1 = R^2$ = Ph; R^3 = COOEt) under alkaline conditions[14] resulted in the formation of 1,3-diphenylimidazolidine-2,4-dione[15b] (**8**, $R^1 = R^2$ = Ph; R^3 = H), the intermediate β-keto acid undergoing spontaneous decarboxylation.

Dimethyl acetylenedicarboxylate underwent cycloaddition with **2** (R = CH_3S; $R^1 = R^2 = R^3$ = Ph) in refluxing benzene forming dimethyl 1,5-diphenyl-2-methylthiopyrrole-3,4-dicarboxylate (**10**, R = CH_3S; $R^1 = R^3$ = Ph; R^4 = $COOCH_3$) (Table II) in very good yield. The intermediate 1:1 cycloadduct **9** was not isolated but was undoubtedly involved in the reaction. Hydrolysis of **10** (R = CH_3S; $R^1 = R^3$ = Ph; R^4 = COOEt) with aqueous methanolic (3:1) NaOH solution gave 1,5-diphenyl-2-methylthiopyrrole-3,4-dicarboxylic acid (**10**, R = CH_3S; $R^1 = R^3$ = Ph; R^4 = COOH) (Table II). Cycloaddition also occurred readily with **2** (R = CH_3S; $R^1 = R^2$ = Ph; R^3 = COOEt) to give the corresponding pyrrole **10** (R = CH_3S; $R^1 = R^2$ = Ph; R^3 = COOEt), although in slightly reduced yield. Thus the 5-ethoxycarbonyl substituent does not retard the "masked" ylide character of this ring system in contrast to a 5-acetyl substituent when all 1,3-dipolar characteristics are suppressed. This is most likely due to a less effective delocalization of the exocyclic negative charge over the 5-ethoxycarbonyl group than in the 5-acetyl group. Dibenzoylacetylene also underwent ready cycloaddition with **2** (R = CH_3S; $R^1 = R^2 = R^3$ = Ph) in refluxing benzene forming 3,4-dibenzoyl-1,5-diphenyl-2-methylthiopyrrole (**10**, R = CH_3S; $R^1 = R^3$ = Ph; R^4 = COPh) (Table II) which was characterized further by conversion into 5-methylthio-1,4,6,7-tetraphenylpyrrolo[3,4-*d*]pyridazine (**11**, R = CH_3S) by reaction with hydrazine.

Other amidines reacted readily with the 1,2-bielectrophiles **6**, in most cases forming the desired *anhydro*-4-hydroxyimidazolium hydroxide system **2**, but in several instances difficulty in effecting adequate purification of the product resulted in their being isolated as their hydrolysis products. *N,N'*-Diphenylbenzamidine[16] (**5**, R = $R^1 = R^2$ = Ph) and α-bromophenylacetyl chloride (**6**, R^3 = Ph) underwent ready reaction as above to give *anhydro*-4-hydroxy-1,2,3,5-tetraphenylimidazolium hydroxide (**2**, R = $R^1 = R^2 = R^3$ = Ph) (Table I) in 77% yield and the corresponding 5-ethoxycarbonyl derivative **2** (R = $R^1 = R^2$ = Ph; R^3 = COOEt) was readily formed when 2-bromo-2-ethoxycarbonylacetyl chloride (**6**, R^3 = COOEt) was used as the 1,2-bielectrophile. This imidazole derivative reacted readily with Meerwein's reagent to form the corresponding ether **7** (R = $R^1 = R^2$ = Ph; R^3 = COOEt) and also underwent ready cycloaddition with dimethyl acetylenedicarboxylate and dibenzoylacetylene forming the corresponding pyrroles in good yields (Table II). Additional characterization of **10** (R = R^1 = Ph; R^3 = COOEt; R^4 = COPh) by reaction with hydrazine gave ethyl 1,4,6,7-tetraphenylpyrrolo[3,4-*d*]pyridazine-5-carboxylate (**11**, R = COOEt).

The symmetrically substituted urea derivatives above present no problem in terms of the structure of the final product. However, use of an unsymmetrically substituted 1,3-binucleophile could lead to four intermediates depending

Table I. *anhydro*-4-Hydroxyimidazolium Hydroxide Derivatives (2)[f]

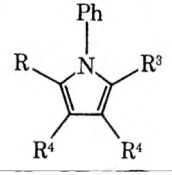


Registry no.	Substituents R	R^2	R^3	Mp, °C	Yield,[a] %	Mol formula	$M^{+\cdot}$ (rel int)	Spectral data: λ_{max} (CH_3OH), nm (log ϵ)	ν_{CO}	$\nu_{C=N}$, cm^{-1}	NMR, δ ($CDCl_3$)
61505-47-3	CH_3S	Ph	Ph	177–180[b]	49	$C_{22}H_{18}N_2OS$	358 (32)	237[c] (4.20), 264[c] (3.91), 353 (3.63)	1635	1600	7.65–6.90 (m, 15, aromatic), 1.90 (s, 3, SCH_3)
61505-48-4	CH_3S	Ph	COOEt	158–160[b]	52	$C_{19}H_{18}N_2O_3S$	354 (43)	226[c] (4.12), 247[c] (4.01), 327 (4.00)	1690 1670	1600	7.53 (s, 10, aromatic), 4.18 (q, 2, $COOCH_2CH_3$), 1.85 (s, 3, SCH_3), 1.17 (t, 3, $CO_2CH_2CH_3$)
54563-03-0	Ph	Ph	Ph	174–177[d]	77	$C_{27}H_{20}N_2O$		255[c] (4.23), 347 (3.73)	1640	1595	7.7–6.7 (m, aromatic)

61505-49-5	Ph	Ph	COOEt	236–238[e]	50	$C_{24}H_{20}N_2O_3$	384 (31)	244 (4.15), 316 (4.10)	1690 1655	1600	7.45–6.65 (m, 15, aromatic), 4.15 (q, 2, $CO_2CH_2CH_3$), 1.11 (t, 3, $CO_2CH_2CH_3$)
61505-50-8	Ph	CH_3	Ph	183–185	51	$C_{22}H_{18}N_2O$	326 (11)	232[c] (3.97), 290 (3.83), 340 (3.98)	1630	1600	7.6–6.8 (m, 15, aromatic), 3.47 (s, 3, NCH_3)
61505-51-9	Ph	CH_3	COOEt	308–310[b]	32	$C_{19}H_{18}N_2O_3$	322 (53)	223[c] (4.10), 247 (3.97), 309 (4.10)	1690 1665	1605	7.24 (s, 10, aromatic), 4.13 (q, 2, $CO_2CH_2CH_3$), 3.34 (s, 3, NCH_3), 1.18 (t, s, $CO_2CH_2CH_3$)

[a] All obtained as colorless or cream prisms or needles from $CHCl_3/Et_2O$. [b] Decomposition. [c] Shoulder. [d] Lit.[8] mp 166–168 °C. [e] Purification by PLC on silica gel using EtOAc. [f] Satisfactory analytical values (±0.4% for C, H, N) were reported for all compounds in table.

Table II. Pyrroles (10) Obtained from 2 and Acetylenic Dipolarophiles[f]



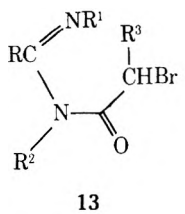
	Substituents							Spectral data		
Registry no.	R	R^3	R^4	Mp, °C	% yield[a]	Formula	M^+· (rel int)	λ_{max} (CH_3OH), nm (log ε)	ν_{CO} (KBr), cm^{-1}	NMR, δ ($CDCl_3$)
61505-52-0	CH_3S	Ph	$COOCH_3$	155–156.5	81	$C_{21}H_{19}NO_4S$	381 (100)	270[b] (4.07)	1725 1705	7.4–6.8 (m, 10, aromatic), 3.93 (s, 3, CO_2CH_3), 3.66 (s, 3, CO_2CH_3), 2.15 (s, 3, SCH_3)
61505-53-1	CH_3S	Ph	COOH	213–215	87	$C_{19}H_{15}NO_4S$	353 (1.5)	283[b] (3.90)	1695	7.25 (m, 10, aromatic), 2.14 (s, 3, SCH_3)[c]
61505-54-2	Ph	COOEt	$COOCH_3$	168.5–170.5	55[d] 72[e]	$C_{23}H_{21}NO_6$	407 (100)	268 (4.25)	1740 1720 1710	7.17 (s, 10, aromatic), 4.1 (q, 2, $CO_2CH_2CH_3$), 3.98 (s, 3, CO_2CH_3), 3.83 (s, 3, CO_2CH_3), 1.1 (t, 3, $CO_2CH_2CH_3$)
61505-55-3	CH_3S	Ph	PhCO	197–198	72	$C_{31}H_{23}NO_2S$	473 (40)	253 (4.54), 315 (3.75)	1650	7.83–6.8 (m, 20, aromatic), 2.17 (s, 3, SCH_3)
61528-39-0	Ph	COOEt	PhCO	176–178	60	$C_{33}H_{25}NO_4$	499 (100)	256 (4.58), 286[b] (4.18)	1700 1670 1645	8.1–6.77 (m, 20, aromatic), 3.83 (q, 2, $CO_2CH_2CH_3$), 0.73 (t, 3, $CO_2CH_2CH_3$)

[a] All obtained as colorless prisms from ethanol. [b] Shoulder. [c] Me_2SO-d_6. [d] Derived from 2 (R^2 = Ph). [e] Derived from 2 (R^2 = CH_3). [f] Satisfactory analytical values (±0.4% for C, H, N) were reported for all compounds in table.

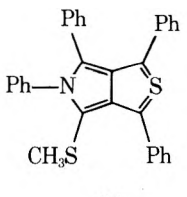
on the site of initial condensation with the 1,2-bielectrophile, and two final products could result. 1,2-Dimethyl-3-phenyl-2-pseudothiourea (**5**, R = CH_3S; R^1 = CH_3; R^2 = Ph) and α-bromophenylacetyl chloride (**6**, R^3 = Ph) underwent ready reaction with the final isolaton of a mixture of two products, one the *anhydro*-1,5-diphenyl-4-hydroxy-2-methylthio-3-methylimidazolium hydroxide (**2**, R = SCH_3; R^1 = R^3 = Ph; R^2 = CH_3) and its hydrolysis product 1,5-diphenyl-3-methylimidazolidine-2,4-dione[17] (**8**, R^1 = R^3 = Ph; R^2 = CH_3), the former being converted into the latter by hot water. Similarly reaction of **5** (R = CH_3S; R^1 = CH_3; R^2 = Ph) with 2-bromo-2-ethoxycarbonylacetyl chloride (**6**, R^3 = COOEt) and subsequent hydrolysis of the reaction product with water resulted in a product assigned the structure 5-ethoxycarbonyl-3-methyl-1-phenylimidazolidine-2,4-dione (**8**, R^1 = Ph; R^2 = CH_3; R^3 = COOEt) as its physical characteristics (mp 123–125 °C) were quite different from those of the isomeric 5-ethoxycarbonyl-1-methyl-3-phenylimidazolidine-2,4-dione[18] (**8**, R^1 = CH_3; R^2 = Ph; R^3 = COOEt) (mp 95–97 °C). This was confirmed by the hydrolysis of **8** (R^1 = Ph; R^2 = CH_3; R^3 = COOEt) with alkali to 3-methyl-1-phenylimidazolidine-2,4-dione[15a] (**8**, R^1 = Ph; R^2 = CH_3; R^3 = H).

However, the *anhydro*-4-hydroxyimidazolium hydroxide system obtained from *N*-methyl-*N'*-phenylbenzamidine (**5**, R = R^2 = Ph; R^1 = CH_3) and α-bromophenylacetyl chloride (**6**, R^3 = Ph) was obtained free of its hydrolysis product and *anhydro*-4-hydroxy-3-methyl-1,2,5-triphenylimidazolium hydroxide (**2**, R = R^1 = R^3 = Ph; R^2 = CH_3) obtained in this way is isomeric with *anhydro*-4-hydroxy-1-methyl-2,3,5-triphenylimidazolium hydroxide (**2**, R = R^2 = R^3 = Ph; R^1 = CH_3) obtained from *anhydro*-2,4-diphenyl-5-hydroxy-3-methyloxazolium hydroxide and phenyl isocyanate.[7] The physical characteristics of these two products are quite dissimilar. An interesting feature of the NMR spectrum of **2** (R = R^1 = R^3 = Ph; R^2 = CH_3) is the chemical shift of the NCH_3 group at δ 3.47; the corresponding methyl group in **2** (R = R^2 = R^3 = Ph; R^1 = CH_3) is at δ 3.03, and the downfield shift in the former is probably due to the adjacent carbonyl group. Similarly *anhydro*-5-ethoxycarbonyl-1,2-diphenyl-4-hydroxy-3-methylimidazolium hydroxide (**2**, R = R^1 = Ph; R^2 = CH_3; R^3 = COOEt) was readily formed from **5** (R = R^2 = Ph; R^1 = CH_3) and **6** (R^3 = COOEt), and in this product the chemical shift of the methyl group was at δ 3.34, indicating its closeness to the 4-carbonyl function. Additional characterization of **2** (R = R^1 = Ph; R^2 = CH_3; R^3 = COOEt) by ready cycloaddition with dimethyl acetylenedicarboxylate gave dimethyl 5-ethoxycarbonyl-1,2-diphenylpyrrole-3,4-dicarboxylate (**10**, R = R^1 = Ph; R^3 = COOEt; R^4 = $COOCH_3$) in 72% yield.

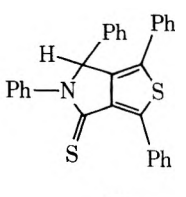
These collective results, together with the cycloaddition to pyrroles described above, remove two possibilities from consideration as the initial mode of condensation, leaving the condensation of the acid chloride function with the NCH_3 group in the amidine or reaction between the α-bromo carbon and the NPh group of the amidine to be the actual pathway followed. Unfortunately, with our present data this point cannot be resolved. Other studies[20] however, suggest a reaction sequence involving initial attack of the amidine at the acyl chloride function followed by intramolecular cyclization of the α-haloacylamidine **13**.



13



14



15

Use of a guanidine with one replaceable hydrogen atom as a 1,3-binucleophile in the initial condensation such as 1,1-diethyl-2,3-diphenylguanidine[19] (**5**, R = NEt_2; R^1 = R^2 = Ph) resulted in a product from its reaction with α-bromophenylacetyl chloride (**6**, R^3 = Ph) that could not be satisfactorily purified. The stability of the *anhydro*-4-hydroxyimidazolium hydroxide system was not improved by the introduction of a 5-ethoxycarbonyl substituent, a similar experience resulting from the use of several other guanidines. However, use of a guanidine with two replaceable hydrogen atoms, although not leading to a mesoionic system, readily gave an imidazole derivative. Thus, 1,2,3-triphenylguanidine (**5**, R = NHPh; R^1 = R^2 = Ph) and α-bromophenylacetyl chloride readily gave 2-phenylimino-1,3,5-triphenylimidazolidin-4-one (**12**). Confirmation of this structure was readily obtained by hydrolysis of the product to 1,3,5-triphenylimidazolidine-2,4-dione (**8**, R^1 = R^2 = R^3 = Ph).

The pyrroles obtained via the cycloadditions described above contain functional substituents in the α position of the nucleus that are not readily introduced by other procedures and these *anhydro*-4-hydroxyimidazolium hydroxides are quite useful in this respect. An interesting application is the possible conversion of 3,4-dibenzoyl-1,5-diphenyl-2-methylthiopyrrole (**10**, R = R^1 = Ph; R^3 = CH_3S; R^4 = PhCO) with P_4S_{10} in pyridine into the substituted thieno[3,4-c]pyrrole system **14** which has only been isolated with phenyl substituents in the 1, 3, 5, and 6 positions.[21] The product obtained was identified as **15** having been formed from **14** by loss of the methyl group. This ready demethylation may be due to **15** being the thermodynamically more stable product or indicative of the already noted highly reactive nature of this fused ring system but no conclusion can be made from the data currently available.

Experimental Section[22]

General Procedure for the Reaction of the Amidines 5 with the Bielectrophiles. Formation of *anhydro*-4-Hydroxy-2-methylthio-1,3,5-triphenylimidazolium Hydroxide (2, R = CH_3S; R^1 = R^2 = R^3 = Ph). 1,3-Diphenyl-2-methyl-2-pseudothiourea (727 mg, 3 mmol) in ether (10 mL) was treated dropwise with α-bromophenylacetyl chloride[10a] (0.7 g, 3 mmol) in ether (10 mL) and the reaction mixture was stirred at room temperature for 10 min. To this stirred mixture, a solution of triethylamine (606 mg, 6 mmol) in ether (5 mL) was added slowly. After stirring for 10 min the precipitate was separated by filtration and washed with water, leaving a yellow solid. Recrystallization from chloroform/ether gave cream prisms, 595 mg (49%), mp 177–180 °C dec (Table I).

4-Ethoxy-2-methylthio-1,3,5-triphenylimidazolium Tetrafluoroborate (7, R = CH_3S; R^1 = R^2 = R^3 = Ph). *anhydro*-4-Hydroxy-2-methylthio-1,3,5-triphenylimidazolium hydroxide (727 mg, 2 mmol) in methylene chloride (10 mL) was treated with a slight excess of Meerwein's reagent[11] (0.4 g, 2.1 mmol) and the reaction mixture stirred at room temperature for 24 h. Anhydrous ether was added and the resultant precipitate recrystallized from methylene chloride/ether yielding colorless prisms: 935 mg (93%); mp 262–264 °C; IR (KBr) 3060, 2985, 2925 (CH), 1640 (CO), 1600 (C=N), 1110–1020 cm^{-1} (BF_4^-); λ_{max} (CH_3OH) 239 nm (log ε 4.12), 287 (3.93); NMR ($CDCl_3$) δ 8.15–7.05 (m, 15, aromatic), 3.94 (q, 2, OCH_2CH_3), 2.09 (s, 3, SCH_3), 0.9 (t, 3, OCH_2CH_3).

Anal. Calcd for $C_{24}H_{23}BF_4N_2OS$: C, 60.77; H, 4.87; N, 5.91. Found: C, 60.64; H, 4.86; N, 5.79.

Similarly, 5-ethoxycarbonyl-4-ethoxy-1,2,3-triphenylimidazolium tetrafluoroborate (**7**, R^1 = R^2 = Ph; R^3 = COOEt) was obtained from methylene chloride/ether as colorless prisms (81%): mp 249–251 °C; IR (KBr) 3060, 2985, 2940, 2910 (CH), 1730 (CO), 1615 (C=N), 1120–1020 cm^{-1} (BF_4^-); λ_{max} (CH_3OH) 253 nm sh (log ε 4.13); NMR ($CDCl_3$) δ 7.87–6.97 (m, 15, aromatic), 4.5 (q, 2, $CO_2CH_2CH_3$), 4.15 (q, 2, OCH_2CH_3), 1.15 (t, 3, $CO_2CH_2CH_3$), 1.05 (t, 3, OCH_2CH_3).

Anal. Calcd for $C_{26}H_{25}BF_4N_2O_3$: C, 62.42; H, 5.04; N, 5.60. Found: C, 62.81; H, 5.01; N, 5.49.

1,2-Dimethyl-3-phenyl-2-pseudothiourea (5, R = CH_3S; R^1 = Ph; R^2 = CH_3). 1,2-Dimethyl-3-phenyl-2-pseudothiourea hydriodide[23] (60.0 g, 0.195 mol) and ammonium hydroxide (300 mL) were

stirred at room temperature for 2 h. The solid precipitate was collected, washed well with water, and dried. Extraction with ether and concentration of the solution in vacuo gave an oil which solidified to colorless prisms upon cooling: 25.8 g (75%); mp 60–62 °C; IR (KBr) 3250, 3150, 2980, 2920, 1585, 1535, 1510 cm^{-1}; λ_{max} (CH_3OH) 231 nm sh (log ϵ 4.03), 277 sh (3.65); NMR ($CDCl_3$) δ 7.37–6.70 (m, 5, aromatic), 4.42 (s, 1, NH), 2.87 (s, 3, SCH_3), 2.2 (s, 3, NCH_3); mass spectrum *m/e* (rel intensity) M^+·180 (43).

Anal. Calcd for $C_9H_{12}N_2S$: C, 59.96; H, 6.71; N, 15.54. Found: C, 59.83; H, 6.71; H, 15.35.

3-Methyl-1,5-diphenylimidazolidine-2,4-dione (8, $R^1 = R^3$, ph; $R^2 = CH_3$). α-Bromophenylacetyl chloride (0.7 g, 3 mmol) in anhydrous ether (5 mL) was added dropwise to a solution of 1,2-dimethyl-3-phenyl-2-pseudothiourea (541 mg, 3 mmol) in ether (5 mL) and then the reaction mixture was stirred at room temperature for 5 min. A solution of triethylamine (606 mg, 6 mmol) in ether (5 mL) was added dropwise. After stirring for 5 min, the precipitate was collected by filtration and refluxed in water (10 mL) for 2 h. Cooling in an ice bath gave colorless crystals which were filtered and recrystallized from aqueous ethanol forming colorless needles: 0.32 g (40%); mp 187–188 °C (lit.[17] mp 185–186 °C); IR (KBr) 3030, 2930 (CH), 1765, 1700 cm^{-1} (CO); λ_{max} (CH_3OH) 237 nm (log ϵ 4.06), 248 sh (4.01); NMR ($CDCl_3$) δ 7.55–7.05 (m, 10, aromatic), 5.40 (s, 1, CH), 3.1 (s, 3, CH_3); M^+·266 (100).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.99; H, 5.50; N, 10.27.

Similarly, 5-ethoxycarbonyl-3-methyl-1-phenylimidazolidine-2,4-dione (8, R^1 = Ph; $R^2 = CH_3$; R^3 = COOEt) crystallized from aqueous ethanol as colorless prisms (13%): mp 123–125 °C; IR (KBr) 2995, 2965, 2915 (CH), 1780, 1745, 1710 cm^{-1} (CO); λ_{max} (CH_3OH) 232 nm (log ϵ 3.98), 246 sh (3.94); NMR ($CDCl_3$) δ 7.6–7.0 (m, 5, aromatic), 5.12 (s, 1, CH), 4.22 (q, 2, $CO_2CH_2CH_3$), 3.10 (s, 3, NCH_3), 1.2 (t, 3, $CO_2CH_2CH_3$); M^+·262 (41).

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.14; H, 5.23; N, 10.54.

General Procedure for the Reaction of *anhydro*-4-Hydroxy-1,2,3,5-tetrasubstituted-imidazolium Hydroxides (2) with Acetylenic Dipolarophiles. Formation of Dimethyl 1,5-Diphenyl-2-methylthiopyrrole-3,4-dicarboxylate (10, R = CH_3S; $R^1 = R^3$ = Ph; R^4 = $COOCH_3$). *anhydro*-4-Hydroxy-2-methylthio-1,3,5-triphenylimidazolium hydroxide (727 mg, 2 mmol), dimethyl acetylenedicarboxylate (0.3 g, 2.1 mmol), and dry benzene (30 mL) were stirred under reflux for 24 h. Removal of the solvent under reduced pressure and trituration of the resultant residue with petroleum ether (bp 35–60 °C) afforded yellow-brown prisms. The crystals were digested with ethanol and filtered. Recrystallization from ethanol gave colorless prisms, 0.62 g (81%), mp 155–156.5 °C (Table II).

Alkaline Hydrolysis of Dimethyl 1,5-Diphenyl-2-methylthiopyrrole-3,4-dicarboxylate (10, R = CH_3S; $R^1 = R^3$ = Ph; R^4 = $COOCH_3$). The pyrrole (0.42 g, 1.1 mmol) was refluxed in a 4% NaOH solution of a 3:1 mixture of methanol and water (20 mL) for 6 h. The methanol was removed in vacuo and the residual suspension acidified with concentrated HCl. Filtration of the precipitated solid and recrystallization from ethanol/water gave 1,5-diphenyl-2-methylthiopyrrole-3,4-dicarboxylic acid (10, R = CH_3S; $R^1 = R^3$ = Ph; R^4 = COOH) as colorless prisms, 0.34 g (87%), mp 213–215 °C (Table II).

Reaction of 3,4-Dibenzoyl-1,5-diphenyl-2-methylthiopyrrole (10, R = CH_3S; $R^1 = R^3$ = Ph; R^4 = COPh) with Hydrazine. The pyrrole (414 mg, 1 mmol) and hydrazine (50 mg, 1.56 mmol) in ethanol (20 mL) were refluxed for 24 h. The reaction mixture was concentrated in vacuo and the residual oil triturated with ether to give a yellow precipitate. Recrystallization from ethanol gave yellow prisms of 5-methylthio-1,4,6,7-tetraphenylpyrrolo[3,4-*d*]pyridazine (11, R = CH_3S): 0.38 g (81%); mp 235–237 °C; IR (KBr) 3060, 2925 (CH), 1600 cm^{-1} (C=N); λ_{max} ($CHCl_3$) 257 nm sh (log ϵ 4.36), 297 sh (4.01), 362 (3.55); NMR ($CDCl_3$) δ 8.0–6.7 (m, 20, aromatic), 1.64 (s, 3, SCH_3); M^+· 459 (100).

Anal. Calcd for $C_{31}H_{23}N_3S$: C, 79.29; H, 4.94; N, 8.95. Found: C, 79.12; H, 5.04; N, 8.80.

Similarly, ethyl 1,4,6,7-tetraphenylpyrrolo[3,4-*d*]pyridazine-5-carboxylate (11, R = COOEt) was obtained as pale yellow prisms: 0.37 g (75%); mp 236–237 °C; IR (KBr) 3055, 2975 (CH), 1705 (CO), 1600 cm^{-1} (C=N); λ_{max} ($CHCl_3$) 265 nm sh (log ϵ 4.29), 298 sh (3.97), 354 (4.04); NMR ($CDCl_3$) δ 8.00–6.65 (m, 20, aromatic), 3.60 (q, 2, $CO_2CH_2CH_3$), 0.7 (t, 3, $CO_2CH_2CH_3$); M^+· 495 (100).

Anal. Calcd for $C_{33}H_{25}N_3O_2$: C, 79.98; H, 5.08; N, 8.48. Found: C, 80.01; H, 5.15; N, 8.49.

Hydrolysis of *anhydro*-5-Ethoxycarbonyl-1,3-diphenyl-4-hydroxy-2-methylthioimidazolium Hydroxide (2, R = CH_3S; $R^1 = R^2$ = Ph; R^3 = COOEt). The mesoionic compound (0.1 g, 2.82×10^{-4} mol) in a 1:1 mixture of water/ethanol (10 mL) and 4 drops of concentrated HCl were refluxed for 7 h. The ethanol was removed in vacuo and the solid precipitate was filtered and washed with water. Recrystallization from aqueous ethanol gave 5-ethoxycarbonyl-1,3-diphenylimidazolidine-2,4-dione (8, $R^1 = R^2$ = Ph; R^3 = COOEt) as colorless prisms: 30 mg (33%); mp 134.5–135.5 °C (lit.[13] mp 134.5 °C); IR (KBr) 3065, 3000, 2975, 2950, 1790, 1740, 1725, 1600 cm^{-1}; λ_{max} (CH_3OH) 233 nm (log ϵ 4.31); NMR ($CDCl_3$) δ 7.44 (s, 10, aromatic), 5.29 (s, 1, CH), 4.28 (q, 2, $CO_2CH_2CH_3$), 1.20 (t, 3, $CO_2CH_2CH_3$); M^+· 324 (55).

Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.83; H, 4.93; N, 8.64.

Alkaline Hydrolysis and Decarboxylation of 8 ($R^1 = R^2$ = Ph; R^3 = COOEt). 5-Ethoxycarbonyl-1,3-diphenylimidazolidine-2,4-dione (0.1 g, 0.31 mol) in 1 N NaOH solution (5 mL) was heated until all the solid dissolved and then stirred at room temperature for 1 h. Acidification with HCl precipitated an oil which gradually solidified on cooling. Filtration and subsequent recrystallization from ethanol gave 1,3-diphenylimidazolidine-2,4-dione as colorless prisms which were shown to be identical with an authentic sample, 60 mg (90%), mp 135–137 °C (lit.[15] mp 136.5–137.5 °C).

Alkaline Hydrolysis and Decarboxylation of 8 (R^1 = Ph; $R^2 = CH_3$; R^3 = COOEt). 5-Ethoxycarbonyl-3-methyl-1-phenylimidazolidine-2,4-dione (0.1 g, 0.31 mmol) in 1 N NaOH solution (5 mL) was stirred at room temperature for 1 h and then acidified with concentrated HCl. The solid was recrystallized from ethanol yielding 3-methyl-1-phenylimidazolidine-2,4-dione (8, R^1 = Ph; $R^2 = CH_3$; R^3 = H) as colorless prisms, 45 mg (62%), mp 184–186 °C (lit.[15a] mp 183–185 °C).

1,3,5-Triphenylimidazolidine-2,4-dione (8, $R^1 = R^2 = R^3$ = Ph). *anhydro*-4-Hydroxy-2-methylthio-1,3,5-triphenylimidazolium hydroxide (0.15 g, 0.42 mmol) in water/ethanol (3:1) (6 mL) was refluxed for 3 h. Upon cooling, a precipitate separated and was recrystallized from aqueous ethanol forming colorless prisms: 80 mg (58%); mp 119–120 °C (lit.[12] mp 124–126 °C); IR (KBr) 3040 (CH), 1775, 1720 cm^{-1} (CO); λ_{max} (CH_3OH) 233 nm (log ϵ 4.41); NMR ($CDCl_3$) δ 7.65–6.65 (m, 15, aromatic), 5.55 (s, 1, CH); M^+· 328 (75).

Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.43; H, 4.83; N, 8.54.

2-Phenylimino-1,3,5-triphenylimidazolidin-4-one (12). A solution of α-bromophenylacetyl chloride (700 mg, 3 mmol) in benzene (10 mL) was added dropwise to a solution of 1,2,3-triphenylguanidine (862 mg, 3 mmol) in benzene (10 mL) and the reaction mixture was then stirred at room temperature for 5 min. To this stirred mixture was added dropwise a solution of triethylamine (606 mg, 6 mmol) in benzene (10 mL). After about 10 min, the precipitated triethylamine hydrohalide salts were removed by filtration and the filtrate evaporated in vacuo. Trituration of the oily residue with ethanol gave 700 mg (58%) of colorless solid which crystallized from ethanol as colorless prisms: mp 162–163.5 °C; IR (KBr) 1750, 1660 (CO), 1595 cm^{-1} (C=N); λ_{max} (CH_3OH) 275 nm (log ϵ 4.08); Nmr)me_2SO-d_6) δ 7.65–6.50 (m, 20, aromatic), 5.82 (s, 1, CH); M^+· 403 (100).

Anal. Calcd for $C_{27}H_{21}N_3O$: C, 80.37; H, 5.25; N, 10.41. Found: C, 80.31; H, 5.26; N, 10.44.

4-Thio-4,6-dihydro-1,3,5,6-tetraphenylthieno[3,4-*c*]pyrrole (15). 3,4-Dibenzoyl-1,5-diphenyl-2-methylthiopyrrole (474 mg, 1 mmol), phosphorus pentasulfide (222 mg, 1 mmol), and dry pyridine (10 mL) were refluxed for 6 h. Upon cooling, the reaction mixture was poured into 5% sodium hydroxide solution. A dark brown solid was separated by filtration and washed well with water. Recrystallization from ethanol or chloroform/ether gave golden-yellow prisms: 400 mg (87%); mp 219–220 °C; IR (KBr) 1590, 1480, 1450, 1380 cm^{-1}; λ_{max} ($CHCl_3$) 281 nm (log ϵ 4.46), 316 sh (4.25), 337 sh (4.13); NMR ($CDCl_3$) δ 8.1–6.9 (m, 20, aromatic), 6.0 (s, 1, CH); M^+· 459 (84).

Anal. Calcd for $C_{30}H_{21}NS_2$: C, 78.39; H, 4.61; N, 3.05. Found: C, 78.58; H, 4.66; N, 2.92.

Registry No.—**5** (R = CH_3S; $R^1 = R^2$ = Ph), 5416-30-8; **5** (R = $R^1 = R^2$ = Ph), 2556-46-9; **5** (R = R^1 = Ph; $R^2 = CH_3$), 2397-29-7; **5** (R = CH_3S; R^1 = Ph; $R^2 = CH_3$), 58432-39-6; **5** (R = NHPh; $R^1 = R^2$ = Ph), 101-01-9; **6** (R^3 = Ph), 19078-72-9; **6** (R^3 = COOEt), 41141-81-5; **7** (R = CH_3S; $R^1 = R^2 = R^3$ = Ph), 61505-57-5; **7** (r, $r^1 = R^2$ = Ph; R^3 = COOEt), 61505-59-7; **8** ($R^1 = R^3$ = Ph; $R^2 = CH_3$), 6716-39-8; **8** (R^1 = Ph; $R^2 = CH_3$; R^3 = COOEt), 56598-96-0; **8** ($R^1 = R^2$ = Ph; R^3 = COOEt), 56598-97-1; **8** ($R^1 = R^2 = R^3$ = Ph), 61505-60-0; **11** (R = CH_3S), 61505-61-1; **11** (R = COOEt), 61505-62-2; **12**, 61505-63-3; **15**, 61505-64-4; $R^4C{=}CR^4$ (R^4 = $COOCH_3$), 762-42-5; $R^4C{=}CR^4$ (R^4 = COPh), 1087-09-8; 1,2-dimethyl-3-phenyl-2-pseudothiourea hydriodide, 61505-65-5.

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Mesoionic Compounds. 41. *anhydro*-4-Hydroxy-2,3,5-trisubstituted-1,3-selenazolium Hydroxides and *anhydro*-4-Hydroxy-6-oxo-2,3,5-trisubstituted-4*H*-1,3-selenazinium Hydroxides

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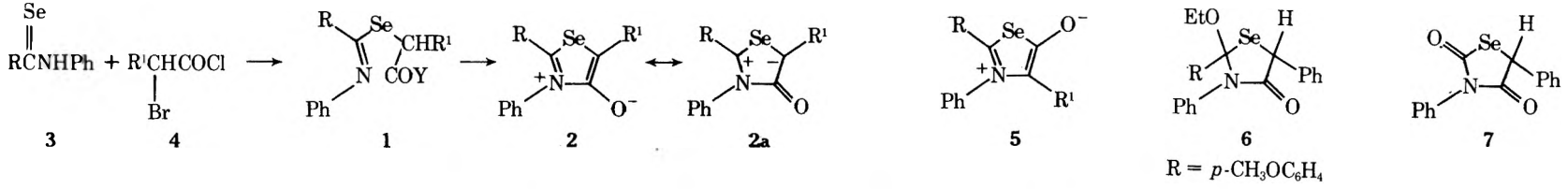
Reaction of a variety of monoprotonic selenoamide derivatives with 1,2-bielectrophiles such as α-bromophenylacetyl chloride and 2-bromo-2-ethoxycarbonylacetyl chloride gave representatives of the *anhydro*-4-hydroxy-1,3-selenazolium hydroxide mesoionic ring system possessing varying degrees of stability. These reacted with dimethyl acetylenedicarboxylate giving the corresponding pyridones with extrusion of selenium from the initial 1:1 adduct, a reaction pathway in contrast to the correspondingly substituted sulfur system where thiophene derivatives were usually formed. With phenyl isothiocyanate, selenium was also extruded from the initial 1:1 adduct leading to the *anhydro*-4-mercapto-6-oxopyrimidinium hydroxide system, the first example of the conversion of a five-membered mesoionic ring system into a six-membered mesoionic system. With chlorocarbonylphenylketene, the selenoamides readily formed the *anhydro*-4-hydroxy-6-oxo-4*H*-1,3-selenazinium hydroxide system.

In the two preceding papers in this series,[2] the introduction of various functional groups into several five-membered mesoionic ring systems was readily achieved by variation of both the 1,3-binucleophilic component of the reaction system and its 1,2-bielectrophilic counterpart, making this general procedure the one of choice for the synthesis of these ring systems. Extension of this method to selenium-containing 1,3-binucleophiles now provides a convenient synthesis of several endocyclic selenium mesoionic systems whose physical and chemical characteristics are described below.

The only example of a selenium-containing mesoionic ring system with an endocyclic selenium atom is *anhydro*-4-hydroxy-2,3,5-triphenyl-1,3-selenazolium hydroxide (**2**, R = R^1 = Ph), which was prepared[3] recently by dehydrative cyclization of the appropriate α-seleno acid (**1**, R = R^1 = Ph; Y = OH) with Ac_2O/Et_3N. Our studies, commenced prior to this report, have also focused in part on this ring system as the selenocarbonyl dipole represented by **2a** would be expected to influence the ability of the ring system to undergo a variety of 1,3-dipolar cycloadditions with dipolarophiles and a comprehensive study of the synthesis and reactions of this ring system is thus of particular interest. The utility of the corresponding sulfur-containing ring system in cycloadditions and as a source of other heterocycles is now well established[4] and the lesser stability of the C–Se bond compared to the C–S bond[5] suggested that the reactions of the ring system **2** would show a surprising individuality.

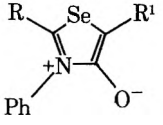
Synthesis. The requisite selenium-containing 1,3-binucleophiles have all been described in the literature[6] and, by the use of the appropriate selenoamide derivatives, it was possible to introduce aryl, alkylthio, and disubstituted amino substituents into the 2 position of **2**. Thus selenoanisanilide (**3**, R = *p*-$CH_3OC_6H_4$), prepared from *N*-phenylanisimidoyl chloride and sodium hydroselenide,[7] and α-bromophenylacetyl chloride (**4**, R^1 = Ph) in anhydrous benzene in the presence of Et_3N gave *anhydro*-3,5-diphenyl-4-hydroxy-2-*p*-methoxyphenyl-1,3-selenazolium hydroxide (**2**, R = *p*-$CH_3OC_6H_4$; R^1 = Ph) as deep-red needles (Table I). It is logical to assume that the intermediate **1** (R = *p*-$CH_3OC_6H_4$; R^1 = Ph; Y = Cl), or the ketene derived from it, was involved in the reaction and that the product formed was not the isomeric system **5**. This was confirmed by ring closure of the acid **1** (R = *p*-$CH_3OC_6H_4$; R^1 = Ph; Y = OH), prepared[3] from selenoanisanilide and α-bromophenylacetic acid, with Ac_2O/Et_3N. Attempted recrystallization of **2** (R = *p*-$CH_3OC_6H_4$; R^1 = Ph) resulted in decomposition and, on warming with ethanol, addition of a molecule of ethanol occurred across the 2,5 positions of the system giving 3,5-diphenyl-2-ethoxy-2-*p*-methoxyphenylselenazolidin-4-one (**6**). This reaction is similar to that occurring when 1,3,4-oxadiazolium salts are treated



3 4 1 2 2a 5 6 7

R = *p*-$CH_3OC_6H_4$

Table I. *anhydro*-2,5-Disubstituted-4-hydroxy-3-phenyl-1,3-selenazolium Hydroxides[e]



Substituents			Yield,			$M^{+\cdot}$	Spectral data		
R	R^1	Mp, °C	%	Crystal habit[a]	Mol formula	(rel int)	λ_{max}, nm (log ϵ)	ν_{CO} (KBr)	NMR, δ ($CDCl_3$)
p-$CH_3OC_6H_4$	Ph	195–197[b]	80	Deep-red needles: A	$C_{22}H_{17}NO_2Se$		510 (4.07), 290 (4.19)[c]	1610	3.7 (s, 3, OCH_3), 6.6–8.1 (m, 4, aromatic)
EtS	Ph	136–138	31	Yellow-orange irreg prisms: A	$C_{17}H_{15}NOSSe$		480 (3.82), 283 (4.05)[d]	1620	1.4 (t, 3, CH_3), 3.1 (q, 2, CH_2), 7.2–7.8 (m, 10, aromatic)
CH_3S	Ph	129–131[b]	43	Red prisms: A	$C_{16}H_{13}NOSSe$	347 (0.5)	480 (3.84), 283 (4.08)[d]	1685	2.63 (s, 3, CH_3), 6.97–8.87 (m, 10, aromatic)
CH_3S	COOEt	153–155	33	Yellow, irreg prisms: B	$C_{13}H_{13}NO_3SSe$	343 (2)	408 (3.78), 245 (4.11)[d]	1700 1625	1.32 (t, 3, CH_2CH_3), 2.70 (s, 3, CH_3), 4.27 (q, 2, CH_2CH_3), 7.10–7.70 (m, 5, aromatic)
EtS	COOEt	154–156[b]	56	Yellow needles: C	$C_{14}H_{15}NO_3SSe$	357 (0.1)	410 (4.85), 243 (4.11)[d]	1670 1620	1.25 (t, 3, SCH_2CH_3), 1.50 (t, 2, $CO_2CH_2CH_3$), 3.22 (q, 2, SCH_2CH_3), 4.30 (q, 2, CO_2CH_2-CH_3), 7.12–7.67 (m, 5, aromatic)
$(CH_3)_2N$	Ph	145–150	22	Yellow, irreg prisms: A	$C_{17}H_{16}N_2OSe$			1625	2.7 [s, 6, $(CH_3)_2N$], 6.8–7.7 (s, 10, aromatic)

[a] Recrystallization solvents: A, not recrystallized; B, $CHCl_3/Et_2O$; C, benzene. [b] Decomposition. [c] CH_3CN. [d] $CHCl_3$. [e] Satisfactory analytical values (±0.4% for C, H, N) were reported for all compounds in table.

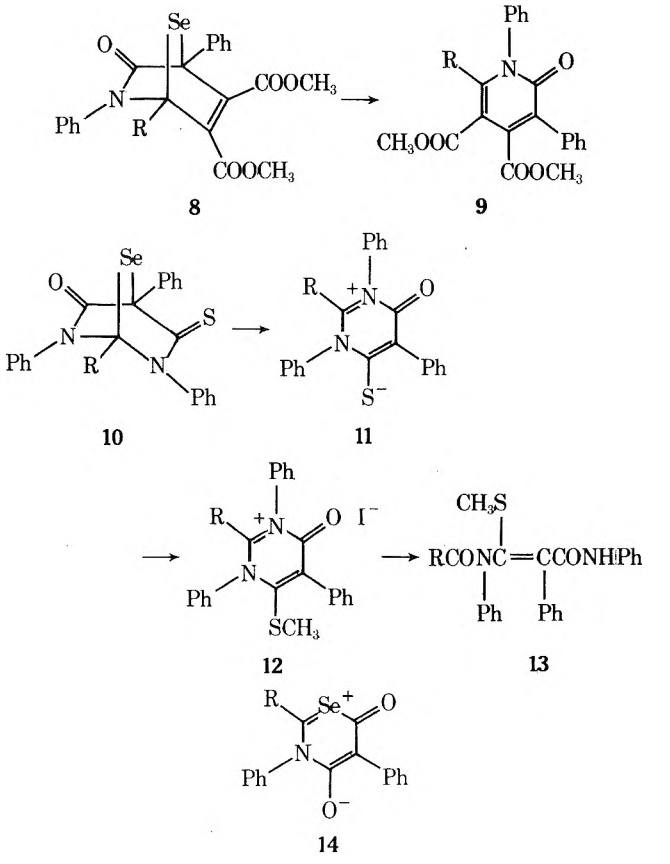
with nucleophiles such as sodium ethoxide.[8] Similarly reaction of *S*-methyl-*N*-phenylselenothiocarbamate[9] (**3**, R = CH_3S) with α-bromophenylacetyl chloride (**4**, R^1 = Ph) in anhydrous ether in the presence of Et_3N (2 mol) gave the corresponding 2-methylthio product **2** (R = CH_3S; R^1 = Ph). This product was sensitive to moisture and underwent decomposition on standing over several days; in water ready hydrolysis occurred giving 3,5-diphenyl-1,3-selenazolidine-2,4-dione (**7**). Use of 2-bromo-2-ethoxycarbonylacetyl chloride (**4**, R^1 = COOEt) in the reaction with **3** (R = CH_3S) gave *anhydro*-5-ethoxycarbonyl-4-hydroxy-2-methylthio-3-phenyl-1,3-selenazolium hydroxide (**2**, R = CH_3S; R^1 = COOEt). The introduction of the 5-ethoxycarbonyl substituent resulted in a considerably more stable product that did not undergo decomposition on standing.

The preparation of the corresponding 2-ethylthio derivative of **2** (R = EtS; R^1 = Ph) was more satisfactorily accomplished by Ac_2O/Et_3N (1:1) cyclization of **1** (R = EtS; R^1 = Ph; Y = OH), prepared from **3** (R = EtS) and α-bromophenylacetic acid. Although the 2-ethylthio product decomposed on attempted recrystallization, it was sufficiently stable to be handled conveniently, and underwent cycloaddition with dimethyl acetylenedicarboxylate as described below. Reaction of **3** (R = EtS) with 2-bromo-2-ethoxycarbonylacetyl chloride (**4**, R^1 = COOEt) gave the corresponding 5-ethoxycarbonyl derivative **2** (R = EtS; R^1 = COOEt) directly, the 5-ethoxycarbonyl substituent again imparting stability to the system.

Reaction of 1,1-dimethylamino-3-phenyl-2-selenourea[9] [**3**, R = $(CH_3)_2N$] and α-bromophenylacetyl chloride in benzene/Et_3N readily gave the corresponding *anhydro*-2-dimethylamino-3,5-diphenyl-4-hydroxy-1,3-selenazolium hydroxide [**2**, R = $(CH_3)_2N$; R^1 = Ph] which was sufficiently stable to moisture for isolation but which underwent decomposition on standing and heating.

The spectral characteristics shown in Table I, together with the syntheses described above, strongly support the assigned structure **2**. It was possible to eliminate structure **5** from consideration by studying the reaction of these selenazolium derivatives with dimethyl acetylenedicarboxylate and phenyl isothiocyanate. With the former, the selenazolium hydroxide **2** (R = *p*-$CH_3OC_6H_4$; R^1 = Ph) in refluxing benzene over 10 h in the dark gave dimethyl 1,3-diphenyl-6-(*p*-methoxyphenyl)-2-oxopyridine-4,5-dicarboxylate (**9**, R = *p*-$CH_3OC_6H_4$), the intermediate **8** (R = *p*-$CH_3OC_6H_4$) decomposing by elimination of selenium. This is in contrast[4a] to the corresponding sulfur-containing mesoionic system in which the corresponding intermediate **8** undergoes elimination of phenyl isocyanate with the formation of a tetrasubstituted thiophene. No doubt the ease of elimination of selenium is the guiding force in this present reaction. A similar ready loss of selenium was also reported[3] in the reaction of **2** (R = R^1 = Ph) with dimethyl acetylenedicarboxylate. Similarly **2** (R = EtS; R^1 = Ph) and dimethyl acetylenedicarboxylate in boiling benzene gave dimethyl 1,3-diphenyl-2-oxo-6-ethylthiopyridine-4,5-dicarboxylate (**9**, R = EtS). In several other representatives of **2** studied, the thermal stability of the ring system was such that decomposition occurred before significant cycloaddition was realized. Should the structure of these derivatives be represented by the ring system **5**, then under these reaction conditions pyrrole derivatives would be anticipated, formed by elimination of COSe from the initial 1:1 cycloadduct.[10]

Interconversions of five-membered mesoionic ring systems are now well established, thermal,[11] hydrolytic,[12] and reactions of the mesoionic system with heterocumulenes[10,13] having all been reported. Conversion of a five-membered mesoionic system into a six-membered mesoionic system has not yet been accomplished and the ready loss of selenium from the intermediate **8** suggested that it would also be readily extruded from **10** (R = *p*-$CH_3OC_6H_4$), the 1:1 adduct formed from **2** (R = *p*-$CH_3OC_6H_4$; R^1 = Ph) and phenyl isothiocyanate. This was found to be the case when **2** (R = *p*-$CH_3OC_6H_4$; R^1 = Ph) and phenyl isothiocyanate were refluxed in xylene over 72 h, *anhydro*-1,3-diphenyl-4-mercapto-2-*p*-methoxyphenyl-6-oxopyrimidinium hydroxide (**11**, R = *p*-$CH_3OC_6H_4$) being obtained in 66% yield. This pyrimidinium derivative reacted with methyl iodide giving the corresponding salt **12** (R = *p*-$CH_3OC_6H_4$) and on heating the iodide with aqueous ethanol, hydrolytic ring opening occurred giving **13** (R = *p*-$CH_3OC_6H_4$). This represents a very convenient synthesis of the mesoionic ring system **11** which cannot be made easily by direct synthesis. The corresponding *anhydro*-4-hydroxy-6-oxopyrimidinium hydroxide system is readily available by reaction of monoprotonic amidines with carbon suboxide or chlorocarbonylphenylketene but its reaction with phenyl isothiocyanate resulted in thermal rearrangement occurring under the high temperatures involved.[14]



Replacement of the 1,2-bielectrophile in the reaction with selenoamide derivatives with a 1,3-bielectrophile such as chlorocarbonylphenylketene should provide a convenient synthesis of six-membered mesoionic systems containing selenium. This reaction, analogous to the formation of the *anhydro*-4-hydroxy-6-oxo-4*H*-1,3-thiazinium hydroxide system[15] from thioamides and chlorocarbonylphenylketene,[16] occurred readily when the ketene and *N*-phenyl *S*-methylselenothiocarbamate (**3**, R = CH_3S) were mixed in anhydrous ether at room temperature, *anhydro*-3,5-diphenyl-4-hydroxy-2-methylthio-6-oxo-4*H*-1,3-selenazinium hydroxide (**14**, R = CH_3S) being obtained in 53% yield. The corresponding 2-ethylthio product (**14**, R = EtS) was similarly formed from **3** (R = EtS) and the ketene. Both products decomposed on attempted recrystallization but could be obtained in an analytical pure form as described in the Experimental Section. They were considerably less stable than their corresponding sulfur analogues and decomposed on standing over several weeks.

Experimental Section[17]

General Procedures for the Preparation of 2. A. Formation of *anhydro*-3,5-Diphenyl-4-hydroxy-2-*p*-methoxyphenyl-1,3-selenazolium Hydroxide (2, R = *p*-$CH_3OC_6H_4$; R^1 = Ph). A mixture of selenoanisanilide (0.258 g, 0.0009 mol) in dry benzene (35 mL) and α-bromophenylacetyl chloride[18] (0.21 g, 0.0009 mol) was stirred together for 30 min. The yellow precipitate was suspended in anhydrous Et_2O (30 mL) and Et_3N (0.18 g, 0.002 mol) was added, the color of the reaction mixture turning violet and deep-red crystals soon separating. These were collected, washed with H_2O, EtOH, and Et_2O, and dried in vacuo; an additional crop of deep-red needles separated from the filtrate, 0.30 g (90%), mp 195–197 °C dec (Table I).

B. *anhydro*-5-Ethoxycarbonyl-4-hydroxy-2-methylthio-3-phenyl-1,3-selenazolium Hydroxide (2, R = CH_3S; R^1 = COOEt). A solution of 2-bromo-2-ethoxycarbonylacetyl chloride[19] (0.46 g, 0.002 mol) in anhydrous ether (10 mL) was added to a solution of *S*-methyl *N*-phenylselenothiocarbamate[9] (0.46 g, 0.002 mol) in anhydrous ether (25 mL) and the mixture stirred at room temperature under N_2 for 10 min. Et_3N (0.202 g, 0.002 mol) was added and stirring continued for an additional 1.5 h. The resulting mixture was extracted with hot benzene and, after concentration and cooling, yellow needles separated, 0.8 g (56%), mp 154–156 °C dec. Alternatively the initial yellow precipitate may be separated and resuspended in anhydrous Et_2O before addition of Et_3N (Table I).

Cycloaddition with Dimethyl Acetylenedicarboxylate. Preparation of Dimethyl 1,3-Diphenyl-2-oxo-6-ethylthiopyridine-4,5-dicarboxylate (9, R = EtS). *anhydro*-3,5-Diphenyl-4-hydroxy-2-ethylthio-1,3-selenazolium hydroxide (0.5 g, 0.0012 mol) and the ester (0.4 g, 0.003 mol) in dry benzene (25 mL) were refluxed for 72 h, the initial orange-red color of the reaction mixture disappearing in 10 h. After filtration of the reaction mixture, the solvent was concentrated in vacuo and the initial precipitate of amorphous selenium (0.1 g, 90%) was removed. Complete evaporation of the solvent gave a solid residue which was washed with hexane and then recrystallized from $CHCl_3$/hexane forming off-white coral-shaped crystals: mp 128–129 °C; IR (KBr) ν_{CO} 1760, 1730, 1655 cm^{-1}; NMR ($CDCl_3$) δ 1.06 (t, 3, SCH_2CH_3), 2.6 (q, 2, SCH_2CH_3), 3.65 (s, 3, OCH_3), 3.8 (s, 3, OCH_3), 7.35 (m, 10, aromatic); mass spectrum *m/e* (rel intensity) M^+· 423 (70).

Anal. Calcd for $C_{23}H_{21}NSO_5$: C, 65.25; H, 4.96; N, 3.31. Found: C, 64.90; H, 4.97; N, 3.42.

In the preparation of the corresponding 5-*p*-methoxyphenylpyridone (9, R = *p*-$CH_3OC_6H_4$), purification was effected by chromatography on silica gel after removal of the selenium. Dimethyl 1,3-diphenyl-6-*p*-methoxyphenyl-2-oxopyridine-4,5-dicarboxylate (9, R = *p*-$CH_3OC_6H_4$) crystallized from chloroform/hexane as colorless needles: 35%; mp 230–231 °C; λ_{max} ($CHCl_3$) 355 nm (log ε 3.51); IR (KBr) ν_{CO} 1740, 1730, 1660, 1610 cm^{-1}; NMR ($CDCl_3$) δ 3.45 (s, 3, CO_2CH_3), 3.6 (s, 3, CO_2CH_3), 3.7 (s, 3, OCH_3), 6.8–7.5 (m, 14, aromatic); mass spectrum *m/e* (rel intensity) M^+· 469 (40).

