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VOLUME 42, NUMBER 6 MARCH 18, 1977

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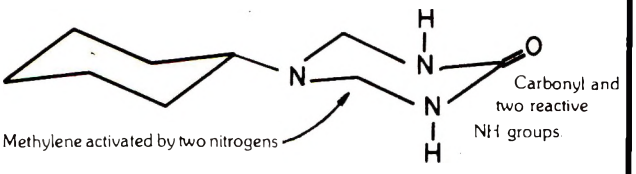

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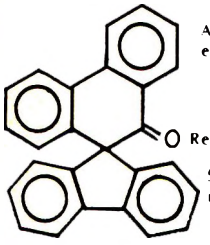

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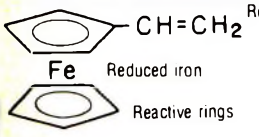

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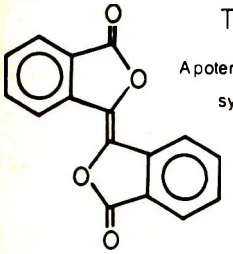

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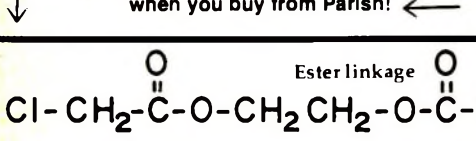

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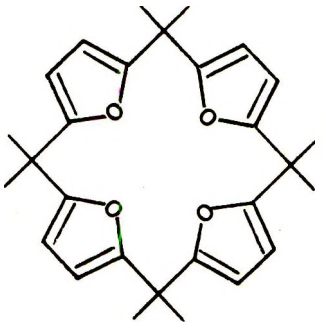

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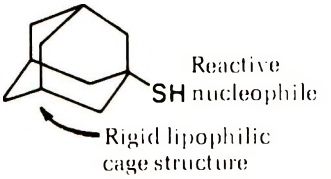

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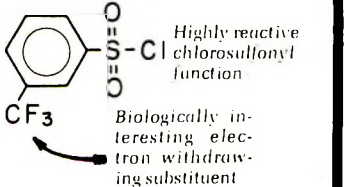

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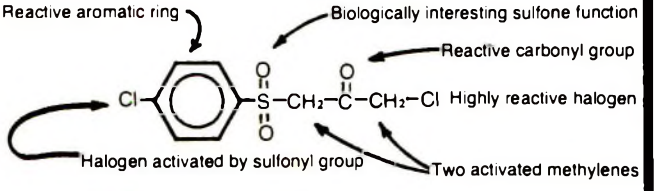

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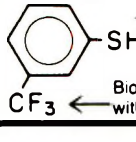

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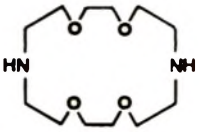

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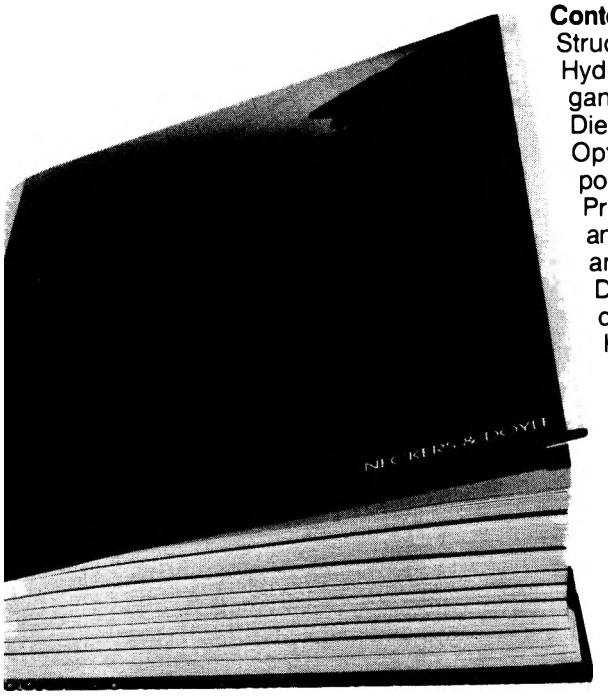

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THE JOURNAL OF Organic Chemistry

VOLUME 42, NUMBER 6

MARCH 18, 1977

Synthesis and Reactions of Tetracyclo[4.2.0.0^{2,4}.0^{3,5}]octanes

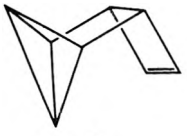
Leverett R. Smith,[1a] George E. Gream,[1b] and Jerrold Meinwald*[1a]

Spencer T. Olin Laboratory, Department of Chemistry, Cornell University, Ithaca, New York 14853, and the Department of Organic Chemistry, University of Adelaide, Adelaide, Australia

Received August 16, 1976

Tetracyclo[4.2.0.0^{2,4}.0^{3,5}]oct-7-ene (I) was prepared in four steps, starting with benzvalene. The adduct (V), which forms readily by addition of dichloroketene to benzvalene, was dehalogenated with triphenyltin hydride, and the resulting ketone (VII) was converted into I by the reaction of its *p*-toluenesulfonylhydrazone (X) with lithium 2,2,6,6-tetramethylpiperidide. Isomerization of I to cyclooctatetraene occurs thermally, photochemically, and in a silver ion catalyzed reaction. Reaction of I with *N*-phenyltriazolinedione yields the hexacyclic adduct (XII); reaction of I with hexafluoro-2-butyne yields a mixture of products, two of which were found to interconvert via a Cope rearrangement under the reaction conditions used. The preparation and pyrolysis of the parent tetracyclo[4.2.0.0^{2,4}.0^{3,5}]octane (XIX) are described. Reaction of V with nitrogen nucleophiles gives 3,4-disubstituted tricyclo[3.1.0.0^{2,6}]hexanes by a very facile ring cleavage. ^{13}C NMR spectra are tabulated for most of the compounds encountered in this study.

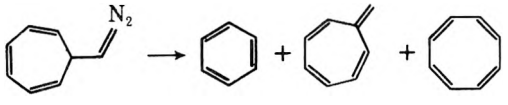
Our incursion into the tetracyclo[4.2.0.0^{2,4}.0^{3,5}]octane system, and particularly the synthesis of tetracyclo[4.2.0.0^{2,4}.0^{3,5}]oct-7-ene (I),[2] was prompted by a desire to use these compounds as precursors for tricyclo[5.1.0.0^{2,8}]octa-3,5-diene ("octavalene", II). Earlier unsuccessful approaches



I

II

to the synthesis of II involved carbenoid species generated from different ring systems. Zimmerman and Sousa, for example,[3] subjected cycloheptatrienyldiazomethane (III) to thermal and photochemical reactions which yielded a variety of products:

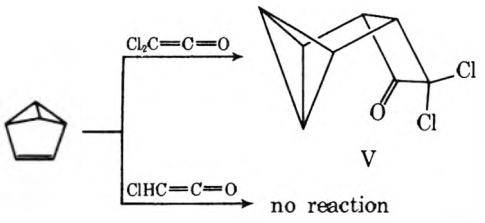


III

In these laboratories, Meinwald and van Vuuren treated 8,8-dibromobicyclo[5.1.0]octa-2,4-diene (IV) with methyllithium and obtained a labile mixture of dihydropentalenes; use of the tricarbonyliron complex of IV gave an unexpected insertion product; a more recent study has been carried out by Baird and Reese.[4] While II has not yet been prepared, the chemistry of I and its precursors has been sufficiently explored to justify presentation in its own right.