Anal. Calcd for $C_{28}H_{23}NO_6$: C, 71.63; H, 4.94; N, 2.98. Found: C, 71.27; H, 4.83; N, 2.95.

3,5-Diphenyl-2-ethoxy-2-*p*-methoxyphenyl-1,3-selenazolidin-4-one (6). The mesoionic system 2 (R = *p*-$CH_3OC_6H_4$; R^1 = Ph) (0.10 g, 0.0003 mol) was refluxed in ethanol (25 mL) for 1 h. After concentrating to 10 mL and standing at 0 °C overnight, a pink product was obtained. It crystallized from ethanol/petroleum ether (bp 40–60 °C) as needles with a slight pink color: 0.32 g (28%); mp 190–191 °C; IR (KBr) ν_{CO} 1675 cm^{-1}.

Anal. Calcd for $C_{24}H_{23}NSeO_3$: C, 63.86; H, 5.10; N, 3.10. Found: C, 63.68; H, 5.14; N, 3.01.

Hydrolysis of *anhydro*-3,5-Diphenyl-4-hydroxy-2-methylthio-1,3-selenazolium Hydroxide (2, R = CH_3S; R^1 = Ph). *S*-Methyl *N*-phenylselenothiocarbamate (0.690 g, 0.003 mol) in $CHCl_3$ (25 mL) was treated with α-bromophenylacetyl chloride (0.704 g, 0.003 mol). After 10 min at room temperature, Et_3N (0.61 g, 0.006 mol) was added and the reaction mixture stirred for an additional 10 min. The reaction mixture was washed twice with H_2O (25 mL) and the $CHCl_3$ solution dried ($MgSO_4$). On concentration of the solvent a product separated and 3,5-diphenyl-1,3-selenazolidine-2,4-dione crystallized from $CHCl_3$/Et_2O as colorless needles: 0.31 g (33%); mp 168–170 °C; IR (KBr) ν_{CO} 1740, 1675 cm^{-1}; λ_{max} (CH_3OH) 265 nm (log ε 3.54), 220 (3.84); NMR ($CDCl_3$) δ 5.63 (s, 1, CH), 7.33–7.57 (m, 10, aromatic); mass spectrum *m/e* (rel intensity) M^+· 317 (29).

Anal. Calcd for $C_{15}H_{11}NO_2Se$: C, 56.97; H, 3.51; N, 4.43. Found: C, 56.78; H, 3.58; N, 4.39.

***anhydro*-1,3-Diphenyl-4-mercapto-2-*p*-methoxyphenyl-6-oxopyrimidinium Hydroxide (11, R = *p*-$CH_3OC_6H_4$).** A mixture of *anhydro*-3,5-diphenyl-4-hydroxy-2-*p*-methoxyphenyl-1,3-selenazolium hydroxide (2, R = *p*-$CH_3OC_6H_4$; R^1 = Ph) (1.0 g, 0.003 mol) and phenyl isothiocyanate (0.54 g, 0.004 mol) in dry xylene (30 mL) was refluxed for 72 h, the initial violet color of the reaction mixture turning brown during this time. On cooling a yellow, crystalline product mixed with selenium separated. This was dissolved in $CHCl_3$, the selenium separated, and, after removal of the $CHCl_3$, the residue was recrystallized from benzene forming yellow needles: 0.75 g (66%); mp 275–276 °C; IR (KBr) ν_{CO} 1675 cm^{-1}; λ_{max} (CH_3CN) 325 nm (log ε 4.02), 270 (4.09); NMR ($CDCl_3$) δ 3.6 (s, 3, OCH_3), 6.5–7.6 (m, 19, aromatic); mass spectrum *m/e* (rel intensity) M^+· 462 (22).

Anal. Calcd for $C_{29}H_{22}N_2O_2S$: C, 75.31; H, 4.80; N, 6.06. Found: C, 75.41; H, 4.85; N, 6.00.

The methiodide of 11 (R = *p*-$CH_3OC_6H_4$; R^1 = Ph) was prepared by refluxing with an excess of CH_3I in dry benzene for 3 h. The product separated from the cooled solution and crystallized from acetone as yellow needles: 0.15 g (62%); mp 272–274 °C; IR (KBr) ν_{CO} 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.9 (s, 3, SCH_3), 3.64 (s, 3, OCH_3), 6.5–8.3 (m, 19, aromatic).

Anal. Calcd for $C_{30}H_{25}IN_2O_2S$: C, 59.60; H, 4.14; N, 4.63. Found: C, 59.53; H, 4.10; N, 4.52.

Hydrolysis of 2-*p*-Methoxyphenyl-4-methylthio-6-oxo-1,3,5-triphenylpyrimidinium Iodide (12, R = *p*-$CH_3OC_6H_4$). The iodide was refluxed in 95% EtOH for 1 h. The product that separated on cooling crystallized from EtOH as colorless prisms: mp 154–155 °C; IR (KBr) ν_{NH} 3340, ν_{CO} 1670 cm^{-1}; NMR ($CDCl_3$) δ 2.19 (s, 3, SCH_3), 3.7 (s, 3, OCH_3), 6.5–7.7 (m, 20, aromatic and NH).

Anal. Calcd for $C_{30}H_{26}N_2O_3S$: C, 72.87; H, 5.26; N, 5.66. Found: C, 72.93; H, 5.45; N, 5.51.

***anhydro*-3,5-Diphenyl-4-hydroxy-2-methylthio-6-oxo-4*H*-1,3-selenazinium Hydroxide (14, R = CH_3S).** Chlorocarbonylphenylketene (0.18 g, 0.001 mol) in anhydrous Et_2O (5 ml) was added to *S*-methyl *N*-phenylselenothiocarbamate (3, R = CH_3S) (0.23 g, 0.001 mol) in anhydrous Et_2O (25 mL). After stirring at room temperature under N_2 for 1 h, the product was collected and washed with anhydrous Et_2O, giving orange, irregular prisms: 0.2 g (53%); mp 96–98 °C dec; IR (KBr) ν_{CO} 1675, 1615 cm^{-1}; λ_{max} ($CHCl_3$) 325 nm (log ε 4.02), 247 sh (4.12); NMR ($CDCl_3$) δ 2.58 (s, 3, CH_3), 7.10–7.70 (m, 10, aromatic).

Anal. Calcd for $C_{17}H_{13}NO_2SSe$: C, 54.55; H, 3.50; N, 3.74. Found: C, 54.15; H, 3.66; N, 3.75.

The corresponding 2-ethylthio product (14, R = EtS) was also obtained as orange, irregular prisms: 62%; mp 128–130 °C dec; IR (KBr) ν_{CO} 1670, 1610 cm^{-1}; λ_{max} ($CHCl_3$) 332 nm (log ε 3.85), 270 (3.89); NMR ($CDCl_3$) δ 1.27 (t, 3, CH_3), 2.95 (q, 2, CH_2), 7.03–7.66 (m, 10, aromatic).

Anal. Calcd for $C_{18}H_{15}NO_2SSe$: C, 55.52; H, 3.88; N, 3.60. Found: C, 55.45; H, 4.10; N, 3.85.

Registry No.—2 (R = *p*-$CH_3OC_6H_4$; R′ = Ph), 61521-79-7; 2 (R = EtS; R′ = Ph), 61521-80-0; 2 (R = CH_3S; R′ = Ph), 61521-81-1; 2 (R = CH_3S; R′ = COOEt), 61521-82-2; 2 (R = EtS; R′ = COOEt), 61521-83-3; 2 (R = $(CH_3)_2N$; R′ = Ph), 61521-84-4; 3 (R = *p*-$CH_3OC_6H_4$), 61521-85-5; 3 (R = CH_3S), 21347-34-2; 3 (R = $(CH_3)_2N$), 21347-32-0; 3 (R = EtS), 61521-86-6; 4 (R′ = Ph), 19078-72-9; 4 (R′ = COOEt), 41141-81-5; 6 (R = *p*-$CH_3OC_6H_4$), 61521-87-7; 7, 61521-88-8; 9 (R = EtS), 61521-89-9; 9 (R = *p*-$CH_3OC_6H_4$), 61521-90-2; 11 (R = *p*-$CH_3OC_6H_4$), 61521-91-3; 12 (R = *p*-$CH_3OC_6H_4$), 61521-92-4; 13 (R = *p*-$CH_3OC_6H_4$), 61521-93-5; 14 (R = CH_3S), 61521-94-6; 14 (R = EtS), 61521-95-7; phenyl isothiocyanate, 103-72-0; CH_3I, 74-88-4; chlorocarbonylphenylketene, 17118-70-6.

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Notes

Cycloaddition of *N*-Iminothiazolium Ylides with Acetylenic Dipolarophiles. Formation of Pyrazoles[1]

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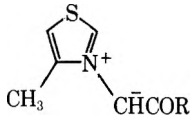
The cycloaddition of ylides derived from suitable heterocycles[2] with acetylenic dipolarophiles provides a convenient method of annelation of a second ring. We have shown[3] recently that in the reaction of the thiazolium ylide **1** with acetylenic dipolarophiles, the initial cycloadduct **2** underwent ready transformation to the 1*H*-pyrrolo[2,1-*c*][1,4]thiazine **3**. The reaction of the corresponding *N*-imino ylide **4** (R = H) with dimethyl acetylenedicarboxylate has been reported[4] to give the 7,9a-dihydrothiazolo[3,2-*b*][1,2]diazepine (**7**, R^1 = $COOCH_3$), a 1:2 adduct whose structure was assigned on the basis of spectral data. However, we have now found that although the data indicate that a 1:2 adduct was formed, rearrangement had occurred during the reaction and the product is the pyrazole **6**.



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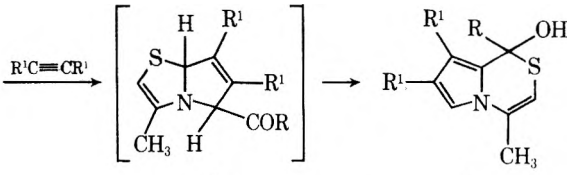
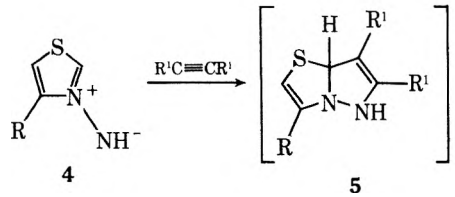
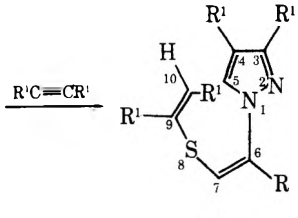


2 **3**



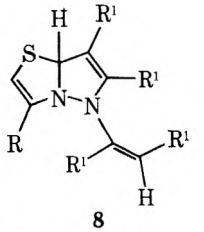
4 **5**



6

a, R = H; R^1 = $COOCH_3$
b, R = CH_3; R^1 = $COOCH_3$
c, R = CH_3; R^1 = COPh

7



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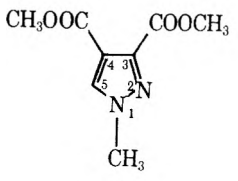

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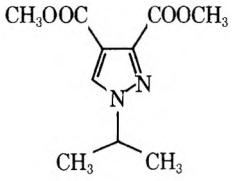

10

The ylide **4** (R = H, CH_3), generated in situ from the corresponding 3-aminothiazolium mesitylsulfonate[4] and NEt_3 (1 equiv) in DMF at room temperature, reacted readily with dimethyl acetylenedicarboxylate (2 equiv). After quenching the reaction from **4** (R = H) with ice–water and purification of the separated product by chromatography on silica gel, colorless needles of the pyrazole **6a** were obtained. Analytical and mass spectral data established the 1:2 composition of this product, and the ^1H NMR (100 MHz) data (Experimental Section) are consistent with this structure. These data are in agreement with those reported earlier for **7** but, rather than being definitive for structure **7**, they are also consistent with both structures **6a** and **8**. In terms of structure **7**, the observed coupling constant (8.0 Hz) between H_2 and H_3 is too large for these protons in a thiazoline ring, this coupling constant normally being ca. 5 Hz.[5] Similarly the chemical shift δ 8.08 of the proton assigned to the bridgehead H_{9a} is at too low a field compared to those observed for protons in an analogous environment.[3] However, structure **6a** readily accommodates the chemical shifts at δ 8.08, 7.02, 6.18, and 6.10 by protons at positions 5, 6, 7, and 10, respectively. The coupling constant $J_{6,7}$ = 8.0 Hz is consistent with maintaining a cis stereochemistry in the intermediate vinyl sulfide formed by fission of the C–S bond in **5**. The chemical shift of H_5 at δ 8.08 is also in agreement with that observed (δ 7.88) for H_5 in dimethyl 1-methylpyrazole-3,4-dicarboxylate (**9**) synthesized[6] from *N*-methylsydnone and dimethyl acetylenedicarboxylate.

^{13}C NMR data[7] provided decisive evidence in support of structure **6** (Table I). The absence of a resonance assignable to an sp^3 bridgehead carbon atom excludes structures **7** and **8**, and the seven sp^2 carbon atoms observed are readily accounted for by structure **6**. Off-resonance decoupling established that four of these carbon atoms bear a hydrogen atom,

Table I. ^{13}C Chemical Shift Assignments (ppm) for Some Pyrazole Derivatives ($CDCl_3$)

Structure	Carbon atoms at positions								
	3	4	5	6	7	9	10	CO	Ester CH_3
6a	145.8	115.9	134.2	124.5	111.0	114.4	118.9	165.4	53.2
								163.8	52.7
								161.6	52.1
6b[a]	147.0	115.7	133.0	135.0	109.7	144.2	118.0	165.7	53.2
								164.1	52.7
								162.2	52.1
								161.9	
9[b]	143.5	115.1	135.5					162.2	52.5
									51.7

[a] C_6CH_3, 21.4 ppm. [b] NCH_3, 39.8 ppm.

and the chemical shifts of C_9 and C_{10} were found to be analogous to those of the related carbon atoms in bis(2-carboethoxyvinyl) sulfide which occurred at 147.8 and 116.3 ppm, respectively.

From the reaction of the ylide **4** (R = CH_3) with dimethyl acetylenedicarboxylate, in addition to the pyrazole **6b** a small amount of a nonseparable mixture (mp 105–109 °C) of **6b** and an isomeric product was isolated. NMR data of the mixture indicated that the isomer (ν_{CO} 1725, 1745 cm^{-1}) was present to ca. 10% of the total mixture. The ^1H NMR spectrum of **6b** showed chemical shifts consistent with the assigned structure as were the ^{13}C chemical shifts shown in Table I. A very small splitting (<1 Hz) of the C_6CH_3 and H_7 indicated the cis relationship of these two groups to each other in **6b** and also in the isomeric product. This suggests that the two isomers are most likely cis–trans isomers formed in the addition of the intermediate vinyl sulfide obtained from **5** by fission of the C–S bond to a second molecule of dimethyl acetylenedicarboxylate, such additions usually occurring in a trans fashion.[8] Dibenzoylacetylene also reacted with **4** (R = CH_3) giving the pyrazole **6c**.

Chemical evidence for structure **6b** was obtained by desulfurization with Raney nickel (W-2). Methyl 1-isopropylpyrazole-3,4-dicarboxylate (**10**) was isolated by preparative TLC (silica gel, benzene–acetone, 9:1) as a colorless oil and the NMR spectrum of the crude reaction mixture also showed the presence of an equivalent amount of dimethyl succinate [δ 3.68 (s, 6, $COOCH_3$), 2.61 (s, 4, CH_2)].

Experimental Section[9]

Preparation of the *N*-Aminothiazolium Salts. An ice-cold solution of the thiazole (20 mmol) in dry dichloromethane (15 mL) was treated dropwise with a solution of *O*-mesitylenesulfonylhydroxylamine (20 mmol) in dichloromethane (15 mL). After stirring for 10 min at room temperature anhydrous ether (10 mL) was added. On cooling colorless needles of 3-aminothiazolium mesitylenesulfonate, mp 93–95 °C, the precursor of **4** (R = H), and 3-amino-4-methylthiazolium mesitylenesulfonate, mp 128 °C, the precursor of **4** (R = CH_3), separated.[4]

Reaction of the *N*-Iminothiazolium Ylides with Activated Acetylenes. A stirred solution (0 °C) of the appropriate thiazolium salt and 2 equiv of the acetylene in dry dimethylformamide was treated dropwise with an equimolar amount of triethylamine. After stirring for 4 h at room temperature, the mixture was poured into ice–water and the precipitated solid was collected, dried (**6a** was chromatographed on silica gel), and recrystallized from the appropriate solvent.

The pyrazole **6a** crystallized as colorless needles from ethanol: mp 120–121 °C (lit.[4] mp 122–124 °C), 32%; IR (KBr) 1710, 1730, 1740 cm^{-1} (CO); λ_{max} (CH_3OH) 315 nm (log ϵ 4.29), 230 sh (4.0); NMR (100 MHz, $CDCl_3$) δ 8.08 (s, 1, H_5), 7.02 (AB d, 1, J = 8.0 Hz, H_6), 6.18 (AB d, 1, J = 8.0 Hz, H_7), 6.10 (s, 1, H_{10}), 3.92, 3.84, 3.80, 3.68 (each s, 12, $COOCH_3$); M^+·384 (17).

Anal. Calcd for $C_{15}H_{16}N_2O_8S$: C, 46.87; H, 4.19; N, 7.29. Found: C, 46.77; H, 4.11; N, 7.22.

The pyrazole **6b** formed colorless needles from ethanol: mp 118 °C, 40%; IR (KBr) 1725, 1735 cm^{-1} (CO); λ_{max} (CH_3OH) 317 nm (log ϵ 4.16), 225 sh (4.0); NMR (100 MHz, $CDCl_3$) δ 8.08 (s, 1, H_5), 6.04 (broad s, 2, H_7, H_{10}), 3.93, 3.86, 3.82, 3.70 (each s, 12, $COOCH_3$), 2.35 (d, 3, $J \simeq 1$ Hz, CH_3); M^+·398 (20).

Anal. Calcd for $C_{16}H_{18}N_2O_8S$: C, 48.23; H, 4.55; N, 7.03. Found: C, 48.24; H, 4.49; N, 6.98.

The mother liquor from the crystallization of **6b** was concentrated, giving a yellow, crystalline product shown to be a mixture of **6b** and an isomer: mp 105–109 °C; NMR (100 MHz, $CDCl_3$) δ 8.27, 8.08 (each s, 1, H_5), 6.04 (broad d, 2, H_7 and H_{10}), 3.94, 3.86, 3.82, 3.76, 3.70 (each s, 12, $COOCH_3$), 2.35, 2.31 (each d, 3, $J \simeq 1$ Hz, C_6CH_3).

Anal. Calcd for $C_{16}H_{18}N_2O_8S$: C, 48.23; H, 4.55; N, 7.03. Found: C, 48.29; H, 4.51; N, 7.03.

The pyrazole **6c** formed cream prisms from dichloromethane–pentane: mp 150 °C, 29%; IR (KBr) 1655, 1675 cm^{-1} (CO); NMR (60 MHz, $CDCl_3$) δ 8.17–7.22 (m, 22, aromatic, H_5 and H_{10}), 6.13 (broad s, 1, H_7), 2.35 (broad s, 3, CH_3); M^+·582 (4).

Anal. Calcd for $C_{36}H_{26}N_2SO_4$: C, 74.23; H, 4.47; N, 4.81. Found: C, 73.95; H, 4.55; N, 4.81.

Desulfurization of Pyrazole 6b with Raney Nickel. The pyrazole (0.4 g, 1 mmol), freshly prepared Raney nickel[10] (4 g), and ethanol (15 mL) were refluxed with stirring for 2.5 h and filtered. The filtrate was stripped of solvent. Methyl 1-isopropylpyrazole-3,4-dicarboxylate (**10**) was isolated from the crude product by PLC (silica gel, benzene–acetone, 9:1) as a colorless oil: IR (film) 1750, 1740, 1725 cm^{-1} (CO); NMR (60 MHz, $CDCl_3$) δ 7.93 (s, 1, H_5), 4.58 (septet, 7, >CH), 3.95 (s, 3, $COOCH_3$), 3.83 (s, 3, $COOCH_3$), 1.53 (d, 6, J = 6.7 Hz, CH_3); M^+·226 (23).

Registry No.—**4** (R = H), 59046-20-7; **4** (R = CH_3), 61544-00-1; **6a**, 61558-10-9; **6b**, 61544-01-2; **6b** isomer, 61544-02-3; **6c**, 61544-03-4; **9**, 22050-80-2; **10**, 61544-04-5; thiazole, 288-47-1; 4-methylthiazole, 693-95-8; *O*-mesitylenesulfonylhydroxylamine, 36016-40-7; 3-aminothiazolium mesitylenesulfonate, 52197-73-6; 3-amino-4-methylthiazolium mesitylenesulfonate, 61544-06-7; dimethly acetylenedicarboxylate, 762-42-5; dibenzoylacetylene, 1087-09-8.

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Synthesis and Absolute Configuration of the Optically Active Forms of 2-[Bis(2-chloroethyl)amino]-4-methyltetrahydro-2*H*-1,3,2-oxazaphosphorine 2-Oxide (4-Methylcyclophosphamide)

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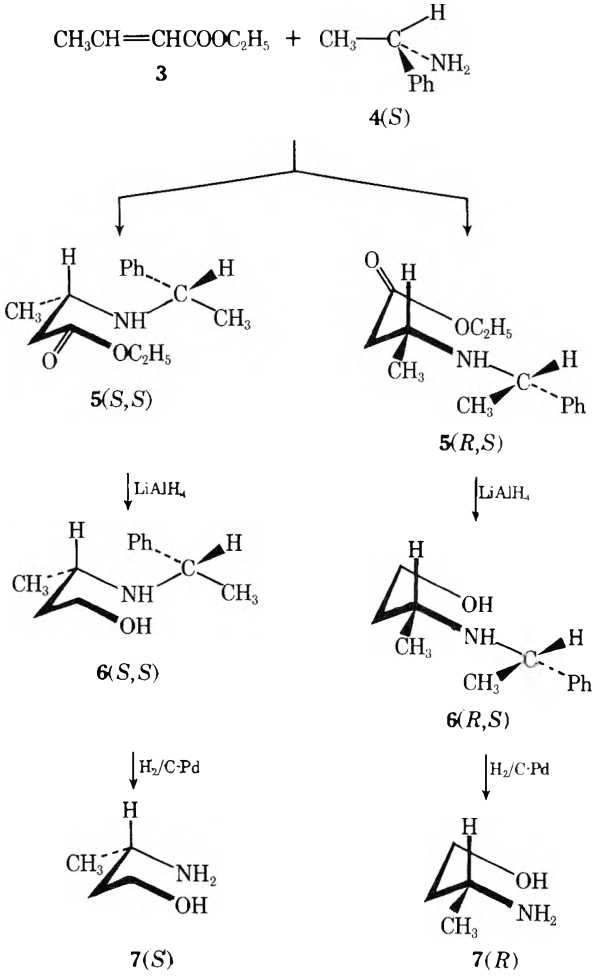
The cytochrome P450 mediated oxidation of the antitumor agent 2-[bis(2-chloroethyl)amino]tetrahydro-2*H*-1,3,2-oxazaphosphorine 2-oxide (cyclophosphamide **1**) to give the 4-hydroxy derivative is well documented[1] and has prompted many detailed investigations.[2] 4-Methylcyclophosphamide (**2**) is of interest since the methyl group prevents further oxidative metabolism of the 4-hydroxy derivative.[3] The isolation and configurational assignment of the cis and trans forms of 4-methylcyclophosphamide (**2**) has been described recently by Struck et al.[4] We now report evidence which indicates that these configurational assignments are erroneous and also describe the synthesis of the optically active forms of *cis*- and *trans*-4-methylcyclophosphamide.

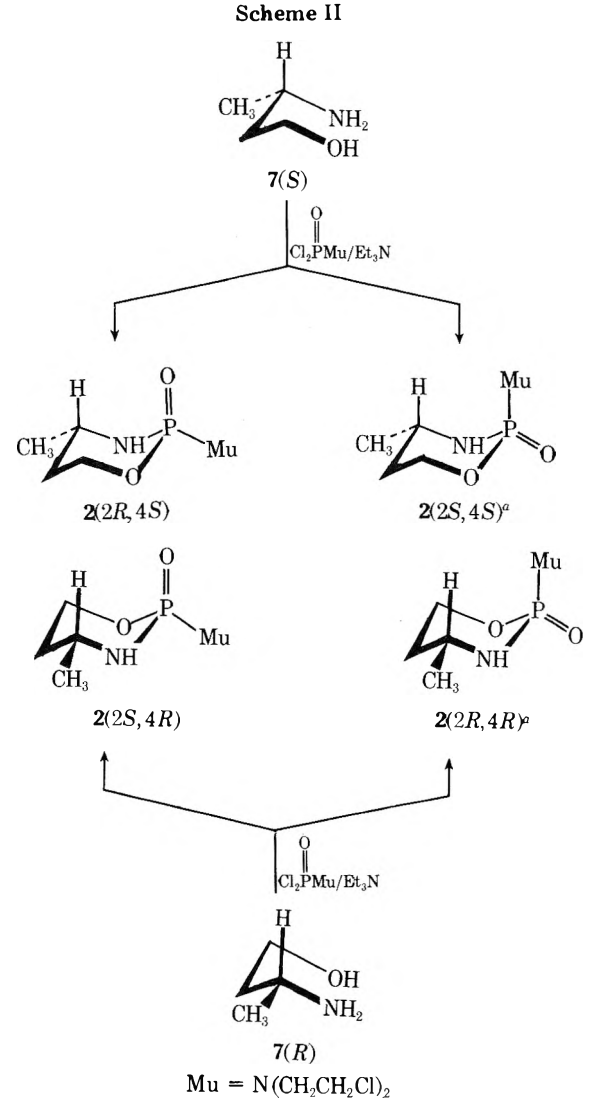
The synthesis of the four optically active forms of 4-methylcyclophosphamide (**2**) was based on (+)- and (−)-3-aminobutan-1-ol (**7**) as depicted in Scheme I. Treatment of ethyl crotonate (**3**) with (−)-1(*S*)-phenylethylamine [**4**(*S*)] gave the separable diastereoisomers of ethyl 3-*N*-[1(*S*)-methylbenzyl]aminobutyrate (**5**) having readily determinable absolute configurations at the newly introduced asymmetric carbon atom (C-3).[5] These were reduced in two stages to give the requisite enantiomers of 3-aminobutan-1-ol (**7**). Condensation of each of these enantiomers with *N*,*N*-bis(2-chloroethyl) phosphoramidic dichloride gave in each case a mixture of two separable isomers of 4-methylcyclophosphamide, designated "fast" and "slow" according to their relative mobilities on TLC. Since the absolute configuration of the starting materials **7** is known, the four enantiomeric 4-methylcyclophosphamides have predetermined configurations at C-4.

Determination of the absolute configurations at phosphorus for the pairs of diastereoisomers **2** for which the absolute configuration at C-4 is known is equivalent to the assignment of cis and trans geometry to the "fast" and the "slow" isomers **2**. Contrary to the assignments made by Struck et al.[4] for the faster migrating racemic **2** (mp 72–74 °C) and the slower migrating racemic **2** (mp 102 °C) we assign, taking the example of the fast and the slow products derived from 3-(*R*)-aminobutan-1-ol, the spatial arrangement 4-Me_{eq}-2NR_{2eq} (trans) to the slower migrating **2** (and hence the configuration 2*S*,4*R*) and 4-Me_{eq}-2NR_{2ax} ⇌ 4-Me_{ax}-2NR_{2eq} (cis) to the faster migrating **2** (2*R*,4*R*) on the basis of the following arguments: (1) **2** (2*S*,4*R*) absorbs at lower field in its ^{31}P NMR spectrum ($\delta_{^{31}P}$ −13.5 ppm, external H_3PO_4) than **2** (2*R*,4*R*) ($\delta_{^{31}P}$ −11.0 ppm);[6a] (2) **2**(2*S*,4*R*) exhibits a lower ν_{PO} value (1218 cm^{-1} in

Scheme I



Scheme II



[a] For simplicity one conformation shown only.

CCl_4) than **2**(2*R*,4*R*) (1231 cm^{-1});[6b,7] (3) The value (2.9 Hz) of $^4J_{PNCCH_3}$ (^1H NMR) for **2**(2*S*,4*R*) is higher than that (1.9 Hz)[8] for **2**(2*R*,4*R*).

The conformational stability of **2**(2*S*,4*R*) was established on the basis of the data $^3J_{POCH_{eq}}$ = 22.75 (^1H NMR), $^3J_{PNCC_5}$ = 3.2, and $^3J_{PNCCH_3}$ = 12.1 Hz (^{13}C NMR). Although analysis of the ^1H NMR spectrum of **2**(2*R*,4*R*) was not possible because of its complexity, the ^{13}C NMR spectrum gave the data $^3J_{PNCC_5}$ = 7.0 and $^3J_{PNCCH_3}$ = 7.6 Hz, which suggested rapid equilibrium of two or more conformations of **2**(2*R*,4*R*). The assignment 4-Me_{eq}-2NR_{2eq} to **2**(2*S*,4*R*) and its conformational stability is consistent with the known equatorial preference of the 4-methyl and 2-dialkylamino groups in dioxa- and oxazaphosphorine ring systems.[9a,b]

Arguments analogous to those applied to the products from 3-(*R*)-aminobutan-1-ol enabled the assignment of absolute configuration to the products from the 3-(*S*) isomer, namely, **2**(2*S*,4*S*) and **2**(2*R*,4*S*).

The metabolism and antitumor activity of the optically active forms of *cis*- and *trans*-4-methylcyclophosphamide are being investigated. In this context it is interesting that the (+) and (−) forms of cyclophosphamide[10] exhibit markedly different antitumor activities against an experimental mouse tumor (ADJ/PC6A) and undergo differential metabolism in man.[11] Configuration around phosphorus would therefore appear to be an important factor in metabolic transformations of this clinically important drug.

Experimental Section

All melting points and boiling points are uncorrected. Solvents and commercial reagents were distilled and dried by conventional methods before use.

^1H NMR spectra were recorded at 60 MHz with a JEOL C-60H spectrometer equipped with Hetero-Spin-Decoupler SNH-SD-HC or at 80 MHz with a Tesla BS 487 C spectrometer with Me_4Si as an internal standard. ^{31}P NMR spectra were obtained on the first-mentioned instrument at 24.3 MHz with external H_3PO_4 as the reference. Negative chemical shift values are reported for compounds absorbing at lower fields than H_3PO_4. ^{13}C spectra were measured at 22.63 MHz with a Bruker HX-72 system using the FT technique. Chemical shifts are related to internal Me_4Si. Mass spectra were obtained on a LKB 9000S spectrometer at 70 eV ionizing energy. Optical activity measurements were made with a Perkin-Elmer 241 MC photopolarimeter. Product purities were determined from integrated ^1H and ^{31}P NMR spectra or TLC (silica gel 60, F254). Silica gel for column chromatography was 100–200 mesh.

Starting Materials. 1(*S*)-Phenylethylamine had bp 94–95 °C (28 mm), n^{25}_D 1.5240, $[\alpha]^{20}_D$ −37.0° (neat). 1-Phenylethylamine was resolved into optical antipodes according to ref 14.

(−)-Ethyl 3(*S*)-*N*-[1(*S*)-Methylbenzyl]aminobutyrate [5(*S*,*S*)] and Its 3(*R*),1(*S*) Isomer [5(*R*,*S*)]. A solution of ethyl crotonate (**3**, 25 g, 0.22 mol) and 1-(*S*)-phenylethylamine [**4**(*S*)] (22 g, 0.18 mol) in ethanol (50 mL) was heated under reflux for 6 h, then concentrated. Distillation of the residue gave unchanged **4**(*S*) [15 g, bp 35 °C (0.1 mm)] and the mixture of diastereoisomers (**5**) [12 g, bp 99 °C (0.1 mm), n^{25}_D 1.4968]. To the recovered **4**(*S*) was added a further 10 g of **3** and the foregoing procedure was repeated to yield a further 8 g of **5**. A portion (20 g) of the resulting equimolar mixture of **5**(*S*,*S*) and **5**(*R*,*S*) was fractionated on a column of silica gel using benzene–dioxane–acetone (40:2:1) as eluent, to give first the **5**(*S*,*S*) isomer [8 g (after distillation); bp 76–77 °C (0.05 mm); $[\alpha]^{25}_D$ −48.5° (*c* 7.4, benzene); n^{25}_D 1.4924; R_f 0.26 (TLC, benzene–dioxane–acetone, 20:2:1); mass spectrum M^+ *m/e* 235 (1), 105 (100). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.50; H, 8.93; N, 5.96. Found: C, 71.23; H, 8.80; N, 5.80%], followed by the **5**(*R*,*S*) isomer [7 g; bp 76–77 °C (0.05 mm); $[\alpha]^{25}_D$ −35.2° (*c* 6.8, benzene); n^{25}_D 1.4943; R_f 0.19; mass spectrum M^+ *m/e* 235 (0.2), 105 (100). Anal. Found: C, 71.42; H, 8.95; N, 5.88].

3(*S*)-*N*-[1(*S*)-Methylbenzyl]aminobutan-1-ol [6(*S*,*S*)] and Its 3(*R*),1(*S*) Enantiomer [6(*R*,*S*)]. A solution of **5**(*S*,*S*) (7 g, 0.03 mol) in dry ether (30 mL) was added to a solution of $LiAlH_4$ (2.4 g, 0.063 mol) in ether (75 mL). After heating under reflux for 5 h followed by standing overnight at room temperature water was added, followed by 10 M NaOH (12.5 mL). The ether layer was separated and the aqueous phase further extracted with ether (2 × 25 mL). The combined extracts were dried (KOH) and concentrated to an oil which was distilled to give **6**(*S*,*S*): 5.05 g, 88%; bp 82–87 °C (0.1 mm); $[\alpha]^{25}_D$ +13.6° (*c* 4.9, benzene); n^{25}_D 1.5200. Anal. Calcd for $C_{12}H_{19}NO$: C, 74.62; H, 9.83; N, 7.25. Found: C, 74.30; H, 9.63; N, 7.13.

By an identical procedure **5**(*R*,*S*) afforded **6**(*R*,*S*) except that this product was crystallized from *n*-hexane: yield 4.90 g, 85%; mp 59–60 °C; $[\alpha]^{25}_D$ −89.0° (*c* 4.4, benzene). Anal. Found: C, 74.50; H, 9.71; N, 7.22.

3(*S*)-Aminobutan-1-ol [7(*S*)] and Its Enantiomer [7(*R*)]. A solution of **6**(*S*,*S*) (11.5 g, 0.06 mol) in 96% ethanol (30 mL) was added to a suspension of 10% Pd/C (0.5 g) in ethanol (50 mL) in an atmosphere of H_2. The stirred mixture was maintained at 50 °C until the theoretical volume of H_2 was consumed (ca. 2 days). Catalyst was removed by filtration, the filtrate was concentrated, and the residue was distilled to give **7**(*S*): 3.66 g, 69%; bp 80 °C (20 mm); $[\alpha]^{25}_D$ +10.5° (*c* 5.1, ethanol).

By an identical procedure, **6**(*R*,*S*) was converted into 3(*R*)-aminobutanol [**7**(*R*)]: 70%; bp 80 °C (20 mm); $[\alpha]^{25}_D$ −11.2° (*c* 5.1, ethanol).

Physical and chemical properties of **7**(*R*) and **7**(*S*) were identical with those reported for racemic **7**.[12]

Preparation of the Four Diastereoisomers of 4-Methylcyclophosphamide [2(*S*)-Bis[(2-chloroethyl)amino]-4(*S*)-methyltetrahydro-2*H*-1,3,2-oxazaphosphorine 2-Oxide [2-(2*S*,4*S*)(*cis*)], the (2*R*,4*S*)(*trans*), the (2*R*,4*R*)(*cis*), and the (2*S*,4*R*)(*trans*) Isomers]. To a solution of 3(*S*)-aminobutan-1-ol [**7**(*S*), (3.66 g, 0.04 mol)] in dry dioxane (100 mL) containing triethylamine (9.1 g, 0.09 mol) was added a solution of *N*,*N*-bis(2-chloroethyl)phosphoroamidic dichloride[13] (10.6 g, 0.04 mol) in dioxane (100 mL). After stirring for 15 h at room temperature, Et_3N·HCl was removed by filtration. The concentrated filtrate was applied to a column of silica gel (400 g) which was eluted with acetone–chloroform (3:1) to give first the faster migrating (TLC in the same solvent) cis isomer [**2**(2*S*,4*S*)] obtained as colorless crystals from ether [1.80 g, 31.8%; mp 83–83.5 °C; $[\alpha]^{25}_D$ +16.5° (*c* 3.0, methanol); $\delta_{^{31}P}$ −11.0 ppm ($CDCl_3$); R_f 0.57] followed by the slower moving trans isomer [**2**(2*R*,4*S*)] which crystallized from light petroleum [1.45 g, 25.6%; mp 56–57 °C; $[\alpha]^{25}_D$ +7.7° (*c* 3.0, methanol); $\delta_{^{31}P}$ −13.5 ppm ($CDCl_3$); R_f 0.48].

Similarly prepared from 3(*R*)-aminobutan-1-ol [**7**(*R*)] were the cis isomer [**2**(2*R*,4*R*)] [1.50 g, 26.5%; mp 83–84 °C (from ether); $[\alpha]^{25}_D$ −17.8° (*c* 2.2, methanol); $\delta_{^{31}P}$ −11.0 ppm ($CDCl_3$); R_f 0.57] and the trans isomer [2(2*S*,4*R*)] [1.10 g, 19.5%; mp 56–57 °C (from light petroleum); $[\alpha]^{25}_D$ −8.3° (*c* 3.0, methanol); $\delta_{^{31}P}$ −13.5 ppm ($CDCl_3$); R_f 0.48].

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Registry No.—(2*S*,4*S*)-**2**, 61520-80-7; (2*R*,4*R*)-**2**, 61520-81-8; (2*R*,4*S*)-**2**, 61520-82-9; (2*S*,4*R*)-**2**, 61520-83-0; **3**, 10544-63-5; (*S*)-**4**, 2627-86-3; (*S*,*S*)-**5**, 61477-36-9; (*R*,*S*)-**5**, 61477-37-0; (*S*,*S*)-**6**, 61477-38-1; (*R*,*S*)-**6**, 60920-20-9; (*S*)-**7**, 61477-39-2; (*R*)-**7**, 61477-40-5; *N*,*N*-bis(2-chloroethyl)phosphoroamidic dichloride, 127-88-8.

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Epimerization of Acyclic Diastereomers. 2.[1] Bis(alkylphenylcarbinyl) Ether

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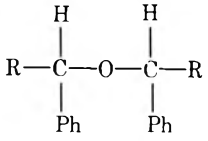
The epimerization of cyclic compounds has been extensively investigated[2-11] and it has been shown that the thermodynamic stabilities of cyclic diastereomers differed considerably in several cases.[2-5,10,11] On the other hand, thermodynamic stabilities of acyclic diastereomers do not differ by much in general.[12,13] However, in one case, i.e., 2,4-dichloropentane, a large energy difference between two diastereomers has been reported by Billups et al.[14,15] and calculated by MacMahon et al., assuming Lennard-Jones type interactions between nonbonded atoms.[16,17] In the preceding paper,[1] we reported the notable stability of the *dl* isomer compared to the meso isomer in bis(α-phenylethyl) ether and suggested that this stability of the *dl* isomer could not be explained entirely by steric factors (nonbonded interactions).

In the present report the even greater preference of the *dl* isomers of bis(alkylphenylcarbinyl) ether compared to the meso isomers is shown and the source of this preference of *dl* isomers is described.

Results and Discussion

Epimerization of three compounds (Ia, Ib, and Ic) catalyzed by boron trifluoride etherate in carbon tetrachloride or nitrobenzene was carried out.



Ia, R = Et
b, R = *n*-Bu
c, R = cyclohexyl

As reported before,[1] an epimerization of bis(alkylphenylcarbinyl) ether is accompanied by an elimination reaction. The results of epimerization of Ia in carbon tetrachloride or nitrobenzene are shown in Figures 1 and 2. One might suppose that the meso isomer would be preferentially destroyed and that epimerization of the ether would not take place. To clarify this point, a reaction of Ia consisting of 3.5% *dl* and 96.5% meso isomers in carbon tetrachloride was carried out and the result is shown in Figure 3. This figure indicates that epimerization of the ether takes place in carbon tetrachloride giving an ether consisting of 100% *dl* isomer at prolonged time. The results of epimerization reactions of Ia, Ib, and Ic in carbon tetrachloride and nitrobenzene are summarized in Table I. The epimerization reaction of Ib was also started with equal concentrations of the *dl* and meso isomers, and a large excess of the meso isomer. A separation of isomers of Ic was unsuccessful. Each run was allowed to continue until the composition of the ether was constant. In the determination of the ether composition after epimerization of Ic in nitrobenzene by means of NMR (see Experimental Section), the signals of the methine proton doublet of the meso isomer overlapped with those of unknown by-products, making the isomeric composition uncertain. Since the reactions of Ia, Ib, and Ic in carbon tetrachloride were slow, boron trifluoride etherate was used in higher concentration than in nitrobenzene.

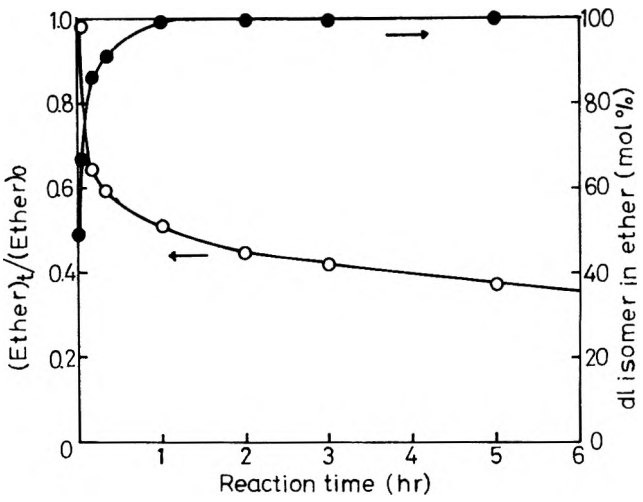


Figure 1. Epimerization and elimination of bis(ethylphenylcarbinyl) ether in carbon tetrachloride at 25 °C. Ether consisting of equal moles of *dl* and meso isomer was used. Ether, 0.05 mol/L; BF_3OEt_2, 0.04 mol/L. ○, decrease of ether; ●, mol % of *dl* isomer in ether.

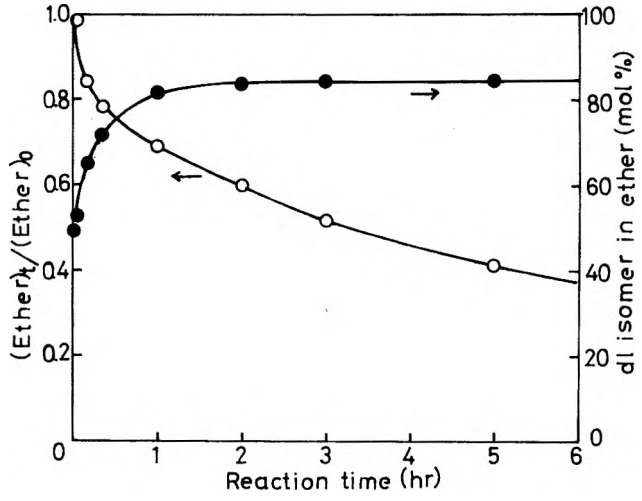


Figure 2. Epimerization and elimination of bis(ethylphenylcarbinyl) ether in nitrobenzene at 25 °C. Ether consisting of equal moles of *dl* and meso isomer was used. Ether, 0.05 mol/L; BF_3OEt_2, 0.01 mol/L. ○, decrease of ether; ●, mol % of *dl* isomer in ether.

Steady-state values of ether composition shown in Table I do not depend on the composition of starting ether and do not change even after prolonged reaction time. These results indicate that destruction of both isomers (*dl* and meso isomers) and epimerization of isomers took place. Since the rate of the epimerization reaction is faster than that of the destruction, the reaction of the ether with boron trifluoride etherate should give the steady-state composition of ether. Although, strictly speaking, the product compositions in Table I are not equilibrated but kinetically controlled, these values would indicate thermodynamic stabilities of these isomers. Generally speaking, the difference in thermodynamic stabilities between two isomers is even greater in the less polar solvent than in the polar solvent. Therefore, although the destruction of ether in carbon tetrachloride seriously competes

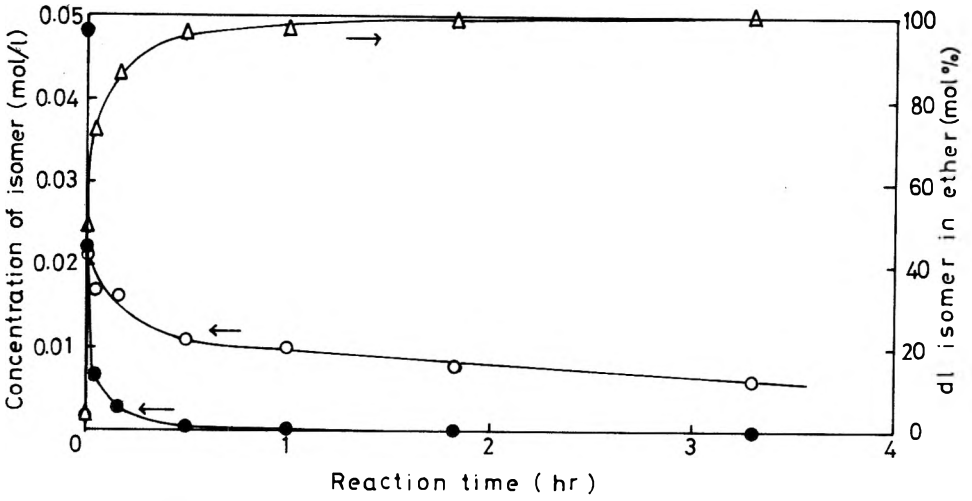


Figure 3. Epimerization and elimination of bis(ethylphenylcarbinyl) ether consisting of 3.5% *dl* and 96.5% meso isomer in carbon tetrachloride at 25 °C. Ether, 0.05 mol/L; BF_3OEt_2, 0.06 mol/L. ○, concentration of *dl* isomer; ●, concentration of meso isomer. △, mol % of *dl* isomer in ether.

Table I. Composition of Ether Obtained by Epimerization of Bis(alkylphenylcarbinyl) Ether at 25 °C

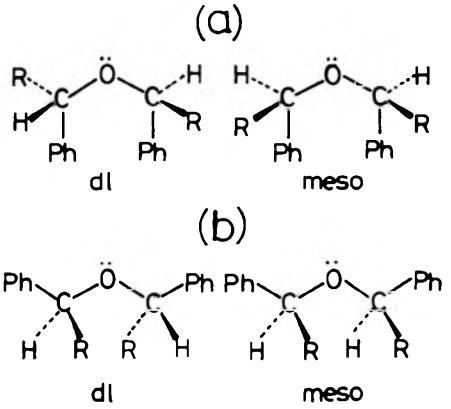
	Reaction conditions						Products, mol %			
							In CCl_4		In $C_6H_5NO_2$	
Registry no.	R	mol % *dl*	mol % meso	Concn, mol/L	$[BF_3OEt_2]$, mol/L	Time, h	*dl*	meso	*dl*	meso
	CH_3[a]						89.0	11.0	68.1	31.9
61462-92-8 (*dl*)	C_2H_5	50	50	0.05	0.04	3	100	0		
61446-47-7 (meso)		3.5	96.5	0.05	0.06	3.3	100.	0		
		50	50	0.05	0.01	3			84.5	15.5
		3.5	96.5	0.05	0.01	3 (days)			84.7	15.3
61446-48-8 (*dl*)	*n*-C_4H_9	50	50	0.05	0.06	0.5	100	0		
61446-49-9 (meso)		14.4	85.6	0.05	0.08	1	100	0		
		50	50	0.05	0.01	2			87.8	12.2
		14.4	85.6	0.05	0.01	4 (days)			87.5	12.5
61446-50-2 (*dl*)	C_6H_{11}	50	50	0.04	0.02	24	100	0		
61446-51-3 (meso)										

[a] From the preceding paper.[1]

with the epimerization reaction (see Figure 3), a comparison of the steady-state values in carbon tetrachloride with those in nitrobenzene would afford the conclusion that the results (100% *dl* and 0% meso) can be attributed to the difference in thermodynamic stabilities between the two isomers. Such a result appears to be a first example of an overwhelming preference of one isomer compared to the other isomer in an acyclic diastereomer.

Data in Table I indicate that as the size of the alkyl group increases so does the relative concentration of the *dl* isomer compared to the meso isomer. If the source of the energy difference is steric as described in the literature,[12,16] the isomers of Ic, having two similarly sized alkyl groups (cyclohexyl and phenyl) on an asymmetric carbon, should have similar thermodynamic stabilities while for bis(α-phenylethyl) ether they should not have similar thermodynamic stabilities. In the preceding paper,[1] it was reported that a change from phenyl to *n*-hexyl caused a remarkable difference in the results. These facts would suggest that the presence of two phenyl groups in a molecule caused a special effect on thermodynamic stabilities of the isomers. This special effect would favor conformer a or b (Scheme I). Both conformers well explain an increase of the preference of the *dl* isomer compared to the meso isomer on changing from a small alkyl group to a bulkier one. If

Scheme I



two phenyl groups attract each other through space, conformer a should be favored. The thermodynamic preference of cis or gauche conformers in some 1,2-disubstituted ethylenes or 1,2-disubstituted ethanes, respectively, has been explained by a conjugative destabilization which is transmitted through bonds.[18] If a conjugative destabilization is transmitted through bonds in an ether, the syn conformer such as

a or b should be favored. Since UV absorption spectra of these ethers well coincide with those of corresponding alcohols, a direct through-space interaction between two phenyl groups in ether presumably does not operate. On the basis of the information presently available a possible explanation for *dl* preference is that a conjugative destabilization which has been suggested by Bingham favors conformation a or b.

Experimental Section

Preparation of Ethers. Bis(ethylphenylcarbinyl) ether was obtained as follows. A mixture of water, concentrated sulfuric acid, and ethylphenylcarbinol (obtained by the reaction of benzaldehyde with ethylmagnesium iodide[19]) in the ratio of 2:3:15 by volume was stirred for 2 h at room temperature and was washed with water several times and then distilled under reduced pressure. Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.71. Found: C, 85.22; H, 8.36.

The preparation procedure for bis(*n*-butylphenylcarbinyl) ether was similar to that for Ia using *n*-butylmagnesium chloride instead of ethylmagnesium iodide.[20] Anal. Calcd for $C_{22}H_{30}O$: C, 85.11; H, 9.76. Found: C, 85.24; H, 9.66.

Bis(cyclohexylphenylcarbinyl) ether was obtained as follows. A mixture of water, concentrated sulfuric acid, and cyclohexylphenylcarbinol (obtained by the reaction of benzaldehyde with cyclohexylmagnesium chloride) in the ratio 2:3:15 by volume was stirred for 30 min at 40 °C and was dissolved in diethyl ether. The solution was washed with water prior to the ether being removed under reduced pressure. Anal. Calcd for $C_{26}H_{34}O$: C, 86.13; H, 9.45. Found: C, 85.88; H, 9.33.

General Procedure of Epimerization. The procedure of epimerization was described in the preceding paper.[1] The composition of starting ethers used is listed in Table I. Separation and analyses of isomers were carried out by GLC using a 4.5-m ethylene glycol adipate polyester, 20% on Chromosorb W, column at 180 °C (for Ia) or at 200 °C (for Ib). In these analyses the isomers which had shorter retention time were assigned the *dl* configuration as described in the preceding paper.[1] Since the two isomers of Ic did not sufficiently separate in GLC, these were analyzed by NMR, in which the isomer with the methine protons signal at higher field was assigned the *dl* configuration as described in the preceding paper.[1]

Registry No.—Ethylphenylcarbinol, 93-54-9; *n*-butylphenylcarbinol, 583-03-9; cyclohexylphenylcarbinol, 945-49-3.

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An Improved Procedure for the Preparation of Bicyclo[2.2.2]octa-2,5,7-triene (Barrelene)

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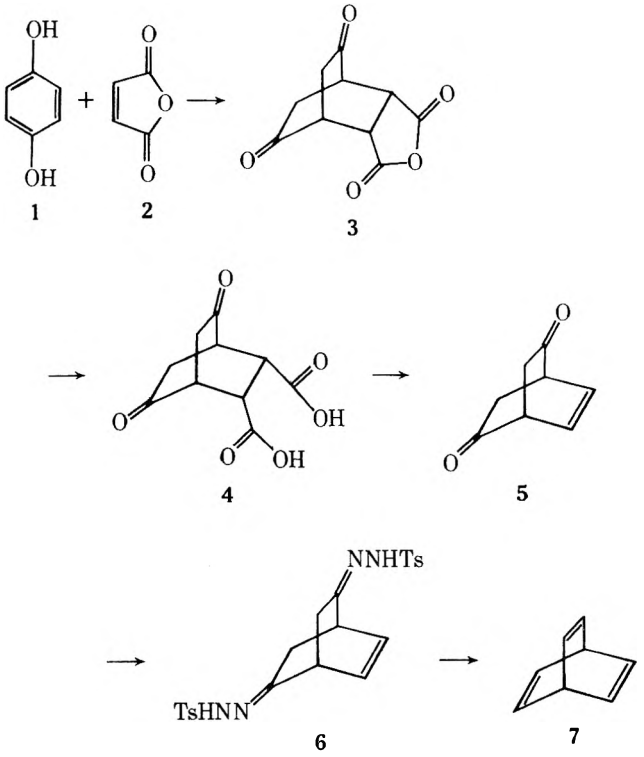
Barrelene (**7**) is a molecule of considerable theoretical and experimental interest.[1] However, each of the methods for its preparation [2-4] has its disadvantages. The recently published method of Dauben et al.[4] is undoubtedly the most efficient, but requires the rare and costly cyclooctatetraene as starting material.[5] The method of Taylor[3] is simple in that bicyclo[2.2.2]oct-2-ene is essentially halogenated and dehalogenated to give **7** together with bicyclo[2.2.2]octa-2,5-diene. Nevertheless, the manipulation is bothersome as the starting olefin has to be prepared in an autoclave and the products, which are only obtained in low yields, need to be separated by programmed gas–liquid chromatography. We report another method of preparation, which is short, easy to carry out, and makes use of cheap, readily available starting materials.