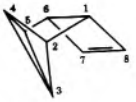
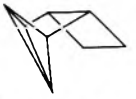
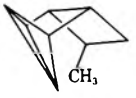
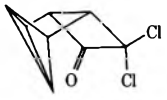
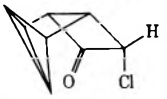
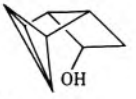
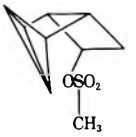
The "ready-made" bicyclobutane moiety in benzvalene, which is readily prepared by the method of Katz and coworkers,[5] made it an attractive starting point for our work. In initial attempts to exploit benzvalene by additions to the double bond, reactions with ozone, with ethyl diazoacetate, and (photochemically) with maleic anhydride were explored. While reactions related to the first two of these have been carried out successfully by Christl and Brüntrup,[6] in our particular cases conveniently usable adducts were not obtained; nor was the reaction with maleic anhydride of any use. The reagent which did give useful results was dichloroketene.

The [2 + 2] cycloadditions of ketenes to olefins have received much attention, most extensively by Brady and coworkers, as well as by Ghosez and others.[7] The olefin most commonly used for these investigations has been cyclopentadiene, usually used in excess, to give yields ranging from very good to very poor based on a variety of ketenes generated in situ. Dichloroketene's combination of high reactivity for such cycloadditions and its relative stability made it the most attractive choice for the reaction with benzvalene. Yields in this step proved gratifyingly high: after correcting for unconsumed (and recoverable, if aqueous workup is avoided) benzvalene, adduct V could be isolated in 86% yield. Even without this



correction, 70% yields of V are obtained routinely if one is careful to use scrupulously pure starting materials. While one might expect that other ketenes might add comparably well to the highly reactive double bond of benzvalene, attempts to

Table I. ^{13}C NMR Data on Compounds in the Tetracyclo[4.2.0.0.^{2,4}.0^{3,5}]octane Series[a]

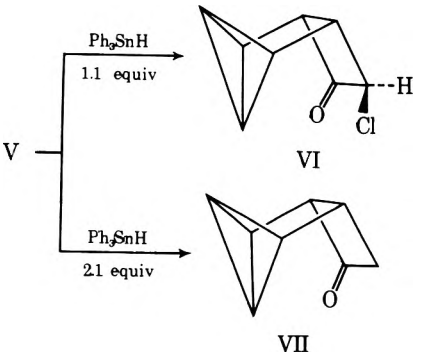
Compd	C-1	C-2	C-3 (syn)	C-4 (anti)	C-5	C-6	C-7	C-8	Other
	47.7	37.2	−0.7	16.2			139.4		
	37.1 (d, 145)	39.8 (d, 170)	−0.6 (d, 215)	7.0 (d, 210)			21.4 (tr, 135)		
	29.6*	39.5	−0.1	7.4	34.4	46.4*	38.9*	29.7*	22.1 (methyl)
	53.6 (d, 155)	36.9 (d, 170)	0.4 (d, 220)	9.8 (d, 215)	33.9 (d, 170)	63.7 (d, 150)	194.9 (s)	84.0 (s)	
	39.7 (d, 150)	35.1 (d, 170)	−0.4 (d, 215)	8.6 (d, 215)	33.7 (d, 170)	59.0 (d, 150)	204.4 (s)	64.0 (d, 145)	
	29.2 (d, 150)	39.1 (d, 165)	−2.0 (d, 215)	10.5 (d, 215)	33.4 (d, 170)	66.1 (d, 145)	209.1 (s)	45.8 (tr, 135)	
	30.6 (d, 140)	40.4 (d, 170)	−0.5 (d, 215)	4.8 (d, 210)	32.7 (d, 170)	46.0 (d, 140)	63.8 (d, 150)	34.4 (tr, 135)	
	31.4 (d, 145)	39.9 (d, 165)	0.0 (d, 210)	5.4 (d, 210)	33.4 (d, 170)	45.0 (d, 140)	71.7 (d, 150)	31.2 (tr, 135)	36.7 (q, 140, methyl)

[a] All samples were run in $CDCl_3$ on a Bruker HX-90 in the FT mode, both with and (sample size permitting) without broad-band proton decoupling. Assignments were based on shift, multiplicity, J_{C-H} (noted under each value in hertz, in parentheses), and internal consistency, and are reported in δ (Me_4Si) taking the center of the $CDCl_3$ triplet as δ 76.9. Values for J_{C-H} are generally ±5 Hz. Asterisks indicate uncertainty in assignments.

generate an adduct by addition of monochloroketene to benzvalene failed dismally.

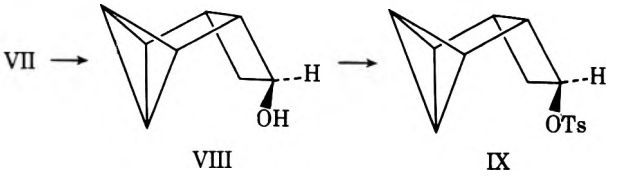
It should be mentioned that some of the "unexpected" additions that benzvalene has been shown to undergo[8] made the course of this ketene reaction less than entirely certain. However, the carbonyl stretching frequencies in V and the ketones derived from it gave convincing initial evidence[7,9] that the cycloaddition had gone as desired. Later, ^{13}C NMR measurements further verified these structures—characteristic in this regard are particularly the pair of upfield signals associated with the bicyclobutane bridge, as well as the multiplicities and coupling constants which identify the other atoms in the tetracyclic framework. In these assignments, references by Christl,[10] Grover et al.,[11] and Levy and Nelson[12] were helpful. A summary of data for the tetracyclic derivatives appears in Table I.

With V in hand, a mild method for reductive dehalogenation was desired. Possible methods included use of a hydrogen radical donor, a hydride donor, or dissolving metal reduction. Of these, the first seemed by far the gentlest, and in retrospect is probably the only method that could have worked while keeping the ring structure intact, as a later section of this discussion will illustrate. While dehalogenation by tributyltin hydride is probably more commonly carried out, we chose to use triphenyltin hydride.[7a,b,13] The reasons for this choice were its higher reactivity, allowing for milder reaction conditions, and its much higher molecular weight, facilitating distillative purification of the product. The desired reduction products were in fact obtained readily. The monochloroketone VI could be obtained using 1 equiv of reducing agent in up to 87% yield, while the parent ketone VII could be prepared in ca. 95% yield when 2 equiv of reductant was used. The endo stereochemistry of VI, expected from the reduction mechanism, is supported

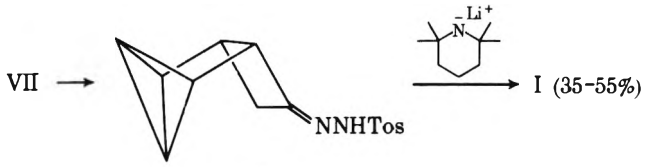


by the NMR pattern of the downfield α hydrogen, which appears as a doublet of doublets (J = 8 and 3 Hz), exhibiting both vicinal and transannular coupling.[7f]

A method for converting VII to I was now sought. In initial attempts, sodium borohydride reduction of VII to the endo alcohol VIII, followed by conversion of VIII to its tosylate (IX)



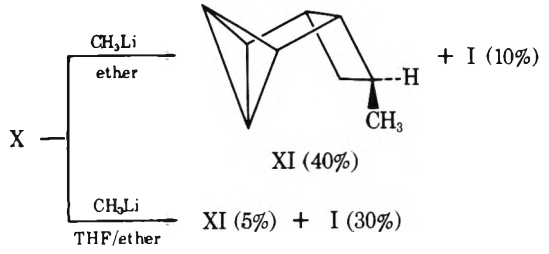
and subsequent treatment with base, failed to yield I even under increasingly vigorous conditions.[14] A milder and more generally effective method for olefin formation uses the Bamford–Stevens reaction of tosylhydrazones with strong bases (usually alkyllithium reagents).[15] This approach appeared especially appropriate because of a recently reported gentle method for preparing tosylhydrazones.[16] There was some difficulty at first in obtaining a crystalline tosylhydrazone (X) from VII. However, through use of very concentrated