The key step, namely the construction of the bicyclo[2.2.2]-octane skeleton, is achieved readily, but in low yield, by simply melting together maleic anhydride (**2**) with hydroquinone (**1**) at 200 °C for 2 h.[6] From the mixture, the adduct (**3**) is isolated and immediately hydrolyzed to the corresponding acid (**4**) in an overall yield of 7%. Oxidative decarboxylation of **4** is crucial, as yields tend toward the low side.[7,8] However, heating **4** with lead tetraacetate in pyridine and dioxane under nitrogen for 10 min gives bicyclo[2.2.2]oct-2-ene-5,7-dione (**5**) in 42% yield. Subsequent conversion to the bistosylhydrazone **6** is



1 2 3 4 5 6 7

straightforward (98% yield). Submission of **6** to methyllithium leads to barrelene (**7**) in 12% yield accompanied by benzene.[9,10] The latter probably arises by competitive fragmentation; in any event its presence will not interfere with any chemical reactions which might be done with **7** and it can be simply removed if needs be.

Experimental Section

5,7-Dioxobicyclo[2.2.2]octane-2,3-dicarboxylic Anhydride (3).[6] A mixture of hydroquinone (**1**, 607.0 g, 5.52 mol) and maleic anhydride (**2**, 1097.0 g, 11.2 mol) are heated in an atmosphere of carbon dioxide under strong reflux in a 2-L round-bottom three-neck flask for 2 h. The mixture, at about 70 °C, just above its solidification point, is carefully poured with stirring into ethyl ether (3.2 L) in a 5-L beaker and left overnight. The Diels–Alder adduct (**3**) is collected on a Buchner funnel and washed with cold ether. The beige crystals, 170.0 g, are used directly.

5,7-Dioxobicyclo[2.2.2]octane-2,3-dicarboxylic Acid (4). The crude anhydride (**3**, 170.0 g) is dissolved in water (1 L) and warmed to 80 °C with mechanical stirring for 2 h. Activated charcoal is added and heating continued for 15 min. Filtration over Celite followed by

recrystallization during 2 days in a cold room gives the diacid (**4**, 87.0 g) as colorless crystals in a 7% yield starting from **1**.

5,7-Dioxobicyclo[2.2.2]oct-2-ene (5). The diacid (**4**, 27.0 g, 0.12 mol) and lead tetraacetate (102.0 g, 0.23 mol) in dioxane (260 mL) are purged with nitrogen for 15 min and then placed in a water bath at 12–15 °C. The mixture is vigorously stirred while nitrogen continues to be passed through it. Pyridine (250 mL) is next admixed. The mixture is kept in a bath of water at 60 °C for 10 min, when the carbon dioxide should all be released. The mixture is then rapidly cooled and poured into nitric acid (2 N, 1350 mL). The acid solution is extracted with chloroform (8 × 100 mL). The organic phase is washed with water (1 × 100 mL), with saturated aqueous sodium bicarbonate (2 × 100 mL), and with saturated sodium chloride solution (1 × 100 mL). Drying over Na_2SO_4 and evaporation gives practically pure (as judged by NMR) diketone (**5**, 7.2 g, 53 mmol) in 42% yield.

The Bistosylhydrazone (6) of 5. The diketone (**5**, 3.8 g, 28 mmol) in ethanol (10 mL) is added dropwise to tosylhydrazine (10.4 g, 56 mmol) in ethanol (64 mL) over 10 min. The solution is then heated under reflux for 4 h; the resulting precipitate is filtered warm, washed with ethanol, and dried in vacuo giving the bistosylhydrazone (13.0 g, 27.5 mmol) as pure product in 98% yield.

Bicyclo[2.2.2]octa-2,5,7-triene (Barrelene, 7). To a solution of bistosylhydrazone (**7**, 5.7 g, 12 mmol) in 1,2-bis(dimethylamino) ethane (70 mL) cooled to −23 °C is added dropwise during 1 h a solution of methyllithium (2 M) in ether (48 mL).[9,10] The mixture is stirred under nitrogen for 4 h at −23 °C and then overnight at 20 °C. Excess reagent is decomposed carefully with water (ca. 150 mL). Ether extraction (5 × 30 mL) followed by washing with water (1 × 50 mL), hydrochloric acid (2 N, 2 × 50 mL), water (1 × 50 mL), and saturated aqueous sodium chloride (1 × 50 mL) and drying (over $NaSO_4$) affords a solution which must be carefully evaporated. Most solvent can be removed by distilling at atmospheric pressure using a Vigreux column 20 cm long. In the residue, barrelene (**7**) is present (190–200 mg, 15% yield). Separation of pure **7** can be effected by GLC using a column of 20% SE-30 or 10% OV-17 on Chromosorb W at 150 and 100 °C, respectively. On average, 120 mg (10% yield) of pure barrelene (**7**) is isolated.[11]

Registry No.—**1**, 123-31-9; **2**, 108-31-6; **3**, 61586-14-9; **4**, 61543-84-8; **5**, 17660-74-1; **6**, 61543-85-9; **7**, 500-24-3; tosylhydrazine, 1576-35-8.

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Preparation and Reactivity of a New Spin Label Reagent

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In the course of developing a reagent which could be used to selectively attach a nitroxide spin label to tyrosine residues in proteins, we have prepared *N*-(2,2,5,5-tetramethyl-3-carbonylpyrrolidine-1-oxyl)imidazole (I), a stable, crystalline solid. Preliminary studies indicate that this reagent may be generally useful for attaching the nitroxide spin label to molecules of biological interest. In this communication, we report the preparation of I, its hydrolytic reactivity, and its utility as a reagent for synthesis of spin-labeled molecules.

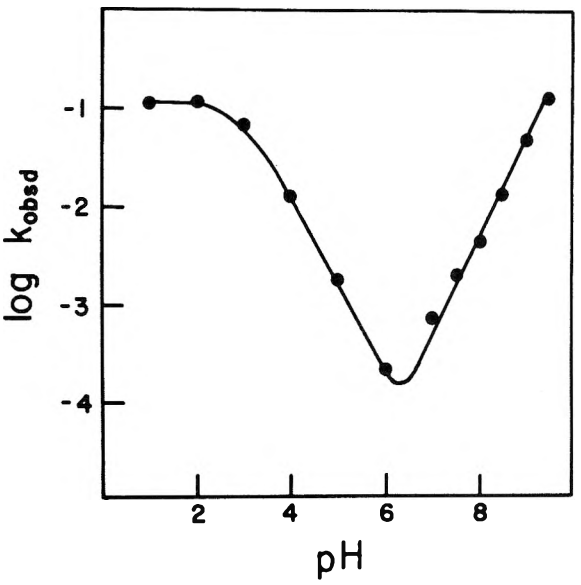
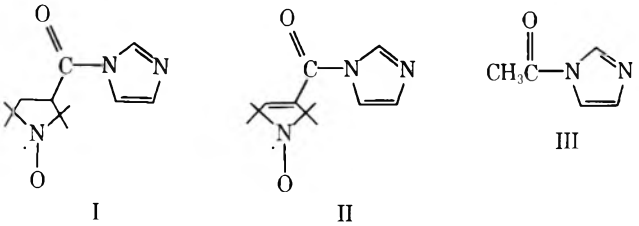


Figure 1. pH profile for hydrolysis of I.



I II III

Preparation of I was achieved by allowing equimolar amounts of *N,N'*-carbonyldiimidazole and *N*-(2,2,5,5-tetramethylpyrrolidine-1-oxyl)-3-carboxylic acid[1] to react for several hours at room temperature as a suspension in dry benzene. After workup and two crystallizations from ether, a 57% yield of I was obtained. This product gave satisfactory elemental analysis, IR spectrum, and EPR spectrum. Several previous attempts to prepare I using various methods and conditions led to either destruction of the nitroxide function or to mixtures of products which could not be readily characterized. Use of solvents which afforded homogeneous solutions did not yield isolable amounts of I.

Preparation of the unsaturated analogue (II) of I has been reported.[2] This material was unstable and decomposed rapidly. In contrast, we have stored crystals of I at 4 °C for more than 1 year without noticeable decomposition.

Hydrolysis of I in aqueous solution was studied over the pH range 1.0–9.5. The results are plotted in Figure 1, where the points are experimental and the solid curve is the computer fit of the data to eq 1.

$$k_{obsd} = \frac{K_a^{SH}}{(H^+) + K_a^{SH}}\left[\frac{k_0^{SH}(H^+)}{K_a^{SH}} + \frac{k_{OH}{}^{S}K_w}{(H^+)}\right] \quad (1)$$

The values of the parameters of eq 1 are listed in Table I, where K_a^{SH} is the acid dissociation constant of the conjugate acid (SH) of I, k_0^{SH} is the water-catalyzed reaction of SH, and $k_{OH}{}^{S}$ is the hydroxide-catalyzed reaction of S.

The rate parameters obtained for hydrolysis of I are compared to those of Jencks[3] for hydrolysis of *N*-acetylimidazole (III). Both the acid term k_0^{SH} and the base term $k_{OH}{}^{SH}$ are

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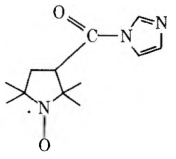
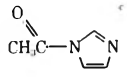
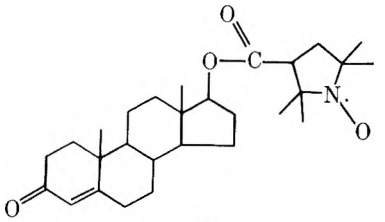
Table I. Hydrolysis Data for Acyl Imidazoles at 25 °C, μ = 0.1[a]

Substrate (S)	k_0^S, s^{-1}	k_0^{SH}, s^{-1}	k_{OH}^S, M^{-1} s^{-1}	pK_a^{SH}
 I	*b*	(1.22 ± 0.17) × 10^{-1}	(4.89 ± 0.4) × 10^3	3.13 ± 0.09
 III	8.3 × 10^{-5}	4.7 × 10^{-2}	3.2 × 10^2	3.6

[a] Rate constants are given with standard deviations. [b] Too small to measure. [c] Data from ref 3.

larger for I than for III. The small neutral term k_0^S observed for III was not detected for I. From these parameters it can be calculated that hydrolysis of I will be faster than hydrolysis of III by a factor of 4 at pH 7 and by a factor of 12 at pH 8.

To explore the utility of I as a reagent for spin labeling other molecules, we prepared a nitroxide-labeled derivative of testosterone (IV). Heating equivalent amounts of testosterone, I, and *t*-BuOK in *t*-BuOH at 55 °C for 8 h followed by crystallization from acetone afforded a 19% yield of IV. (This yield is based on the sum of the two enantiomers which could result.) The melting point of this material was 224–225 °C, which is about 18 °C higher than that reported by Dodd[4] for the same compound. The IR spectrum of our material is similar to that reported by Dodd and we obtained a satisfactory elemental analysis and EPR spectrum. One explanation for the difference in melting points involves the possibility of isolating diastereomeric products. These would be expected to have different melting points but might have similar IR spectra.


IV

In another experiment, we reacted I with poly-L-tyrosine (mol wt 40 000–100 000) in aqueous solution at pH 7.5 according to the procedure of Barratt et al.[2] After dialysis to remove excess reagent and hydrolysis products, we obtained an EPR spectrum identical with the one reported by Barratt for the product obtained from reaction of poly-L-tyrosine with II.[2]

In summary, our results indicated that I can be readily prepared and stored but that it is somewhat more susceptible to aqueous hydrolysis than is *N*-acetylimidazole. The spin-label functionality of I can be transferred to suitable receptor molecules under aqueous or nonaqueous conditions.

We have also explored the use of I to spin label the enzyme carboxypeptidase and will report these results elsewhere.

Experimental Section

General. EPR spectra were recorded on a Varian Model E-3 spectrometer and IR spectra on a Perkin-Elmer Model 137 instrument. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. pH measurements were made with a Radiometer Model PHM62 pH meter equipped with a combination electrode.

***N*-(2,2,5,5-Tetramethyl-3-carbonylpyrrolidine-1-oxyl)imidazole (I).** To 0.5 mmol of *N*-(2,2,5,5-tetramethylpyrrolidine-1-oxyl)-3-carboxylic acid[1] suspended in 10 mL of dry benzene was added 0.5 mmol of *N,N'*-carbonyldiimidazole. The mixture was stirred under N_2 for 2 h. The solvent was removed under a stream of nitrogen and the residue crystallized twice from ether to give 68 mg (57%) of I: mp 128–129 °C; IR (KBr) 1730, 1242 cm^{-1}.

Anal. Calcd for $C_{12}H_{18}N_3O_2$: C, 61.00; H, 7.68; N, 17.78. Found: C, 60.84; H, 7.72; N, 18.06.

O^{17}-(2,2,5,5-Tetramethyl-3-carbonylpyrrolidine-1-oxyl)testosterone (IV). Testosterone (0.5 mmol) and I (0.5 mmol) were combined in 5 mL of *t*-BuOH and 500 μL of 1 M *t*-BuOK/*t*-BuOH (0.5 mmol) was added. The resulting solution was heated at 55 °C for 8 h in a sealed tube. The solvent was removed by rotary evaporation. The residue was dissolved in $CHCl_3$ and extracted with water. The $CHCl_3$ layer was dried and the solvent removed to give 213 mg of crude IV which was crystallized from acetone to give a yield of 19% based on the sum of the two enantiomeric products that could result: mp 224–225 °C (lit.[4] mp 206.5–207.5 °C); IR (KBr) 1725, 1662 cm^{-1} (lit.[4] IR 1725, 1662 cm^{-1}).

Anal. Calcd for $C_{28}H_{42}NO_4$: C, 73.64; H, 9.27; N, 3.07. Found: C, 73.71; H, 9.46; N, 3.25.

Reaction of I with Poly-L-tyrosine. According to the procedure of Barratt,[2] 8 mg of poly-L-tyrosine (Sigma, mol wt 40 000–100 000) was dissolved in basic, aqueous solution and dialyzed against 6 mM, pH 7.5 phosphate buffer at 4 °C. To the resulting solution at pH 7.5 was added 1.5 mg of I. The mixture was stirred for 4 h at 4 °C followed by dialysis against 6 mM, pH 7.5 phosphate buffer. An EPR spectrum of the resulting solution was identical with the EPR spectrum reported by Barratt for poly-L-tyrosine labeled with II.[2]

Kinetic Measurements. Pseudo-first-order rate constants were determined either spectrophotometrically at 250 nm using a Cary 14 instrument or by a pH Stat method using a Radiometer apparatus which included a TTT60 titrator, PHM62 pH meter, ABU12T buret, and a REC61 servograph recorder. Typically, 50 μL of an acetonitrile stock solution of I was used to initiate the reaction. The pseudo-first-order rate constants were fit to eq 1 using a nonlinear least-squares computer program.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Research Corporation for support of this research.

Registry No.—I, 61463-55-6; IV, 56948-71-1; *N*-2,2,5,5-tetramethylpyrrolidine-1-oxyl-3-carboxylic acid, 2154-68-9; *N,N'*-carbonyldiimidazole, 530-62-1; testosterone, 58-22-0.

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Reaction of Dihydrohexamethyl(Dewar benzene) with Singlet Oxygen[1]

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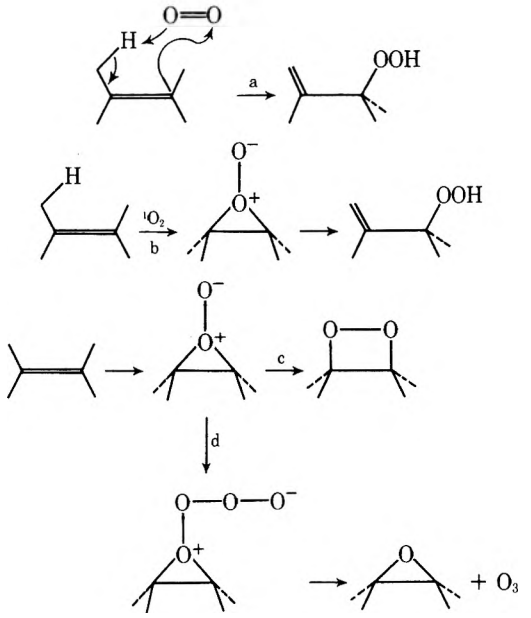
In connection with other studies we were interested in the reaction of hexamethyl(Dewar benzene) (HMDB) or its dihydro derivative 1 with singlet oxygen.

Two plausible mechanisms have been advanced for the "ene" reaction of olefins with $^1O_2$,[2] the concerted mechanism (path a)[3] and the perepoxide mechanism (path b).[4] The latter can be diverted to dioxetanes (path c) or epoxides (path d)

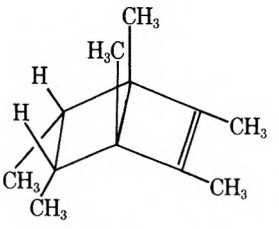


when no hydrogens are available for abstraction to give an "ene" reaction.[5] Intervention of dioxetanes is frequently invoked to explain the appearance of two carbonyl-containing fragments.

HMDB reacted rapidly with singlet oxygen to produce complex mixtures regardless of temperature, time, or method of generation of $^1O_2$. Use of TNB as a radical trap failed to simplify the reaction mixture. In the absence of sensitizer, i.e., with triplet oxygen, the only substances present after 1 h of photooxygenation were HMDB and hexamethylbenzene. The latter can be generated by thermolysis of HMDB,[6] but since the temperature was kept low, it is not clear what mechanism was operating in the present instance to produce hexamethylbenzene.[13]

To avoid these complications, dihydro-HMDB (1)[7] was prepared and photooxygenated in CH_2Cl_2 for 2 h. TLC and NMR analysis of the crude product revealed the presence of two major components, A and B. A was subsequently isolated and identified as the diketone 2 on the basis of spectral evidence [IR band at 1685 cm^{-1}, NMR signals at 1.98 (acetyl methyls), 1.34 (C-1 methyls), and an $X_3AA'X_3'$ system with X_3X_3' signals at 1.02 ppm (C-2 methyls) and AA' signals at 2.23 ppm (H-2's), similar to signals observed in the spectrum of 1]. Since the NMR spectrum of the product mixture also exhibited two downfield one-proton singlets at 4.02 and 5.24 ppm appropriate for $=CH_2$, product B was presumed to be hydroperoxide 3.

The crude product mixture was therefore stirred overnight with NaI in order to reduce the presumed hydroperoxide to 4. However, the "reduction product" was essentially pure 2 and contained only traces of other substances. Similarly, an attempt to separate 2 and B by preparative TLC gave three major bands, all of which contained 2 as the major component, but B was absent. Obviously, B was decomposing on the TLC plate.



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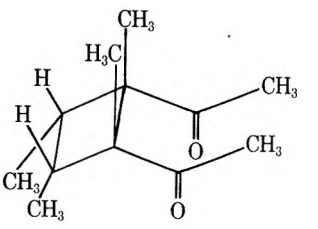

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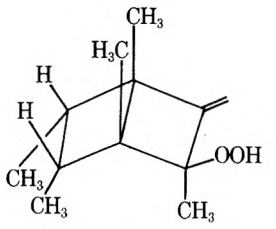

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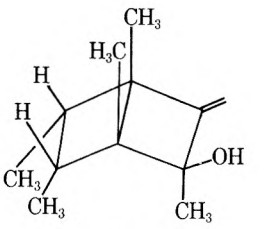

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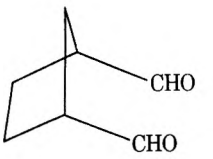

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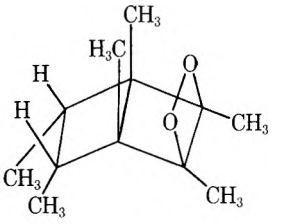

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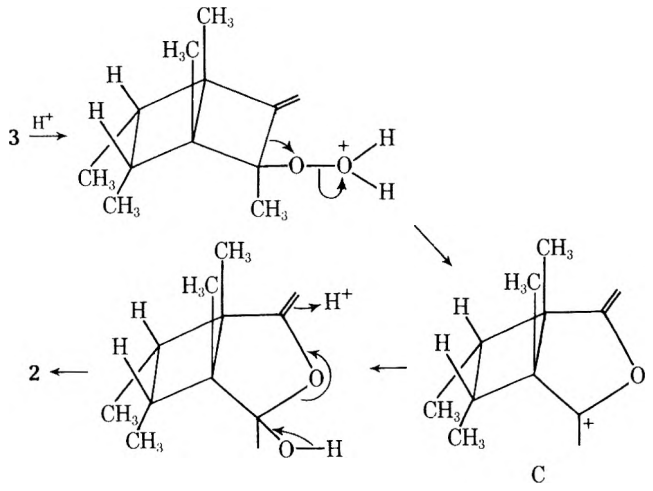
Photooxygenation of dihydro-HMDB at −78 °C followed by removal of solvent CH_2Cl_2 below 0 °C and analysis of the product mixture revealed B as the major product and only traces of 2, but on standing overnight at room temperature in $CHCl_3$, B was converted completely to diketone 2. Isolation of B at low temperature now permitted its identification as hydroperoxide 3 on the basis of its NMR spectrum, which exhibited signals at 5.23 (H-9b), 4.93 (H-9a), 2.38 m (H-5 and H-6), 1.46 (C-2 methyl), 1.13 and 1.09 (C-1 and C-4 methyls), and 1.04 d and 0.88 ppm d (J = 7 Hz, C-5 and C-6 methyls). Furthermore, photooxygenation of 1 at ambient temperature in CH_2Cl_2 in the presence of excess $P(OEt)_3$ resulted in formation of 4 as the only product by in situ reduction of 3. Solvent removal followed by chromatography gave 4 in 55% yield as a low-melting, volatile solid with a camphoraceous odor. Its structure was evident from the spectra [IR bands at 3430, 3042, and 1642 cm^{-1}; NMR signals at 5.17 (H-9b), 4.76 (H-9a), and a singlet at 1.36 ppm characteristic of methyl on carbon carrying hydroxyl, as well as a two-proton multiplet centered at 2.42 (H-5 and H-6) and methyl singlets at 1.15 (C-1 methyl) and 1.09 (C-4 methyl) and doublets at 1.00 and 0.87 (J = 7 Hz, C-5 and C-6 methyls)]. The ^{13}C NMR spectrum (see Experimental Section) was also consistent with the assigned structure. The stereochemical assignment at C-2 is based on analogy to hydrogenation of HMDP and 1 which results invariably in exo addition and on the difference in chemical shift between the two singlet methyls.[7] Similar results have usually,[8] but not always,[9] been observed in other reactions of HMDB.

Dicarbonyls such as 2 may arise by thermal cleavage of dioxetanes. For example, the dialdehyde 5 obtained by photooxygenation of norbornene is almost certainly formed in this manner.[10] Such cleavage, if concerted, requires that one of the carbonyl fragments be produced in an excited state, leading to chemiluminescence or to "photochemistry without light", but unless care is taken to exclude quenching of the excited

molecules, the phenomenon may escape detection. However, there was no evidence of dioxetane (6) formation in the photooxygenation of 1, and indeed, the evidence presented in the previous paragraphs shows that 3, not the dioxetane 6, is the intermediate in the formation of 2. Moreover, when the decomposition of 3 was followed by NMR spectrometry in $CDCl_3$, no intermediate species could be detected and after 18 h, 3 had decomposed completely to 2. That the rearrangement of 3 to 2 is acid catalyzed could be demonstrated in the same manner; addition of a drop of HCl to an NMR tube containing 3 resulted in an exothermic reaction and immediate conversion to 2.

On the basis of these observations, a mechanism (Scheme I) similar to the rearrangement of cumene hydroperoxide to

Scheme I



phenol and acetone can be proposed for the conversion of 3 to 2. Protonation of 3, loss of water, and vinyl migration result in ion C. This reacts with water to form an enolic hemiacetal D which rearranges to 2. Rearrangement of allylic hydroperoxides in this fashion is well known and is referred to as the Hock cleavage.[11] The driving force for the facile rearrangement in the present case is undoubtedly the relief of strain in 3 on transformation to A.

Although the presence of a small amount of dioxetane 6 in the mixture from the photooxygenation of 1 cannot be excluded with certainty, the present work shows that the formation of dicarbonyl compounds or carbonyl fragments in photooxygenation reactions is not necessarily the result of dioxetane cleavage and that in such cases mechanistic speculations must be engaged in with caution unless the intervention of dioxetanes can actually be demonstrated.

Experimental Section[12]

Reaction of HMDB with Singlet Oxygen. A. This reaction was carried out by irradiation of 100 mg of the substrate and 5 mg of methylene blue in 50 mL of CH_2Cl_2 with a 150-W incandescent lamp placed near the reaction vessel. The solvent was removed at reduced pressure and the residue examined by TLC and NMR analysis. The following conditions were used, all giving complicated mixtures by NMR criteria: (1) 3 h, ambient temperature; (2) 1 h, ambient temperature; (3) 1 h, ambient temperature, 2 mg of TNB; (4) 15 min, −78 °C (in this run, the NMR spectrum indicated that little if any reaction had taken place).

B. A solution of 0.20 g of $P(OEt)_3$ in 50 mL of CH_2Cl_2 cooled to −78 °C was purged with oxygen, ozonized to exhaustion, and purged again with oxygen for 30 min. A solution of 0.1 g of HMDB in 20 mL of $CDCl_3$ was cooled to −78 °C, and added to the above. The mixture was allowed to warm to room temperature. Removal of solvent at reduced pressure and NMR analysis of the residue indicated a somewhat cleaner, but still rather complex, reaction.

Reaction of HMDB with Molecular Oxygen. A solution of 0.100 g of HMDB in 50 mL of CH_2Cl_2 was irradiated with a 150-W incandescent lamp for 1 h while a stream of oxygen was bubbled through the solution. After removal of oxygen, NMR and TLC analysis of the residue indicated the presence of starting material, hexamethylbenzene (characterized by a singlet at 2.20 ppm), and only traces of other substances.

Preparation of 1. Hydrogenation of HMDB with Pd/C by the literature method,[7] but purification by column chromatography or preparative TLC rather than distillation gave liquid 1 (which crystallizes in the freezer) whose NMR spectrum was identical with that reported. The ^{13}C NMR spectrum exhibited signals at 140.9 (C-2, C-3), 50.4 (C-1 and C-4), 37.6 d (C-5 and C-6) and 15.4 q, 11.7 q, and 11.1 ppm q (methyls).

Reaction of 1 with Singlet Oxygen. A. A solution of 0.500 g of 1 and 10 mg of methylene blue in 150 mL of CH_2Cl_2 was irradiated in a Hanovia-type reactor vessel using a Sylvania DVY tungsten–halogen lamp as an internal light source. The lamp was operated at 50–70 V and was cooled with a stream of air. A stream of oxygen was passed through the reaction mixture which was kept at ambient temperature by a water jacket placed between lamp and reaction mixture. After 2 h, TLC and NMR analysis indicated disappearance of 1 and formation of 2 and 3. The solution was stirred overnight with saturated aqueous KI, washed with saturated aqueous $Na_2S_2O_3$ and water, dried, and evaporated at reduced pressure. TLC of the residue indicated the presence of only one product. Preparative TLC yielded 371 mg (62%) of 2 as a low-melting solid whose NMR spectrum has been discussed previously. The analytical sample was repurified by preparative TLC.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 72.97; H, 10.14.

B. A solution of 0.500 g of 1 was photooxygenated as in A. The solvent was removed at low pressure below 25 °C and the mixture (two major and two minor products by TLC) purified by preparative TLC (eluent 3:7 ether–hexane). There were three major bands. The least polar band consisted of 2 and two minor products; the band of intermediate polarity contained mainly 2 and three minor products; and the most polar band was pure 2. 3 was completely absent.

C. Photooxygenation of 0.200 g of 1 was carried out as in A, but at −78 °C and with 3 mL of ethanol added to dissolve the sensitizer. After 1 h when TLC indicated disappearance of 1, the solvent was removed at reduced pressure below 0 °C. NMR analysis of the residue revealed the signals of 3 and traces of impurities including 2.

D. Photooxygenation of 0.500 g of 1 for 45 min as in A but with 0.700 g of $P(OEt)_3$ added, removal of solvent, and preparative TLC of the residue (eluent 1:3 ether–hexane) gave 344 mg (55%) of highly volatile 4 which melted below 20 °C. The NMR spectrum has been discussed previously; the ^{13}C NMR spectrum exhibited signals at 162.1 (C-3), 105.6 t (C-9), 80.6 (C-2), 51.1 (two narrowly separated singlets, C-1 and C-4), 39.4 d and 36.9 d (C-5 and C-6), 21.0 q, 19.2 q, and 14.6 q (C-1, C-2, and C-4 methyls), and 12.8 q and 11.1 ppm q (C-5 and C-6 methyls).

Anal. Calcd for $C_{12}H_{20}O$: mol wt, 180.1514. Found: mol wt, 180.1536 (mass spectrum).

Rearrangement of 3 to 2. A. Freshly prepared 3 was dissolved in $CDCl_3$ and placed in an NMR tube. The rearrangement was followed by NMR spectrometry and was complete after 18 h as shown by disappearance of the vinyl proton singlets at 5.23 and 4.93 ppm and the appearance of the methyl ketone singlets at 1.98 and 1.34 ppm.

B. Freshly prepared 3 was dissolved in $CDCl_3$ and placed in an NMR tube. The NMR spectrum showed the presence of a trace of 2. Addition of a drop of concentrated HCl caused a vigorous exothermic reaction. Redetermination of the NMR spectrum showed quantitative conversion of 3 to 2.

Registry No.—1, 2957-96-2; 2, 61477-44-9; 3, 61477-45-0; 4, 61477-46-1; HMDB, 7641-77-2; oxygen, 7782-44-7.

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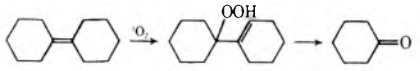
(11) See, for example, the decomposition of the hydroperoxide **8** (from **7**) to



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cyclohexanone; G. O. Schenck and K. H. Schulte-Elte, *Justus Liebigs Ann. Chem.*, **618**, 185 (1958).
(12) For experimental details, see J. A. Turner and W. Herz, *J. Org. Chem.*, in press.
(13) **Note Added in Proof.** Since hexamethylbenzene is a difficultly separable impurity in commercial HMDB, the hexamethylbenzene which we isolated may have been material originally present in the starting material.

Enzymatic and Chemical Resolution of 1-Octyn-4-ol

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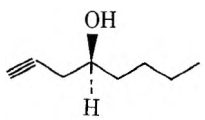
The alcohol 1-octyn-4-ol (I) is an intermediate in certain syntheses of prostaglandin analogues.[1] As such, it was important to have the racemate[2] resolved for stereospecific synthesis. Usually alcohols are converted to the half-phthalates and then resolved using such bases as brucine, dehydroabietylamine, or α-methylbenzylamine. In our hands these reagents were ineffective in this particular case. The enzymatic method of resolution is as old as the chemical method but organic chemists seldom avail themselves of this process.[3] In this note we would like to show that this method may be just as available to the chemist as the more popular chemical procedures.

We screened ten cultures in shaker flasks before finding one which selectively cleaved the benzoate of this alcohol. This culture, *Rhizopus nigricans* (Lederle culture R70), was then grown in a 30-L fermentor and the harvested cells were resuspended in distilled water and incubated with substrate. Using this technique, a free alcohol having a specific rotation of (−) 27 ± 2° (EtOAc) was obtained. This oil was reacted with (−)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) chloride and the resultant ester examined by NMR in the methoxy region at δ 3.44 and 3.54 and found to be better than 95% optically pure.[4]

The (−)-I obtained by microbiological transformation was converted to the crystalline half-phthalate (−)-α-methylbenzylamine (MBA) salt. With the aid of these seed crystals a chemical resolution of (±)-I was achieved.



(−)-I

The unreacted benzoate of 1-octyn-4-ol recovered directly from our transformation work, while exhibiting good positive rotation, was not obtained optically pure. The optically pure positive rotamer was obtained, however, by processing the filtrates from the recrystallizations of (−)-MBA half-phthalate of (−)-I. These filtrates were stripped of (−)-MBA by HCl extraction and then treated with (+)-MBA. Repeated recrystallizations and careful manipulation of solvent composition finally yielded the pure salt (+)-MBA half-phthalate of (+)-I. When both enantiomorphs of 1-octyn-4-ol were obtained, a number of derivatives were made as shown in Table I. This table shows that the diastereoisomeric MBA salts, which are to be fractionally crystallized away from each other, melt only 9 °C apart, which may account in part for some of the difficulties of this resolution.

To assign absolute configuration we carried out the Horeau test[5] on (−)-1-octyn-4-ol and recovered excess (+)-(*S*)-α-phenylbutyric acid. If we assume that the butyl group is larger than the propargyl group as suggested by Landor et al.,[6] then (−)-I should have the *S* configuration. Hence, this material falls in line with the negative rotamers of 1-octyn-3-ol[7] and 1-hexyn-3-ol,[5] both of which are of the *S* configuration. Mindful of the difficulties which Pappo et al.[8] had with the assignment of (−)-1-octyn-3-ol using the Horeau method, we reduced (−)-I to 4-octanol. This sweet-smelling oil failed to give a Horeau response. Indeed the material showed no specific rotation. There is no doubt about its optical activity since the benzoate had a specific rotation of −3° and the phthalate gave a value of −4°. Table II gives CD values on (+)-I, the phthalate of (+)-I, and the phthalate of (+)-4-octanol. There is no reversal of Cotton effect in replacing the ethynyl group by an ethyl group; consequently (+)-4-octanol is likely to have the *S* configuration.

Experimental Section

TLC was carried out on silica gel thin layers with fluorescent indicator supplied by Brinkmann. IR spectra were taken either in KBr pellets or as smears between salt plates using an Infracord spectrophotometer. Mass spectra were run on a high-resolution direct inlet AEI MS9 instrument. NMR spectra were made using a Varian HA-100 instrument. Melting points were taken in capillaries and are uncorrected. CD spectra were supplied by Professor K. Nakanishi of Columbia University and were recorded on a Jasco spectropolarimeter.

Flask Screening Procedure. About 5 mL of sterile medium was used to wash out an agar slant of each culture using a sterile pipet. The inoculum wash was then divided between two Erlenmeyer flasks each containing 50 mL of medium which consisted of 2% edamine, 0.72% corn steep liquor, and 2% dextrose in water with pH adjusted to 6.8. The flasks were set on a rotary shaker at 28 °C for 72 h at which time 50 mg of the benzoate of (±)-I in 0.1 mL of acetone was aded to one of the flasks and the fermentations were continued. Samples of 5-mL volume were taken at 16 and 40 h after substrate addition. The samples were extracted with $CHCl_3$. The extracts were dried, concentrated to dryness, and reconstituted to 0.1 mL with MeOH. Approximately 25 μL of the reconstituted samples was applied to thin layers and developed using 90:10 hexane–EtOAc. The spots were visualized by UV scanning and by H_2SO_4 charring and compared with control spots. By this procedure it was found that *Rhizopus nigricans* (Lederle culture R70) transformed the negative benzoate rotamer to the free alcohol.

Thirty-Liter Tank Conversion of Substrate by R70. Two Erlenmeyer flasks of the previously described medium were inoculated from a slant of culture R70 and grown for 3 days and then used to inoculate a 1-L bottle of the same medium. This second stage inoculum was grown for 1 day and then added to a 30-L fermentor. After 24 h of growth in the tank at 25 °C with aeration and agitation, 8.5 g of the benzoate of (±)-I in 25 mL of acetone was added. The tank was harvested 9.5 h later. The cells were filtered off using cheese cloth and set aside for further work. The filtrate was extracted with ⅕ volume of EtOAc which yielded 6.4 g of an oil. Chromatography of this oil over adsorbent silica yielded 1 g of the benzoate of I, $[\alpha]^{25}_D$ +21 ± 1° (*c* 1.65, EtOAc), and 250 mg of 1-octyn-4-ol, $[\alpha]^{25}_D$ −10 ± 1° (*c* 1.65, EtOAc). The cells from the above procedure were washed with H_2O and then resuspended in 15 L of H_2O with 15.0 g of substrate in 5 mL of acetone added. After agitating overnight without air supply, the cells were again removed using cheese cloth. Extraction of the filtrate with EtOAc yielded 7.0 g of an oil which when subjected to adsorbent silica chromatography yielded 1.8 g of I, $[\alpha]^{25}_D$ −18 ± 2° (*c* 1.60, EtOAc).

About 120 mg of this preparation was distilled in a Kugelrohr apparatus at 75 °C under 250-μm pressure to get 66 mg of a mobile, colorless oil: $[\alpha]^{25}_D$ −27 ± 2° (c 0.41, EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.92 (3 H, t, terminal CH_3), 1.41 [6 H, m, $-(CH_2)_3CH_3$], 1.91 (1 H, t, $-C{\equiv}CH$), 2.28 (2 H, m, $HC{\equiv}CCH_2$), 3.66 (1 H, m, >CHOH); IR

Table I. Physical Constants of Compounds Derived from 1-Octyn-4-ol (I)

Registry no.	Compd	Mp, °C	$[\alpha]^{25}_D$ in EtOAc, deg
56085-20-2	(−)-1-Octyn-4-ol (I)	Oil	−27 ± 2
61303-39-7	(+)-I	Oil	+25 ± 1
56085-18-8	Half-phthalate of (−)-I	48–49	−53.4 ± 1
61586-58-1	Half-phthalate of (+)-I	48–49	+53 ± 1
56007-93-3	Half-phthalate of (±)-I	67–68	0
56085-19-9	Salt (−)-MBA half-phthalate of (−)-I	121–122	−45 ± 1
61586-59-2	Salt (+)-MBA half-phthalate of (+)-I	121–122	+44 ± 1
61586-60-5	Salt (−)-MBA half-phthalate of (+)-I	112.5–113.5	−24 ± 1
61559-27-1	Salt (+)-MBA half-phthalate of (−)-I	112.5–113.5	+23 ± 1

Table II. CD Data on (+)-I and Derivatives

Phthalate of (+)-4-octanol	$\Delta\epsilon_{238}$ +1.25 × 10^{-1}
Phthalate of (+)-1-octyn-4-ol	$\Delta\epsilon_{240}$ +2.76
(+)-1-Octyn-4-ol	$\Delta\epsilon_{222}$ +2.6 × 10^{-3}

(smear) 3300, 2920, sh 2850, 2135, 1050, 852 cm^{-1}; mass spectrum M^+ *m/e* 126.

Despite several attempts microanalytical values on this material were consistently low. Anal. Calcd for $C_8H_{14}O$: C, 76.40; H, 11.18. Found: C, 75.51; H, 11.41 (e.g.).

Use of Mosher's MTPA Reagent to Test for Optical Purity.[3,6] About 100 mg of (−)-I in 0.2 mL of pyridine was reacted with 0.2 mL of (−)-MTPA (α-methoxy-α-trifluoromethylphenylacetic acid) chloride for 1 h at room temperature. The reaction mixture was worked up by standard methods to give 132 mg of an oily product. NMR in C_6D_6 showed a strong methoxy signal (these signals appear as unresolved quartets due to long-range coupling with $-CF_3$ group) at δ 3.54 with the smallest hint of a signal at δ 3.44. Based on this result (−)-I was better than 95% optically pure.

Anal. Calcd for $C_{18}H_{21}O_3F_3$: C, 63.15; H, 6.14. Found: C, 62.72; H, 6.39.

Half-Phthalate (−)-I. This derivative of (−)-I was prepared using phthalic anhydride and dry pyridine to get a crystalline product: mp 48–49 °C: $[\alpha]^{25}_D$ 53.4 ± 1° (c 1.11, EtOAc); ^1H NMR ($CDCl_3$) δ 0.91 (3 H, t, terminal CH_3), 1.36 [4 H, m, $(CH_2)_2CH_3$], 1.76 [2 H, m, $CH_3(CH_2)_2CH_2CHOH$–], 1.92 (1 H, t, HC≡C–), 2.57 (2 H, m, $HCCCH_2$–), 5.11 (1 H, m, –CHOH–), 7.36 (3 H, m, 3 aromatic H), 7.84 (1 H, m, aromatic H ortho to –COOH), 12.59 (1 H, s, exchanges, COOH).

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.15; H, 6.61. Found: C, 69.83; H, 6.72

The (−)-MBA salt of this half-phthalate was prepared and recrystallized from ether–hexane to get a material, mp 121–122 °C, $[\alpha]^{25}_D$ −45 ± 1° (c 1.0, EtOAc).

Anal. Calcd for $C_{24}H_{29}O_4N$: C, 72.88; H, 7.39, N, 3.54. Found: C, 73.14; H, 7.75; N, 3.74.

Chemical Resolution of Half-Phthalate of (±)-I. A solution of 22 g of (−)-MBA in 150 mL of hexane was added to a solution of 50 g of the half-phthalate of (±)-I in 150 mL of EtOAc. The resultant solution was seeded with the MBA salt of the half-phthalate of (−)-I and left in the refrigerator for 3 days. The crystals were recovered and recrystallized with seeding three more times from EtOAc–hexane to get 11 g of crystals, $[\alpha]^{25}_D$ −39 ± 1°. Three such batches were combined and recrystallized from 400 mL of 1:1 EtOAc–hexane without seeding. After two such recrystallizations 27 g of material was obtained, mp 121–122 °C, $[\alpha]^{25}_D$ −45 ± 1° (c 1.0, EtOAc). About 7 g of this material were taken up in 100 mL of 2 N HCl and the solution extracted with 200 mL of ether. The ether solution was dried and concentrated to 4.0 g of an oil which crystallized in the refrigerator, mp 48–49 °C, $[\alpha]^{25}_D$ −53 ± 1° (c 1.0, EtOAc). When 1 g of this half-phthalate was stirred for 4 h in 80 mL of 8% KOH, 380 mg of (−)-I was obtained. Distillation of this oil in the Kugelrohr at 75 °C under 250-μm pressure gave a material with $[\alpha]^{25}_D$ −24.6 ± 1° (c 1.09, EtOAc). The material was better than 99% pure by GLC.

Preparation of (+)-I. Filtrates from crystallization of (−)-MBA salt of the half-phthalate of (−)-I were combined and extracted with HCl. The solvent phase was dried and taken to an oil and 50 g of this oil was reconstituted in 150 mL of EtOAc.

A solution of 20 g of (+)-MBA in 180 mL of hexane was added and the solution refrigerated for 7 days. The product was recrystallized seven times to give a low yield of material, mp 121–122 °C, $[\alpha]^{25}_D$ +44 ± 1° (c 1.22, EtOAc). The NMR of this material was identical with that of the diastereoisomeric salt already described. When the (+)-MBA was removed in the usual fashion, crystals of the half-phthalate of (+)-I were obtained, mp 48–49 °C $[\alpha]^{25}_D$ +53° (c 0.97, EtOAc). The free alcohol (+)-I was obtained as described before, $[\alpha]^{25}_D$ +25 ± 1° (c 0.88, EtOAc).

Catalytic Reduction of (−)-I. About 148 mg of (−)-I were reduced in 10 mL of EtOAc with H_2 at atomospheric pressure in the presence of 15 mg of 10% Pd/C catalyst. The resultant oil had $[\alpha]^{25}_D$ 0° (c 1.0, EtOAc); ^1H NMR ($CDCl_3$) δ 0.91 (6 H, m, 2 terminal CH_3), 1.38 (10 H, m, 5 methylenes), 2.78 (1 H, s, exchanges OH), 3.64 (1 H, m, –CHOH–).

The benzoate of this octanol was prepared and shown to have $[\alpha]^{25}_D$ −3° (c 0.98, EtOAc).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.68; H, 9.46. Found: C, 76.70; H, 9.65.

Catalytic Reduction of Half-Phthalate of (+)-I. This reduction was carried out as described for (−)-I to yield a crystalline product, mp 52.5–53.5 °C, $[\alpha]^{25}_D$ +4 ± 2° (c 0.78, EtOAc).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.46; H, 8.06

Horeau Method on (−)-I. A solution of 70 mg of (−)-I and 0.3 mL of (±)-α-phenylbutyric anhydride in 3 mL of dry pyridine was left overnight at room temperature. Workup of the reaction in the prescribed manner[9] yielded 210 mg of an oil which crystallized overnight, $[\alpha]^{25}_D$ +2 + 0.1° (c 6.5 benzene). TLC and NMR data showed the material to be α-phenylbutyric acid. When the Horeau method was applied to (−)-4-octanol, the recovered acid was essentially optically inactive.

Acknowledgments. We wish to thank our colleagues Dr. H. Tresner and Mrs. J. H. Korshalla for supplying the cultures, Mr. A. J. Shay for growing the 30-L tank, Mr. W. Fulmor for spectral and rotational data, Professor K. Nakanishi for CD data, and Mr. L. Brancone for microanalytical data.

Registry No.—(±)-I, 56007-85-3; (±)-I benzoate, 61284-53-5; (−)-I benzoate, 61303-38-6; (−)-I MTPA ester, 61559-28-2; (−)-MTPA, 20445-33-4; (−)-MBA, 2627-86-3; (+)-MBA, 3886-69-9; phthalic anhydride, 85-44-9; (−)-4-octanol, 61559-29-3; (−)-4-octanol benzoate, 61559-30-6; (+)-4-octanol phthalate, 61559-31-7.

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cis-Stilbene Oxide from *trans*-Stilbene via Dioxetane Deoxygenation—a Stereospecific Sequence Involving Three Inversions

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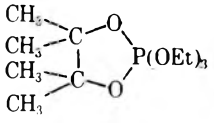
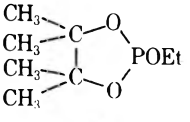
The recently reported[1] photoepoxidation of stilbene with α-diketone sensitizers provides an example of complex configuration control by nonstereospecific mechanisms. Both *cis*- and *trans*-stilbenes are converted into good yields of *trans*-stilbene oxide, but when *trans*-stilbene is the starting material the first step is an energy transfer resulting in its isomerization into *cis*-stilbene. Moreover, the final formation of trans epoxide appears to be a matter of conformational preference in a rotating intermediate.

It is, of course, possible to convert *cis*- and *trans*-stilbenes each into its own epoxide by stereospecific peracid oxidation. The present report concerns a stereospecific sequence for the fourth conversion—*trans*-stilbene to *cis*-stilbene oxide.

The cyclic phosphorane **1** has been prepared from the phosphite **2** and diethyl peroxide; an indication of configurative inversion in its decomposition was that the phosphorane **3**, initially 88% *dl* and 12% meso, yielded a mixture of epoxides



1



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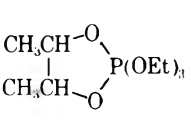
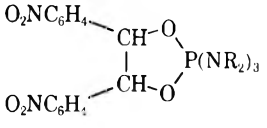


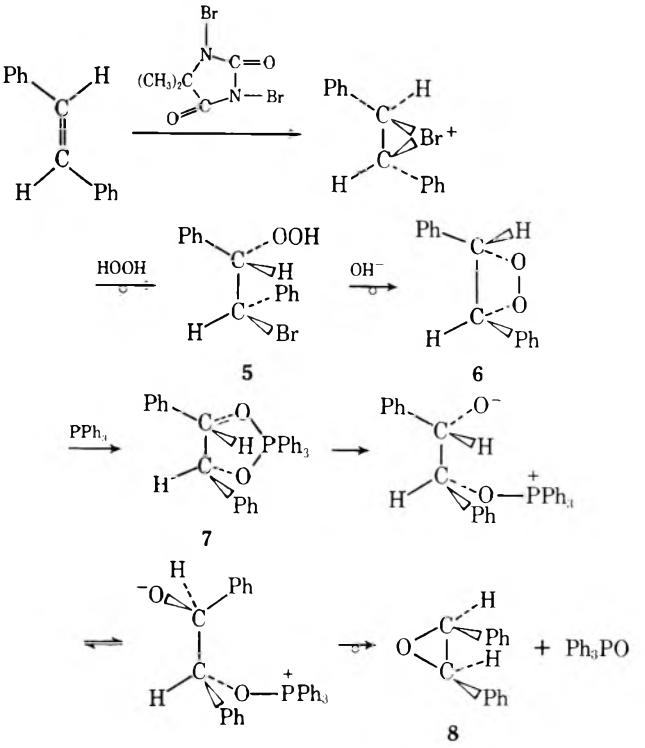
3

with the opposite isomeric composition (85% cis, 15% trans).[2] A similar inversion was reported by Ramirez, Gulati, and Smith[3] in the formation of epoxides from the decomposition of **4**, formed from the corresponding triaminophosphine and two molecules of *p*-nitrobenzaldehyde.



4

trans-3,4-Diphenyl-1,2-dioxetane (**6**) was prepared from the bromohydroperoxide precursor **5**, which was formed from *trans*-stilbene by the method of Kopecky.[4] The dioxetane reacted rapidly with triphenylphosphine at 0 °C to yield a solution of the phosphorane **7** with a singlet at δ 4.50. On warming to 50 °C for 1 h, the phosphorane decomposed to triphenylphosphine oxide and *cis*-stilbene oxide (**8**), characterized by its NMR and IR spectra. The links in this chain of stereochemical control are (1) cis formation of bromonium ion from stilbene and the dibromohydantoin; (2) inversion in attack of the nucleophilic HOOH on the bromonium ion; (3) inversion in the internal attack of the peroxide anion of **5** on the bromine-bearing carbon to form the dioxetane **6**; (4) insertion of the phosphorus into the dioxetane **6** with retention to yield **7**; (5) cleavage, probably ionic, between P and O with ring opening of the phosphorane **7**; and (6) displacement of phosphine oxide by O^- with inversion to form **8**.



5 **6** **7** **8**

Experimental Section

***erythro*-1,2-Diphenyl-2-bromoethyl Hydroperoxide (5).** A solution of 10.26 g (57 mmol) of *trans*-stilbene and 9.0 g of 90% H_2O_2 in 50 mL of ether was cooled to −40 °C and 8.1 g of *N,N*-dibromodimethylhydantoin (57 mmol of Br^+) was then added over a 10-min interval. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The solution was then washed with three separate 15-mL portions of 10% aqueous sodium bicarbonate and dried over $MgSO_4$. Solvent was removed in vacuo and the resulting residue was recrystallized from 1:1 methylene chloride/pentane at −20 °C yielding 7 g (30%) of bromo hydroperoxide **5**: NMR)cdcl$_3$) δ 8.03 (s, 1 H), 7.32–7.8 (m, 10 H), 5.32–5.60 (m, 2 H); IR (thin film on NaCl) 3500 (s), 3060 (m), 3020 (m), 1500 (m), 1450 (s), 1330 (m), 1200 (m), 1150 (m), 1060 (m), 1020 (w), 950 (s), 900 (w), 800 (m), 740 (s), 670 cm^{-1} 670.

***trans*-3-4-Diphenyl-1,2-dioxetane (6).** A solution of 1 g (2.5 mmol) of **5** in 25 mL of CH_2Cl_2 and 10 mL of methanol was cooled to 0 °C, and 5 mL of 0.5 M NaOMe in MeOH (2.5 mmol) was added over a 10-min interval. The reaction mixture was kept in the dark and stirred at 0 °C for an additional 45 min. After this time the solution was washed with 50 mL of water and the organic layer was separated. The aqueous layer was washed with an additional 15 mL of CH_2Cl_2 and the combined organic extracts were washed with three 25-mL portions of water. The solution was dried over $MgSO_4$ and the solvent removed in vacuo. The deep yellow oil was chromatographed at −78 °C on alumina with CH_2Cl_2 as eluent. **6** elutes as a yellow band and is contaminated with benzaldehyde, formed via thermal decomposition of **6**, and a small amount, ca. 10%, of corresponding trans epoxide, from bromohydrin formed along with **5**.

The CH_2Cl_2 was removed in vacuo and the dioxetane was dissolved in 2.5 mL of CCl_4 to which 5 μL of *p*-dioxane was added as internal standard. The yield of **6**, based on internal standard, was 0.33 mmol (13%): NMR (CCl_4) δ 7.5–7.9 (m, 10 H), 6.40 (s, 2 H).

Thermal Cleavage of 6. Dioxetane **6** (0.5 mL, 0.11 M) in CCl_4 was heated at 65 °C for 1 h, during which chemiluminescence was observed. The NMR and IR spectra of the decomposed material were identical with those of authentic benzaldehyde.