X

solutions, crystallization was usually observed within a few hours or overnight at room temperature. (It is convenient to carry out this reaction in small vials to allow centrifugal removal of the mother liquor; yields as high as 85% have been obtained. It is important to note that use of VII which was not of high purity, or use of more than a slight excess of tosylhydrazide, gave mixtures which would not crystallize; these mixtures usually performed poorly in the subsequent elimination step.)

The catalog of bases tried for the elimination need not be reiterated here,[2] but can be summarized by noting that the desired elimination was unexpectedly difficult to achieve. An initial attempt using methyllithium in ether gave a product whose mass spectrum (and eventual more thorough characterization) showed it to be the methylation product (XI).[17]



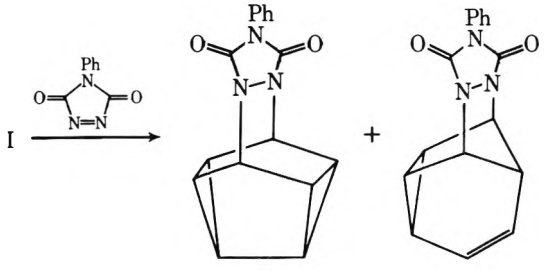
(Mechanistic considerations suggest that XI is the endo derivative. ^{1}H and ^{13}C NMR indicate that only one isomer is present.) Reaction of X with lithium tetramethylpiperidide in THF/ether gave yields of I as high as 55%, however. Use of lithium diisopropylamide as base gave ca. 20% yield; it was found later that methyllithium in THF/ether (where X is completely dissolved rather than reacting as a slurry) gives about 30% yield of I as well.

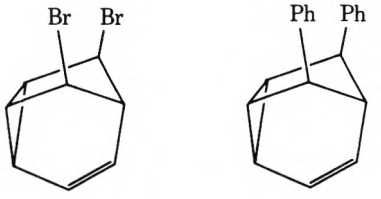
The properties of I are unexceptional. In addition to a very simple ^{1}H NMR spectrum (in which the only pronounced coupling appears in the "AB" pattern of the bicyclobutane bridge protons), a ^{13}C NMR spectrum which shows the expected five signals in places appropriate to the structure, and not very informative infrared and mass spectra,[2] the Raman spectrum of I was taken. This shows a strong double-bond stretching frequency at 1550 ± 2 cm^{-1}, which agrees with expectations for a somewhat strained cyclobutene ring.[18]

The chemistry of I was limited to some extent by its high stability, a stability doubtless due to the "forbiddenness" of all the thermal paths by which it might otherwise shed most of the roughly 100 kcal/mol of strain energy that it has been estimated to carry.[19] Vapor and solution phase pyrolyses were carried out both with and without added trapping reagents. Of these, the latter two yielded the more interesting, if originally unlooked for, results.

Some examples of vapor-phase cyclobutene pyrolyses which provided good precedents were carried out several years ago by Dauben and Cargill, as well as by Chapman et al.[20] These used very brief contact times in an evacuated heated tube with a trap at its exit. One might imagine a variety of C_8H_8 isomers forming from I under such conditions; in fact, the only product found, in a very clean conversion which did not occur much below 250 °C and which was not complete until the tube approached 500 °C, was cyclooctatetraene. Given the severity of the conditions used, it is not surprising that possible intermediates such as the presumably unstable II were not observed here. In solution, similar results were obtained. At 140 °C in chloronaphthalene, conversion to cyclooctatetraene and traces of another C_8H_8 isomer proceeded with a half-life of about a day. Since I underwent little or no isomerization in benzene at 140 °C even after 2 days, it is probable that something in the chloronaphthalene catalyzed the isomerization. This still seemed a reasonable choice of conditions for the first solution trapping experiment, however, since the dienophile we wished to use, 4-phenyl-1,2,4-triazoline-3,5-dione,[21] is not stable above 140 °C. Other dienophiles considered included maleic anhydride (rejected because of its relatively low reactivity) and tetracyanoethylene (not used because of its low solubility and the low solubility of its adducts).