Reduction of 6 to *dl*-Diphenylethanediol. A 0.11 M solution of dioxetane **6** (1 mL) in CCl_4 was added to 40 mg of lithium aluminum hydride in 50 mL of ether and the solution stirred for 10 min at room temperature. A saturated aqueous solution of NH_4Cl was added to quench the reaction. The organic layer was decanted and the solvent removed in vacuo, yielding a semisolid. The NMR spectrum of the crude material indicated 50% benzyl alcohol (from reduction of benzaldehyde) and 50% of diol. Recrystallization from petroleum ether yielded 7 mg (30%) of diol: mp 115.5–117 °C (lit. 119–120 °C);[5] NMR ($CDCl_3$) δ 7.25–7.5 (m, 10 H), 2.90 (broad s, 2 H), 4.80 (s, 2 H); IR ($CDCl_3$) 3600 (s), 3060 (m), 3030 (m), 2990 (m), 1600 (m), 1480 (m), 1450 (m), 1370 (m), 1310 (m), 1260 (w), 1220 (2), 1180 (s), 1020 (s), 860 cm^{-1} (m).

Conversion of Trans Dioxetane 6 to Cis Epoxide 8. Triphenylphosphine (50 mg, 0.19 mmol) was added at 0 °C to 3 mL of 0.064 M dioxetane in CCl_4 (0.192 mmol) containing 0.195 M of the *p*-dioxane as internal standard. The yellow color of **6** disappeared immediately upon mixing. The NMR spectrum of the reaction mixture indicated the presence of phosphorane **7**, δ 4.60 (s, 2 H), formed in 85% yield based on internal standard. The solution was then heated at 50 °C

for 1 h at which time phosphorane decomposed yielding cis epoxide 8 in 91% yield based on internal standard. No appreciable increase of the trans epoxide, present as impurity in the starting dioxetane solution, was observed. Epoxide 8 was isolated from the reaction mixture by preparative VPC, 10 × 0.25 in. 20% Carbowax 20M on Chromosorb P: column 170 °C, injector 240 °C, flow rate 120 mL/min, retention time of cis epoxide 3 min. NMR (CCl_4) δ 7.20 (s, 10 H), 4.31 (s, 2 H); IR (CCl_4) 3100 (m), 3060 (m), 3000 (m), 1630 (w), 1510 (m), 1460 (s), 1420 (m), 1370 (m), 1320 (w), 1290 (w), 1260 (w), 1180 (s), 1120 (w), 1070 (w), 1070 (m), 900 (s), 720 (m), 690 cm^{-1} (s). Identical properties were shown by an authentic sample prepared by the reaction of *cis*-stilbene with *m*-chloroperbenzoic acid.[6]

Acknowledgment. We thank the Robert A. Welch Foundation, the National Science Foundation, and the National Institutes of Health for support.

Registry No.—**5**, 61570-41-0; **6**, 61570-42-1; **7**, 61570-43-2; **8**, 1689-71-0; *trans*-stilbene, 103-30-0; *dl*-diphenylethanediol, 655-48-1.

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Communications

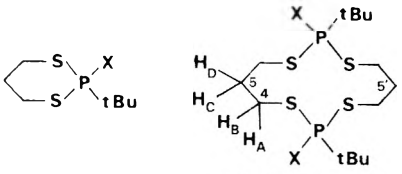
Twelve-Membered-Ring Molecules Containing P and S. Preparation and Identification

Summary: The twelve-membered-ring dimers of 2-*tert*-butyl-1,3,2-dithiaphosphorinane which are in equilibrium with the six-membered-ring monomer and the corresponding 2-thiono derivatives have been prepared, isolated, and identified.

Sir: Macrocyclic molecules containing phosphorus are of potential interest because of the known versatility of phosphorus as a ligand,[1] and as models for stereochemical study. In previous studies, it was shown that twelve- and ten-membered-ring phosphonite molecules can easily be obtained from 1,3,2-dioxaphosphorinanes[2] and 1,3,2-dioxaphospholanes[3] as they dimerize on standing. These large-membered-ring three-coordinated phosphorus molecules which are at room temperature in equilibrium with their monomeric six- and five-membered-ring parent molecules were not isolated. The corresponding thiono derivatives (P=S) were isolated and well characterized as crystalline compounds.

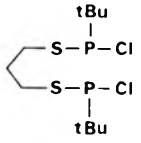
Differences exist in the chemical behavior of the analogous heterocycles where the ring oxygen is replaced by a sulfur. For example, 2-methyl-1,3,2-dithiaphospholane does not show any tendency to ring expansion reaction, whereas the corresponding 1,3,2-dioxaphospholane cannot be isolated as a monomeric species at room temperature.[3] Thus, it was interesting to check if the ring expansion reaction which takes place with 1,3,2-dioxaphosphorinanes[2] can be observed with dithiaphosphorinanes.

We report here some preliminary results which show that twelve-membered-ring molecules containing phosphorus and sulfur atoms in the ring, are formed in the preparation of the corresponding six-membered-ring dithiaphosphorinane by simple ring expansion. It must be pointed out that these twelve-membered rings have been obtained in the trivalent and tetravalent state of phosphorus.



1, X = lone pair
1S, X = S

2, 2′, X = lone pair
2S, 2′S, X = S



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1,3-Propanedithiol was added dropwise to a benzene solution of *tert*-butyldichlorophosphine and pyridine.[4-6] The reaction was conducted under nitrogen at 30 °C, and followed by ^{31}P NMR spectroscopy. After addition of half an equivalent of 1,3-propanedithiol, the ^{31}P (^{1}H) NMR spectrum shows two lines at 182.6 and 182.3 ppm, corresponding to compound **3** which is a mixture of two diastereomeric molecules owing to

Table I. ^{13}C and ^{31}P NMR Spectral Data of Dimeric Species 2, 2′, 2S, 2′S

Compd	Solvent	δ(^{31}P)[a]	δ(C_4)[b]	δ(C_5)	$J(PH_A)$[c]	$J(PH_B)$	$J(PH_C)$	$J(PH_D)$	$J(PC_4)$	$J(PC_5)$
2, cis	C_6D_6	104.0	31.6	34.0					19.4	
2′, trans	C_6D_6	121.0	33.3	34.1	8.0	15.0	1.0	1.0	24.7	4.8
2S cis	$CDCl_3$	116.1	33.0	31.7	13.5	13.0	1.0	1.0	3.8	3.2
2′S trans	$CDCl_3$	120.2	32.1	32.7	17.5	16.0	1.0	1.0	3.8	1.5

[a] The ^{31}P chemical shifts are in parts per million downfield from H_3PO_4 (85%). [b] The ^{13}C chemical shifts are in parts per million downfield from TMS. [c] The coupling constants are in hertz.

Table II. ^{1}H NMR Spectral Data of Dimeric Species 2, 2′, 2S, 2′S

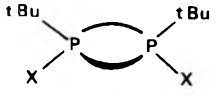
Compd	Solvent	δ(H_A)[a]	δ(H_B)	δ(H_C)	δ(H_D)	δ(*t*-Bu)	$J(H_AH_B{}^b)$	$J(H_AH_C)$	$J(H_AH_D)$	$J(H_BH_C)$	$J(H_BH_D)$
2, cis	C_6D_6			~1.90	~1.90	1.14					
2′, trans	C_6D_6	2.83	2.44	1.90	1.90	1.14	−13.0	6.5	6.5	6.5	6.5
2S, cis	$CDCl_3$	3.24	3.03	2.24	2.22	1.34	−14.0	7.0	7.0	7.0	7.0
2′S, trans	$CDCl_3$	3.31	2.86	2.25	2.25	1.32	−13.8	7.0	7.0	7.0	7.0

[a] The proton chemical shifts are in parts per million downfield from TMS. [b] The coupling constants are in hertz.

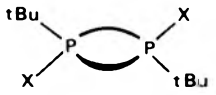
the chiral phosphorus center. Molecule **3** itself was not isolated but its thiono methoxy derivative was characterized by the usual techniques (elemental analysis; ^1H, ^{13}C, ^{31}P NMR spectra; mass spectrometry). After completion of the dithiol addition, the reaction mixture exhibits in the ^{31}P (^1H) NMR spectrum the following peaks, where the chemical shifts are given in parts per million downfield from H_3PO_4 as the external reference: M (97.3), D_2 (104.0), P (115.5), D_1 (121.0 ppm).

A silica column chromatography performed under nitrogen of the final reaction mixture using hexane–benzene (3:1) as eluent allows separation of a first and third pure fraction, each showing one peak in the ^{31}P (^1H) NMR spectrum, D_1 (121.0) and M (97.3 ppm), respectively. A second fraction shows two peaks at D_2 (104.0) and M (97.3 ppm).

By NMR spectral analysis (^1H, ^{13}C, ^{31}P) (Tables I and II), elemental analysis, and mass spectrometry, the species corresponding to peaks M, D_1, and D_2 are unambiguously assigned to 2-*tert*-butyl-1,3,2-dithiaphosphorinane (**1**) and the corresponding twelve-membered-ring dimers **2** and **2′** (mp 119–121 °C), respectively. These dimers differ by the relative orientation of the *tert*-butyl group with respect to the mean plane of the molecule. Up to now, we have been unsuccessful in obtaining a pure sample of **2**, which is always contaminated



2, X = lone pair
2S, X = S



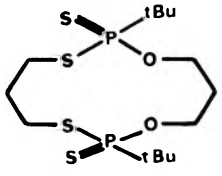
2′, X = lone pair
2′S, X = S

by **1**. Peak P (115.5 ppm) corresponds to higher polymeric species which are now under investigation.

Addition of elemental sulfur[7] to a mixture containing **1**, **2**, and **2′** gives rise to the expected thiono derivatives **1S** (mp 77–78 °C), **2S** (mp 162–164 °C), and **2′S** (mp 250–252 °C). These compounds, separated by silica column chromatography with benzene as eluent, have been characterized by elemental analysis, mass spectroscopy, molecular weight measurement (osmometry), and ^1H, ^{13}C, and ^{31}P NMR spectroscopy (Tables I and II). In the ^1H NMR spectrum, the protons attached to carbons 5 and 5′ are equivalent in **2′S** and nonequivalent in **2S**. Thus, **2′** and **2′S** correspond to the stereoisomers in which the *tert*-butyl groups are in a trans relationship with respect to the mean plane of the twelve-membered ring (presence of an inversion center i).

When a solution of pure dimer **2′** is left in a sealed NMR tube, it shows additional ^{31}P NMR peaks which appear with time. After a few hours at 80 °C, a mixture of both isomers **2** and **2′** is observed. If the tube is heated at 160 °C, a mixture of the two dimers **2** and **2′** (3:1) with the monomeric species **1** is obtained. The equilibrium ratio of the three species **2′**, **2**, and **1** at 160 °C is 3:1:6. A mixture of the species **2** and **1** leads to a similar equilibrium. Thus, the trans isomer **2′** is thermodynamically more stable than **2**. Different kinetics rates are obtained in nonsealed tubes, probably owing to the presence of catalytic reagents which accelerate the reaction.

Besides the synthesis of a new category of heterocyclic phosphorus molecules, one of the interesting point of the reaction described in this paper is the existence of **3** as a stable intermediate. Thus **3** can react with various difunctional



4

compounds (diols, diamines, dithiols, etc.) leading to various large-membered-ring molecules. As an example, the twelve-membered-ring **4** has been prepared.

The synthesis of various rings which differ by the size (11, 12, 13) and the nature of their heteroatoms is being actively continued.

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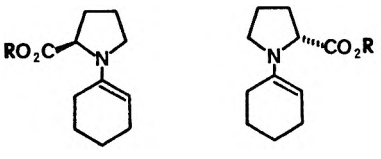
Asymmetric Induction. 2.[1] Enantioselective Alkylation of Cyclohexanone via a Chiral Enamine†

Summary: Asymmetric induction was observed in the alkylation of the cyclohexanone enamine prepared from (+)-*trans*-2,5-dimethylpyrrolidine. Alkylation with methyl iodide, *n*-propyl bromide, and allyl bromide afforded the corresponding 2-*n*-alkylcyclohexanones with optical purities of 83, 93, and 82%, respectively. Very low levels of dialkylation product formation were observed.

Sir: In 1968 Horeau published[2] the first enantioselective alkylation of a ketone, using the imine anion derived from isobornylamine and cyclohexanone. Recent modifications to this scheme have raised the enantiomeric ratio to greater than 9:1.[1,3] We wish to report here a complementary technique that affords similarly high degrees of enantioselectivity in the alkylation of enamines.

In 1969 Yamada reported[4] the first in a series of investigations[5] of the alkylation of the chiral enamines formed using various proline esters, and though the best optical yield obtained was 55%, the more typical values fell in the range from 10 to 30%. These results, taken together, are consistent with the participation of two sets of transition states differing by geometrical isomerization (represented by A and B). Of the



A **B** **I**

four transition states resulting from the distinct pathways of approach of the alkylating agent (back and front on both A

† We wish to dedicate this paper to Professor Robert Burns Woodward on the occasion of his sixtieth birthday.

Table I

Alkylating Agent	Chemical[a] yield, %	% dialkylation[b]	$[\alpha]^{25}_D$ (c, MeOH)[c,d]	Lit. $[\alpha]^{25}_D$ (c, MeOH)	Optical purity, %
CH_3I	50 (24)	6	+11.6° (2.7)	14.0° (0.23)[10]	83
$CH_3CH_2CH_2I$	57	7	+25.9° (1.4)	−27.9° (4.5)[11]	93
$CH_2{=}CHCH_2Br$	80	4	+11.2° (1.5)	13.7° (2.2)[11]	82

[a] VPC yield, based on the crude enamine (isolated yield). [b] The extent of dialkylation was determined at conversions of greater than 90%. [c] Measured with a Perkin-Elmer Model 151 polarimeter using samples carefully purified by preparative GLC to ensure the absence of dialkylation products. Values of −11.7° for 2-methylcyclohexanone and −25.8° for 2-*n*-propylcyclohexanone were obtained using the (−) amine. [d] All of the alkylcyclohexanones were produced with the same absolute chiral sense.

and B), the carboxyl moiety would be expected to exert a significant steric interaction in only one (back on B). Assuming nearly equivalent energies for the three remaining transition states leads to the prediction that induction in this system would be limited to an enantiomeric excess of around 2:1 (34% ee). Clearly what is needed is an amine with a C_2 axis of symmetry.

In the event, the enamine **1**, derived from (+)-*trans*-2,5-dimethylpyrrolidine[6,7] and cyclohexanone,[9] underwent smooth alkylation with excess methyl iodide in refluxing acetonitrile to afford, after hydrolysis in a two-phase system consisting of pentane and buffered, aqueous acetic acid, (*S*)-2-methylcyclohexanone with an optical purity of 83%. Other results are tabulated in Table I.

With the hope of implementing this technique for the enantioselective formation of quaternary centers, we prepared the analogous enamine from racemic 2-methylcyclohexanone. Unfortunately, and contrary to a published report,[12] we found this enamine to be at least 90% the less substituted isomer, and in fact saw no evidence indicating the presence of the more substituted enamine. Hydrolysis as above provided 2-methylcyclohexanone with no measurable rotation.[13]

There appear to exist, a priori, three distinct mechanisms of induction which would explain our observed results.

(I) Both diastereomeric immonium ions are being formed in a relatively nonselective alkylation, with a subsequent, selective hydrolysis providing enantioselectivity by kinetic resolution.

(II) Unselective formation of the immonium ions, as above, with subsequent equilibration under the conditions of alkylation forming predominently one of the diastereomeric ions.

(III) Kinetic control at the point of alkylation affording mainly one of the immonium ions.

The high material balance in the alkylations with propyl iodide (80%) and allyl bromide (99%), as well as the lack of optical activity in the methylcyclohexanone recovered from the hydrolysis of the enamine, preclude the operation of a kinetic resolution (I). The latter experiment is also inconsistent with the second rationale insofar as it is clear that both diastereomeric immonium ions must have been present in this hydrolysis, and were not interconverted under those conditions. We thus conclude that we are observing the result of an enantioselective alkylation.

We would also like to draw attention to the low level of dialkylation products obtained, even at the high level of conversion (greater than 90%) to which these alkylations were taken. These results compare quite favorably with the best heretofore observed.[14]

We are currently pursuing other uses of this enantioselective alkylation as well as a variety of other asymmetric induction schemes using *trans*-2,5-dimethylpyrollidine.

Acknowledgment is gratefully made to the Robert A. Welch Foundation, the Research Corporation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this research.

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(6) This amine was prepared by catalytic reduction[7] of the *N*-amino derivative,[8] and resolved via the salts with mandelic acid. Clearly distinct methyl adsorptions were observed in the ^1H NMR for the diastereomeric salts. The (+) amine, obtained with (−)-mandelic acid, had $[\alpha]^{25}_D$ +10.6° (*c* 1, EtOH), while the (−) amine, obtained using (+)-mandelic acid, had $[\alpha]^{25}_D$ −11.5°. Each amine was obtained from salts judged pure by NMR. The (+) amine is drawn with the *S,S* configuration based solely on the results of alkylation. A single-crystal x-ray analysis on the mandelic acid salt is currently underway.
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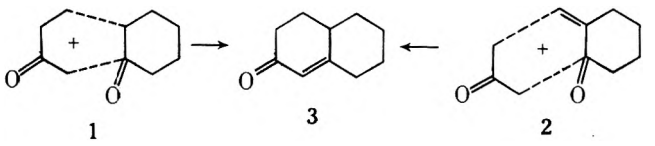
2-Ethoxyallylidene Triphenylphosphorane. A New Reagent for Cyclohexenone Annulation

Summary. 2-Ethoxyallylidene triphenylphosphorane is a new, convenient reagent for the annulation of cyclohexenones onto a variety of α,β-unsaturated ketones, thereby allowing the construction of monocyclic, fused bicyclic, and spiro bicyclic ring systems.

Sir: The Robinson annulation reaction and the many variants thereof are extraordinarily useful synthetic reactions for the construction of a cyclohexenone ring onto an extant ketone.[1] Most of these procedures involve the combination of a two-carbon structural unit with another possessing four carbon atoms (**1** → **3**), but there is an unfortunate lack of synthetic

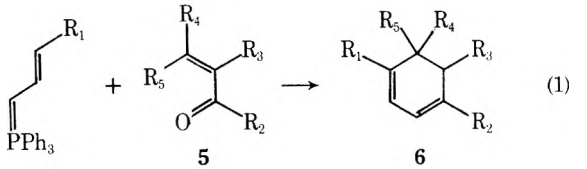
methodology for the formation of cyclohexenones from two structural units, each containing three carbon atoms (**2** → **3**).[2]



1 **3** **2**

Moreover, virtually all of the procedures for the annulation of these six-membered rings produce cyclohexenones as the final step in an aldol–cyclodehydration sequence from 1,5-dicarbonyl compounds, and a wide variety of useful reagents and techniques have been developed for the homologation of the ketones **1** and the α,β-unsaturated ketones **2** to these crucial intermediates. Undoubtedly owing to the paucity of methodology for their preparation, 2-alkoxy-1,3-cyclohexadienes, which contain the enone moiety as a latent functional group, have rarely been employed as precursors to cyclohexenones.[3] Since 2-alkoxy-1,3-cyclohexadienes might also serve as useful dienes in Diels–Alder reactions[4] as well as masked cyclohexenones, a simple procedure for the annulation of such functionalized cyclohexadienes onto pre-existing ketones would possess considerable synthetic utility. Consequently, we now wish to report a general procedure for the facile construction of 2-alkoxy-1,3-cyclohexadienes from starting materials containing three carbon atoms and for their subsequent conversion in situ to cyclohexenones.

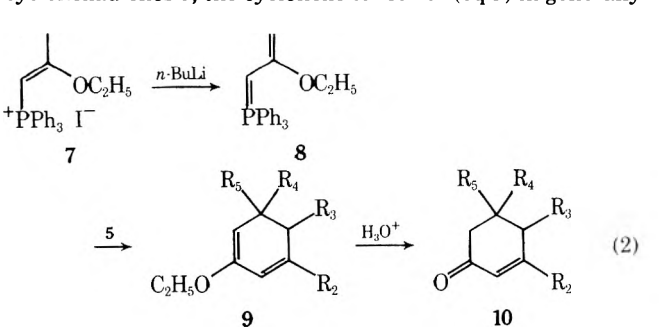
Recently simple allylidene triphenylphosphoranes **4** have been found to react with α,β-unsaturated ketones **5** to give substituted cyclohexadienes **6** (eq 1).[5,6] We reasoned, there-



4 **5** **6** (1)

fore, that the introduction of a heteroatom substituent such as an alkoxy group onto the allylidene phosphorane would allow the construction of alkoxy-functionalized cyclohexadienes which would afford cyclohexenones upon acid-catalyzed hydrolysis.

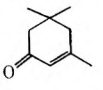
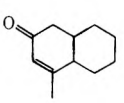
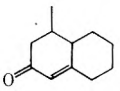
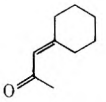
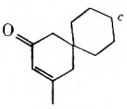
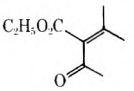
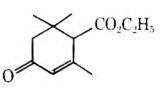
Although there are no known alkoxyallylidene triphenylphosphoranes, we found that 2-ethoxyallylidene triphenylphosphorane (**8**) could be easily generated by treating (2-ethoxy-1-propenyl)triphenylphosphonium iodide (**7**)[7] with *n*-butyllithium. This new functionalized allylidene triphenylphosphorane was found to react smoothly with a variety of structurally different α,β-unsaturated ketones **5** to give, upon acid-catalyzed hydrolysis of the intermediate 2-ethoxy-1,3-cyclohexadienes **9**, the cyclohexenones **10**[8] (eq 2) in generally



7 **8** **9** **10** (2)

fair to good overall yields (Table I). An examination of the entries in Table I reveals that this synthetic procedure, which may be conveniently executed without the isolation of the intermediate 2-ethoxy-1,3-cyclohexadienes **9**, may be em-

Table I. Annulation of Cyclohexenones

Entry	Starting enone 5	Product cyclohexenone 10[a]	% yield[b]
1			48
2			61
3			34
4			36
5			56
6			26

[a] All compounds gave satisfactory IR, MS, and NMR spectral data. [b] Overall yield based on starting enone 5, but not optimized. [c] Exact mass calcd for $C_{12}H_{18}O$, 178.1358. Found, 178.1354.

ployed for the construction of monocyclic, fused bicyclic, and spiro bicyclic ring systems. Moreover, since 4-carboethoxy-3,5,5-trimethylcyclohexenone (see entry 6) has recently been used as an intermediate in the synthesis of α-damascones,[9] the potential application of this new synthetic methodology to the total synthesis of natural products is readily apparent.

The following experimental procedure is representative of this conversion. To a well-stirred suspension of the phosphonium salt **7** (15 mmol) in anhydrous THF (75 mL) cooled to −50 °C under dry nitrogen, *n*-butyllithium in hexane (15 mmol) was slowly added. When the addition had been completed, the red-orange mixture was allowed to warm to about −25 °C, and the stirring was continued at that temperature for 2 h. After the solution of the allylidene phosphorane **8** was again cooled to −50 °C, a solution of the appropriate α,β-unsaturated ketone **5** (10 mmol) in anhydrous THF (5 mL) was added slowly dropwise. The resulting orange-brown reaction mixture was then stirred at room temperature for 18 h, whereupon 1 N HCl (75 mL) was added and the mixture stirred vigorously at room temperature for an additional 6 h. The crude cyclohexenones **10** were isolated by an extractive work-up and purified by vacuum distillation.

Further investigations to explore the synthetic utility of this and other functionalized allylidene triphenylphosphoranes are under active investigation and will be reported independently.

Acknowledgment. We wish to thank the Robert A. Welch Foundation for partial support of this work.

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(6) (a) W. G. Dauben, D. J. Hart, J. Ipaktschi, and A. P. Kozikowski, *Tetrahedron Lett.*, 4425 (1973); (b) W. G. Dauben and J. Ipaktschi, *J. Am. Chem. Soc.*, **95**, 5088 (1973).
(7) The phosphonium salt **7** was prepared in ~60% overall yield from chloroacetone by modifying the literature procedure of F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957).
(8) All compounds were adequately characterized by spectral methods (IR, NMR, and MS), and the new compound (entry 5) gave satisfactory high resolution mass spectral data.
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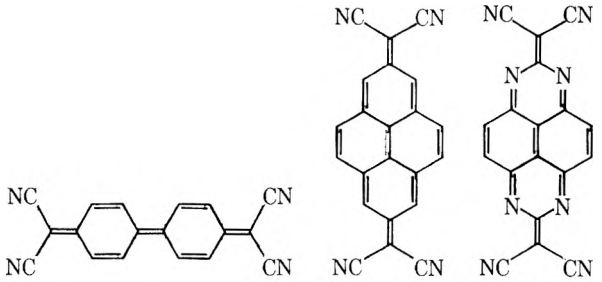
Tetracyanoquinoquinazolinoquinazoline†

Summary: The title compound was prepared as a dianionic salt whose physical properties and electrochemical behavior are reported.

Sir: Since the discovery of the unusual solid state transport properties of TTF,[1] several new donors based on the TTF skeleton have been prepared.[2-4] On the other hand, no new acceptors, except perhaps TNAP,[5] endowed with the crucial characteristic formation of stable mixed valence anionic arrays (i.e., partially filled bands) sui generis to TCNQ have appeared in the literature. For example, tetrafluoro TCNQ,[6] TCM,[7,8] TMCP,[9] and TCNDQ[10] do not appear to fulfill the above requirements.

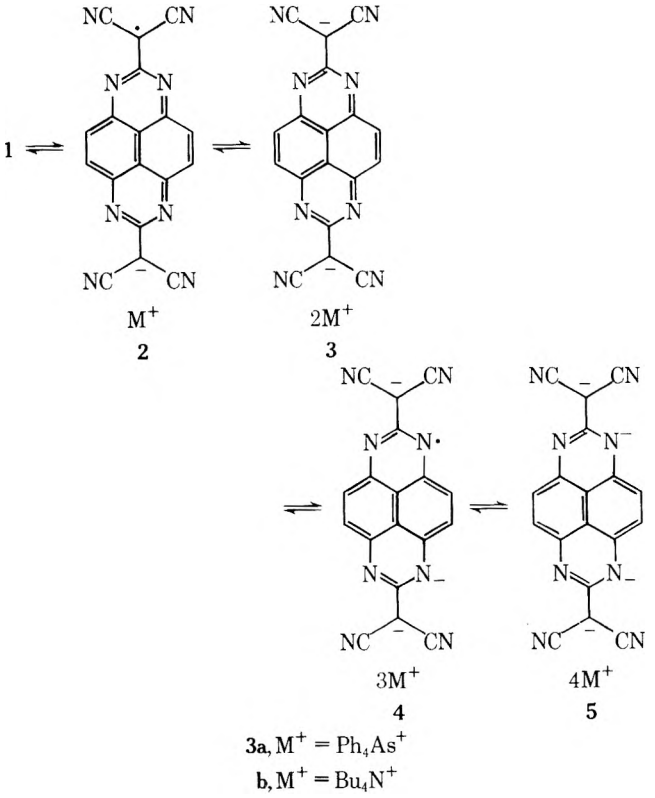
While TCNDQ tends to polymerize, a pyrene analogue (B) would be expected to be more stable because biphenyl interring hydrogen repulsions are eliminated.