Reaction of I at 140 °C in the presence of the triazolinedione gave a major product (44%) whose identity was deduced on spectral grounds to be 4-phenyl-2,4,6-triazahexacyclo[7.4.0.0^{2,6}.0^{8,10}.0^{7,12}.0^{11,13}]trideca-3,5-dione (XII), and confirmed by comparison with an authentic sample.[22] Traces of two other 1:1 adducts were found. One of these was identified as 4-phenyl-2,4,6-triazapentacyclo[7.4.0.0^{2,6}.0^{8,10}.0^{7,13}]tridec-11-ene-3,5-dione (XIII) by an NMR shift reagent experiment. This was confirmed by comparison of XIII's NMR spectrum with published NMR descriptions of the analogous systems XIV and XV.[23] The other trace adduct was

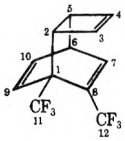
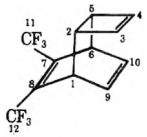
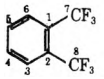




not identified, but by inspection of the rather low quality NMR spectrum obtained, the two cyclooctatetraene adducts of the triazolinedione could definitely be excluded.

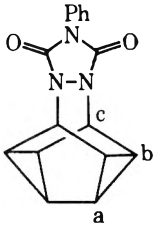
The striking rearrangement required by the formation of XII raises questions about what might have happened "in transit". One might imagine various possibilities, including trapping of a semibullvalene intermediate by a homo-Diels–Alder reaction,[24] polar attack at the double bond, or polar attack at the bicyclobutane moiety. In an attempt to gain some insight into this process, the triazolinedione addition was repeated using I that had been labeled with deuterium in the 3 and 4 positions by treatment with butyllithium followed by quenching with deuterium oxide.[8a,25] The product was then analyzed by ^{1}H NMR to determine the deuterium position.

Table II. ^{13}C NMR on Compounds XVIII, XVII, and XVI[a]

Compd	Shift, δ	Mult	J_{C-H}, Hz	Assignment
	37.5	d	135	2,5,6[b]
	43.2	d	140	
	43.6	d	140	
	120.9	q	J_{C-F} = 270	11,12
	124.9	q	J_{C-F} = 275	
	129.2	d	175	3,4,9,10[c]
	134.1	d	175	
	137.5	d	175	
	138.4	d	170	7
	41.8	d	140	1,2,5,6
	43.4	d	145	
	121	q	J_{C-F} = 265	11,12
	129.4	d	165	3,4
	138.8	d	170	9,10[d]
	122	(J_{C-F} = 270)		7,8[e]
	127			5,4
	131			3,6

[a] All samples were run in $CDCl_3$, using the solvent triplet at δ 76.9 as internal reference. [b] The signals at 43.2 and 43.6 merged in the coupled spectrum. [c] From its intensity, the peak at δ 137.5 contains the two isochronous signals. Carbons 1 and 8 were not visible. [d] Carbons 7 and 8 could not be found with certainty. [e] Carbons 7 and 8 were visible as the central pair of a presumed quartet. Carbons 1 and 2 could not be found with certainty.