A TCNDQ B TCQQ 1

Rather than attempting a synthesis of B, we decided to prepare 1 for the following reasons: (a) projected syntheses of 1 appeared more straightforward than those of B, and (b) substitution of N for C was expected to enhance the electron affinity of the acceptor and also increase the number of available oxidation states (cf. **1–5**). Thus, by increasing the valence, we expected to enhance the probability for formation of partially filled bands.

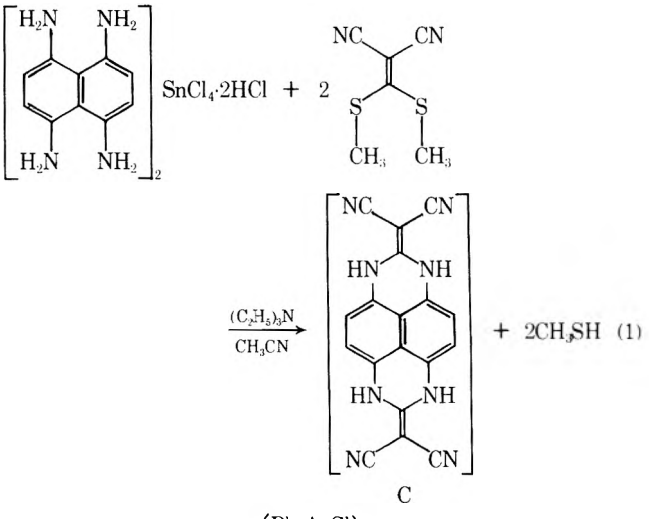
† A systematic name would be 2,7-bisdicyanoquinomethano-2,7,*H*,*H*-quinazolino[6,5,4-*def*]quinazoline (TCQQ).



2 M^+ **3** $2M^+$ **4** $3M^+$ **5** $4M^+$

3a, $M^+ = Ph_4As^+$
b, $M^+ = Bu_4N^+$

Here we report on the preparation of **3a,b** and some of its properties. The dianion was prepared by the sequence of reactions depicted below:[11]



Since attempts to purify the crude reaction mixture obtained from reaction 1 failed, it was treated with base in acetonitrile in the presence of either tetrabutylammonium or tetraphenylarsonium chloride. Even when both reactions (1 and 2) were carried out under strictly anaerobic conditions, **3a(b)** was the only characterizable product isolated. The physical properties of **3a** are given below: **3a** UV (CH_2Cl_2) 680 nm (ϵ 690), 640 (770), 368 (1×10^5), 350 (sh, 4.8×10^4), 323 (3.6×10^4), 310 (3.8×10^4), 297 (3×10^4), 272 (2×10^4), 265 (1.8×10^4), 259 (1.6×10^4). The last three bands were due to the tetraphenylarsonium cation. For **3a**, IR (KBr) ν, 2180, 2170 (d, s), 1550 (s), 1470 (m), 1430 (m), 1380 (s), 1320 (sh), 1300 (m), 1270 (sh), 1180 (w), 1160 (w), 1080 (sh), 1070 (m), 1000 (w), 970 (w), 840 (m), 750 (s), 690 cm^{-1} (s). For **3b**, NMR (CD_3CN) δ 7.8 (s, 4 H), 3.02 (br t, 16 H), 1.4 (br m), 0.9 (s), the

last three are due to Bu_4N^+ with the expected integration ratios for the two high-field lines. We expected the chemical shift of the aromatic protons to appear at higher field than pyrene because the molecule is doubly negatively charged; instead, 7.8 ppm is precisely the chemical shift of the low field set of hydrogens in pyrene.

After several abortive trials to obtain characterizable products from attempted oxidations of **3a** to **2** or **1**, we decided to examine the solution electrochemistry of **3**. Cyclic voltammetry of **3a** in acetonitrile (0.1 M *n*-butylammonium perchlorate as supporting electrolyte and platinum bead as working electrode) revealed a one-electron reversible reduction (with peak-to-peak separation of 60 mV at a scan rate of 50–500 mV s^{-1}) at −1.55 V vs. Ag/0.01 M $AgNO_3$. No oxidation wave was observed in the range from −0.88 to +1.8 V. However, electrolysis at voltages more negative than −0.6 V produced a species which exhibited two irreversible oxidation waves at +0.16 and +0.56 V.[15] The reversible reduction at −1.55 V could be assigned to the couple **3**–**4** on the basis of ESR experiments.

Electrolysis of **3a** in CH_3CN at −1.35 V vs. SCE in an ESR cavity generated a relatively stable radical trianion (**4**) (g = 2.0033, $t_{1/2}$ ca. 2 min., $a_H = a_N$ = 2.53 G) with a 13-line spectrum.[15] From the analysis of the normalized intensities we deduced that the radical had four equivalent hydrogens and four equivalent nitrogens (calcd, 262:232:160:84:32:8:1; found, 262:235:164:82:33:8:1). There is practically no coupling to the nitrile nitrogens.

It is interesting to note that the most stable species among **1**–**5** are **3** and **4** and not **2** or **1**. This, of course, does not mean that the radical anion derived from B will also be unstable.

Current studies on the solid state structure of **3a** and the metathesis products of it with radical cations will be reported in a separate publication.

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(15) Copies of the cyclic voltammogram and the ESR spectrum are available from the authors upon request.

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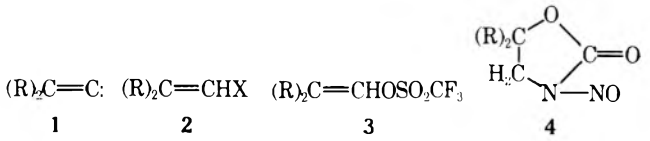
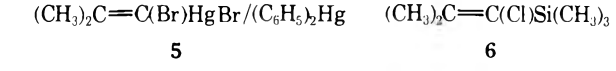
Alkylidene Carbene Generation from Tosylazoalkenes and Silylvinyl Triflates[1,2]

Summary: Thermal decomposition of tosylazoalkenes, $R_2C{=}CHN{=}NTs$, at 25 °C gave unsaturated carbene derived products in 25–40% yield; similarly fluoride ion initiated decomposition of silylvinyl triflates $R_2C{=}C(OTf)Si(CH_3)_3$ in cyclohexene or ethyl vinyl ether gave quantitative yields of carbene adducts in 1–2 h at −20 or 0 °C; these two methods represent the mildest known conditions for alkylidene carbene generation to date.

Sir: There has been considerable interest and work lately in alkylidene, **1**, and other unsaturated carbenes.[3] Such carbenes have primarily been generated by α elimination from primary vinyl halides,[4] **2**, or vinyl triflates,[5] **3**, and base-promoted decomposition of *N*-nitrosooxazolidones, **4**, or related compounds.[6] However, all of these techniques require strong bases such as RLi, *t*-BuOK or ROLi, preventing the possible interaction of **1** with base-sensitive substrates and thereby limiting the potential synthetic uses of these carbenes. Until recently, with the exception of two photochemical processes,[7,8] both in very low yield, and the nitrite deamination of certain unique vinyl amines,[9] there was no known technique for the generation of **1** in the absence of strong base analogous to the diverse nonbasic generation of saturated carbenes.[10] In early 1976 Seyferth and Dagani[11] reported the thermal generation of **1** from organomercurial **5** at 150 °C and Cunico and Han[12]

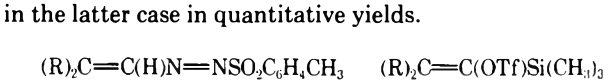


1 **2** **3** **4**



5 **6**

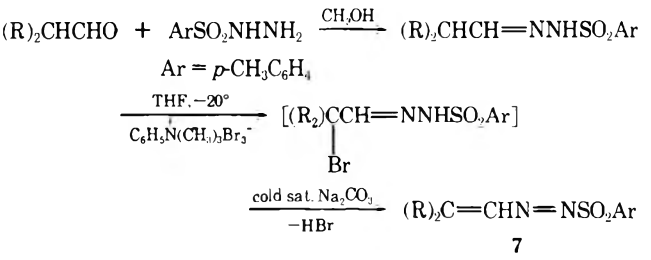
reported the formation of **1** via the fluoride promoted decomposition at 25 °C of α-chlorovinylsilane (**6**), thus providing the first useful generations of **1** under relatively mild and neutral conditions in good yields. Therefore, in this communication we wish to report two additional means of alkylidene carbene **1** generation under even milder conditions involving tosylazoethylenes **7** and silylvinyl triflates **8** as progenitors, in the latter case in quantitative yields.



7 **8**

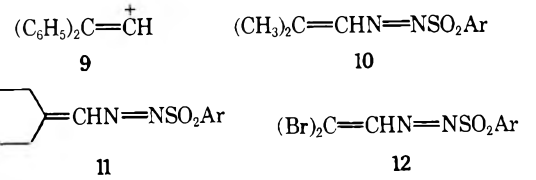
Tosylazoethylenes, **7**, are known[13] and can be readily prepared in good yields according to the procedure of Rosini and coworkers[13] as shown in Scheme I. In fact, Rosini and Cacchi[14]

Scheme I



have shown that the tosylazoethylene derived from diphenylacetaldehyde (**7**, R = C_6H_5) decomposes in chloroform at 25 °C to give >85% diphenylacetylene via either the carbene **1** (R = C_6H_5) or vinyl cation **9**. Since ion **9** would be a primary vinyl cation,[15] and hence energetically extremely unlikely,[15] their decomposition most likely involved carbene **1**. Such diaryl carbenes (**1**, R = C_6H_5) however, cannot be successfully trapped[3,5] intermolecularly and are known[3,5] to intramolecularly rearrange to the acetylene. Therefore we prepared

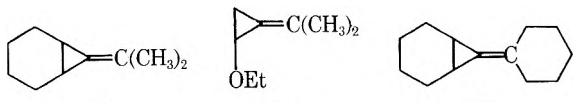
tosylazoalkenes[16] **10, 11,** and **12** and investigated their decomposition in various olefins as both solvents and possible carbene traps.



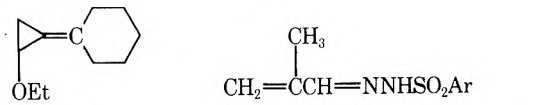
9 **10**

11 **12**

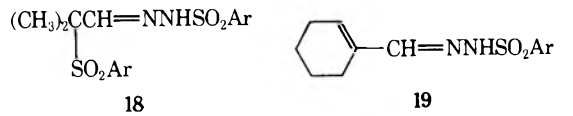
Indeed in both pure cyclohexene and pure ethyl vinyl ether compounds **10** and **11** readily decompose at 25 °C in 8–24 h or at 0 °C in 2–4 days giving, besides N_2 and some $CH_3C_6H_4SO_2H$, 25–40% adducts **13** and **14** and **15** and **16,** respectively, as well as two other products each, **17** and **18** and



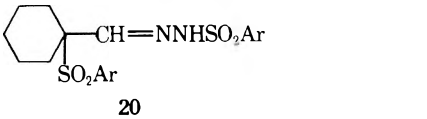
13 **14** **15**



16 **17**

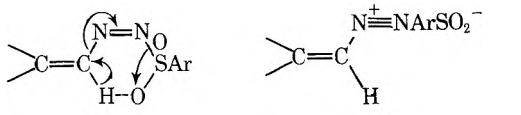


18 **19**



20

19 and **20** from **10** and **11,** respectively.[19] Adducts **13–16** are the products of unsaturated carbenes **1** or carbenoids,[20] and hence represent a simple, mild and presumably general method of thermal dialkyl unsaturated carbene, **1,** generation, albeit in only moderate yields. At the moment we do not know the exact mechanism for the formation of **1** from tosylazoethylenes, but there are at least two reasonable alternatives: one involving a concerted rearrangement via a six-membered cyclic transition state **21,** the other a possible diazonium ion pair,[14] **22.** Tosylhydrazones **17** and **19** arise via known[21] re-



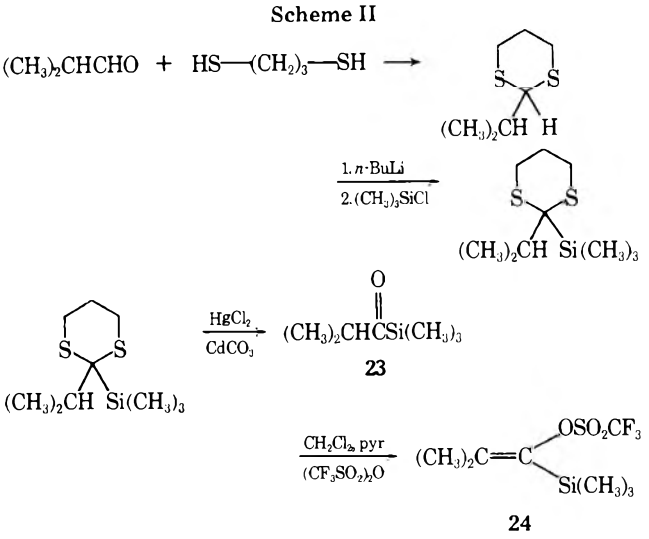
21 **22**

arrangement of tosylazoalkenes, as do compounds **18** and **20** by the known[22] addition of sulfinic acid to the unreacted[23] starting azoalkenes **10** and **11.** Interestingly, for reasons presently unknown, tosylazoalkene **12** does not give any carbene derived products[24] upon thermolysis in cyclohexene. We have also carried out preliminary experiments in the photolysis[25] of **10, 11,** and **12,** but to date no (<1%) carbene derived products have been observed.

Silylvinyl triflate **24**[18] can be prepared in reasonable yield from isobutyraldehyde via[26] the α-silyl ketone **23** that can be obtained by procedures similar to those of Brook[27] and Corey[28] shown in Scheme II.

Silylvinyl triflate **24** gives quantitative yields[19] of adducts **13** and **14** in cyclohexene and ethyl vinyl ether, respectively, in the presence of unencumbered fluoride ion. Reaction may be carried out with KF and crown ethers[29] or with anhydrous $R_4N^+F^-$[30] at −20 or 0 °C in 1–2 h or via KF and phase transfer

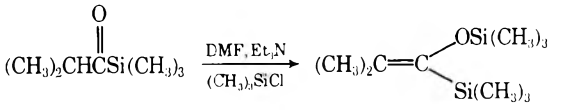
Scheme II



procedures[31] using Aliquat 336 as the transfer agent. These reactions are extremely clean and simple and probably represent the most convenient and mildest alkylidene carbene **1** generation to date.

The mechanism of the reaction is similar to that observed by Cunico and Han[12] in the case of precursor **6** and involves nucleophilic attack by F^- on the silicon[32] and displacement of the triflate leaving group. However, unlike the decomposition of **6** where significant amounts of $(CH_3)_2C{=}CHCl$ were observed,[12] we did not see any $(CH_3)_2C{=}CHOTf$, strongly suggesting a stepwise process in the decomposition of **6** and a concerted process in the decomposition of **24.** This hypothesis is in accord with the superior leaving ability of triflate compared to halides.[15]

Silyl ketone **23** may also be converted to silylsiloxyethylene **25**[18] which in turn decomposes to give carbene, **1,** derived products but at temperatures much too high to be useful.[33]



25

In summary, we have shown that tosylazoalkenes **7** as well as silylvinyl triflates **8** give carbene derived products under mild neutral conditions: in the case of **7** via thermolysis at room temperature in the absence of any base or nucleophile albeit in only moderate yields; in the case of **8** quantitatively at 0 °C in 1–2 h in the presence of F^-. The exact nature[20] of such thermally and nucleophilically generated alkylidene carbenes **1** or carbenoids as well as the potential synthetic uses of these techniques are under active investigation.

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(16) Tosylazoalkenes **11**[13] and **12**[17] are known compounds, whereas **10** is new.[18] It was prepared in 50% overall yield from isobutyraldehyde via Scheme I, mp 45–46 °C dec.
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(18) All new compounds have spectral properties consistent with their assigned structures.
(19) Adducts **13**–**16** were identified by means of GC as well as isolation and spectral comparison with authentic samples.[5] Compounds **17** and **19** were isolated and identified by spectra.[18] Compounds **18** and **20** were identified from the known[22] reaction of such tosylazoalkenes and by addition of $CH_3C_6H_4SO_2H$ to **10** and **11** and TLC comparison.
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(23) The yield of carbene derived adducts could be increased from about 25 to 40% by the use of Na_2CO_3 in the reaction mixture presumably by interaction with the liberated $CH_3C_6H_4SO_2H$ and interception of the addition of this acid to the unreacted tosylazoethylene.[22]
(24) Neither adduct nor BrC≡CBr were observed.
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(33) At 275 °C in a sealed tube containing cyclohexene in 24–48 h 25% adduct **13**, 50% 2-butyne, and 25% $(CH_3)_2C{=}CH[OSi(CH_3)_3]$ were observed. The 2-butyne and the adduct comprising 75% of the products are carbene derived, via deoxysilylation[34] of **25**.
(34) For other examples of deoxysilylation, see A. G. Brook, *Acc. Chem. Res.*, **7**, 77 (1974); F. P. Tsui, Y. H. Chang, T. M. Vogel, and G. Zon, *J. Org. Chem.*, **41**, 3381 (1976).

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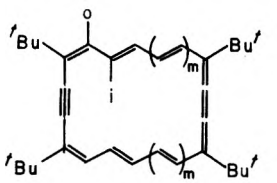
A Linear Relation between Nuclear Magnetic Resonance Chemical Shifts of Tetra-*tert*-butyldehydro[*n*]annulenes and Resonance Energies per π Electron

Summary: A linear correlation has been found between the Hückel resonance energies per π electron of $4N$ and $4N + 2$ systems and the differences between chemical shifts of the inner and outer protons in tetra-*tert*-butyldehydro[*n*]annulenes.

Sir: The question of the aromaticity of the annulenes has been of interest for several decades, and in recent years there has been considerable progress in the synthesis of these compounds. Sondheimer among others has prepared many of the parent systems as well as dehydroannulenes.[1] Vogel,[2] Boekelheide,[3] and Sondheimer[4] have also prepared successfully a number of bridged annulenes. In most cases the two criteria reported for the aromaticity of these annulenes were their observed NMR chemical shifts and stabilities. However, fair agreement has been reached that there is not necessarily any basis for a relationship between NMR chemical shifts and aromatic character or resonance stabilization.[5] On the other hand, in recent papers one of the present authors (M.N.) has determined that there is a decrease in the difference in chemical shifts of the inner and outer protons of both dehydro[$4N + 2$]- (I)[6] and -[$4N$]annulenes (II)[7] as the ring size is



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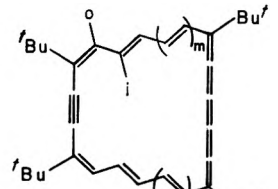

II

increased from 14 to 30 carbons. He suggested that this might be an indication of the decreasing aromaticity and antiaromaticity within this series in possible agreement with theoretical predictions.[8]

In order to test this hypothesis quantitatively we decided to examine these chemical shift differences in both the $4N$ and $4N + 2$ dehydroannulenes and to compare them with the calculated resonance energies per π electron (REPE) of Hess and Schaad.[8e] The calculated REPEs of the annulenes indicate there should be strong alternation between aromatic and antiaromatic character in the smaller annulenes with this alternation becoming less intense as the annulenes increase in size.[9] The two series of annulenes I and II are a particularly good set of compounds for making this comparison as they are all similar in structure and relatively planar. Furthermore, chemical shift data are available for a number of compounds in both series ($4N + 2$ and $4N$) which represent the [*n*]annulenes where *n* is 14,[10] 16,[11] 18,[12] 20,[13] 22,[14] 24,[7] 26,[15] and 30.[16]

Since the overall environment of a proton affects its chemical shift we chose to take the difference ($\tau_o - \tau_i$) as the difference between the outer proton o in I and II and the inner proton i on the adjacent carbon. In most cases the assignments of protons o and i had been made. However, in several compounds the inner and outer proton absorption bands were not well enough resolved to make individual assignments. In these cases the center of the inner or outer proton absorption bands was used. Where this was done the proton patterns were narrow and any error introduced by this would be quite small relative to $\tau_o - \tau_i$.

In Table I are listed the chemical shifts of the inner and outer protons o and i, their differences, and REPE of the corresponding annulenes. A plot of $\tau_o - \tau_i$ vs. REPE (Figure 1) shows a definite linear correlation between these two quantities. This is the first example of a correlation between NMR chemical shifts and calculated resonance energies and

Table I. Chemical Shifts, Their Differences, and REPE of Dehydro[*n*]annulenes

[*n*]	τ_o	τ_i	$\tau_o - \tau_i$	REPE
14	0.68	14.44	−13.76	0.0161
16	5.92	−7.17	13.09	−0.0111
18	0.62	13.42	−12.80	0.0118
20	5.48[a]	−3.78[a]	9.26	−0.0052
22	1.28	10.83[a]	−9.55	0.0096
24	5.00	−1.79[a]	6.79	−0.0020
26	2.07	8.05	−5.98	0.0084
30	2.50[a]	6.50[a]	−4.00	0.0076

[a] Center of band.

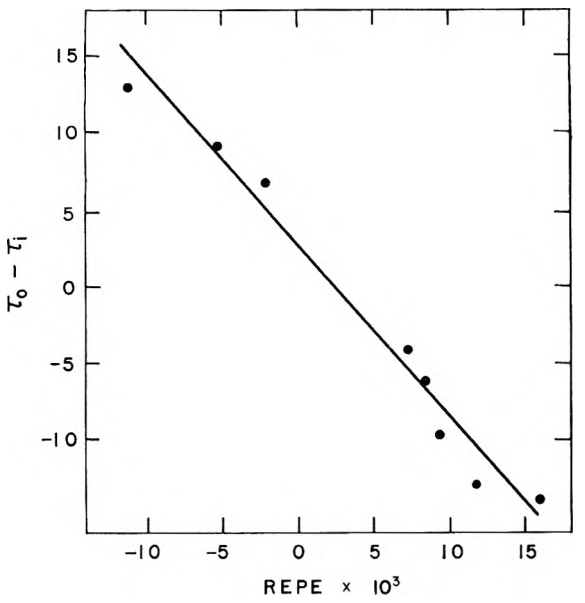

Figure 1. A plot of $\tau_o - \tau_i$ of dehydro[*n*]annulenes vs. REPE (β) of the annulenes.

suggests that, if one treats chemical shift data in this way, one can obtain some quantitative measure of the aromaticity of the annulenes. We have also compared $\tau_o - \tau_i$ with the graph theoretical resonance energies of Aihara[17] and Trinajstić[18] and found a similarly good linear correlation.

Finally we mention that this is now the second correlation that has been found between an experimental property of the annulenes and REPE. We have recently reported[19] a linear correlation between the log of the rate of annulene formation by a Diels–Alder reaction[20] and REPE.

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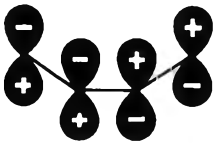

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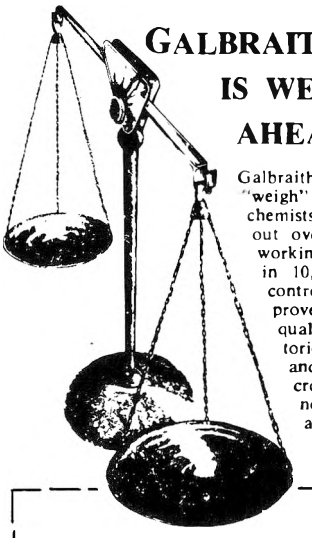

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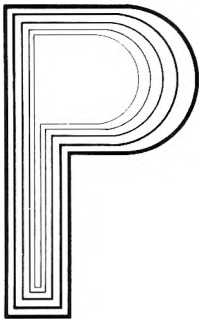

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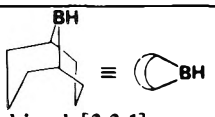

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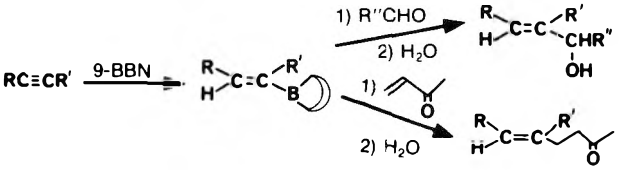
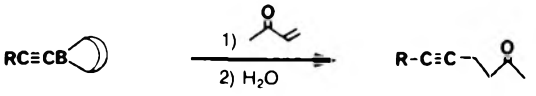
9-BBN is a stereo- and regioselective hydroboration reagent which quantitatively converts alkenes to the corresponding *B*-alkyl-9-BBN derivatives.[1] Many reactions of major significance to synthetic organic chemists have been discovered for these *B*-alkyl-9-BBN compounds.[2] Also, **9-BBN** has recently been shown to be a useful selective reducing agent.[3]

The hydroboration characteristics of **9-BBN** are still under active investigation. For example, the results of a detailed relative rate study of alkene hydroboration utilizing **9-BBN** in THF are now available,[4] and the *B*-alkyl-9-BBN compounds derived from internal alkenes were found to be remarkably resistant to thermal isomerization.[5]

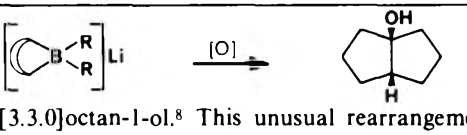
An area of continuing interest is the development of new reactions for **9-BBN** derivatives. Thus, although *B*-alkenyl-9-BBN derivatives add across the carbonyl group of simple aldehydes, they undergo conjugate addition to methyl vinyl ketone.[6] In both cases, stereochemistry is retained.



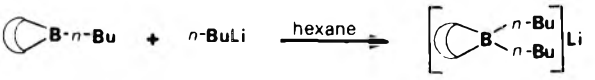
B-Alkynyl-9-BBN derivatives, which are readily prepared from *B*-methoxy-9-BBN and alkynyllithiums, also undergo conjugate addition to methyl vinyl ketone.[7]



Recent investigations of lithium dialkyl-9-BBN "ate" complexes have uncovered some particularly fascinating chemistry. For example, direct oxidation gives *cis*-



bicyclo[3.3.0]octan-1-ol.[8] This unusual rearrangement involves a hydride transfer of the bridgehead hydrogen to an organic substrate.[8] Thus, these "ate" complexes represent an unusual type of reducing agent — *a C-H hydride reducing agent!* The reducing reagent is prepared by combining equimolar amounts of ***B*-*n*-butyl-9-BBN** and ***n*-butyllithium**



in hexane. The "ate" complex precipitates, and the slurry can be used directly. This "ate" complex reducing agent selectively reduces tertiary alkyl, benzyl, and allyl halides to afford the corresponding hydrocarbons in excellent yield without concomitant attack on secondary, primary, or aryl derivatives.[9] Also, selective reductions of carbonyl groups and epoxides are possible with the lithium di-*n*-butyl-9-BBN "ate" complex.[9]

To simplify the preparation of this "ate" complex reducing agent, Aldrich now offers ***B*-*n*-butyl-9-BBN** as a solution in hexane. **9-BBN** is also available as a solution in hexane.

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