The "a" and "b" sets of protons have isochronous shifts, but can be separated by addition of "Resolve-Al EuFOD" (Al-



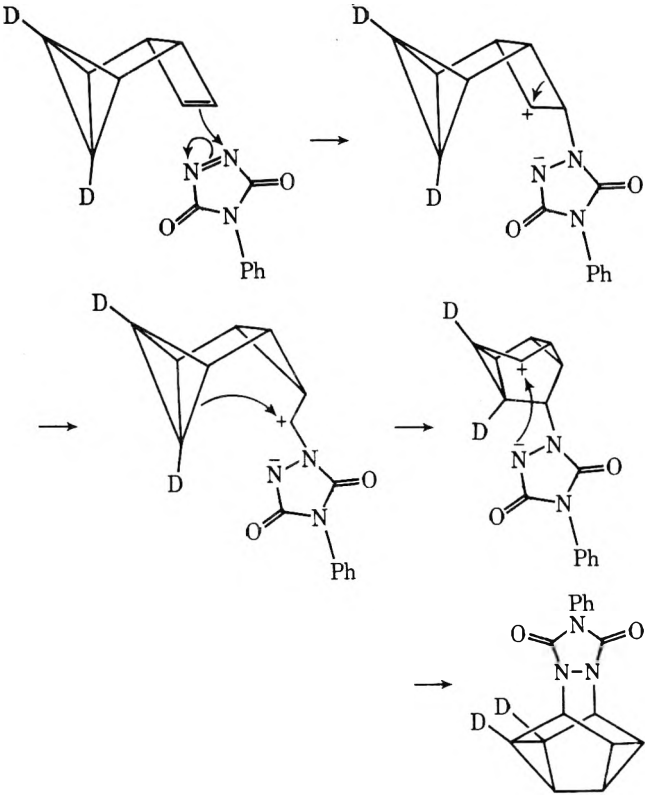
drich) shift reagent. Within the few percent uncertainty of repeated integrations, using both undeuterated and deuterated XII, all the deuterium was found to be at the "b" positions. Other (but ultimately superfluous) evidence for the deuterium location came from examining the splitting pattern of the "c" protons (90 MHz): undeuterated material showed a pentuplet, deuterated material a triplet (J = 3 Hz for each).

This result is compatible with the route shown in Scheme I, involving attack at the double bond, and appears to exclude the other possibilities mentioned above. The sequence of intermediates, cyclobutyl cation/cyclopropylcarbinyl cation/doubly cyclopropylcarbinyl cation/closure also seems plausibly "downhill" energetically. Inspection of models shows that the second bond migration could be facile because of the compact structure of the molecule; initial attack on the bicyclobutane moiety should be unfavorable in any case, since endo attack is thought to be the preferred mode.[26]

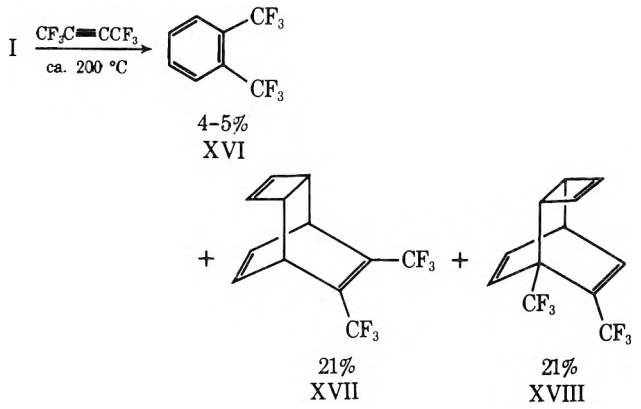
The suggested trapping of a semibullvalene intermediate was to some degree a "straw man", because semibullvalene was never isolated as a pyrolysis product. However, this does raise the queston of whether this might not still be a genuine trapping experiment rather than a simple attack on I by the triazolinedione. Since it was later found that the same reaction occurs readily in benzene at room temperature, where I is indefinitely stable, the former is also excluded. Adduct XIII is formed in about 5% yield in the room temperature reaction. Although no scheme will be proposed for its formation, it may be noted in passing that it is at least formally related to XII by a cyclopropylcarbinyl–homoallyl rearrangement.

The vapor-phase pyrolysis and trapping attempt was carried out using hexafluoro-2-butyne as dienophile; this re-

Scheme I



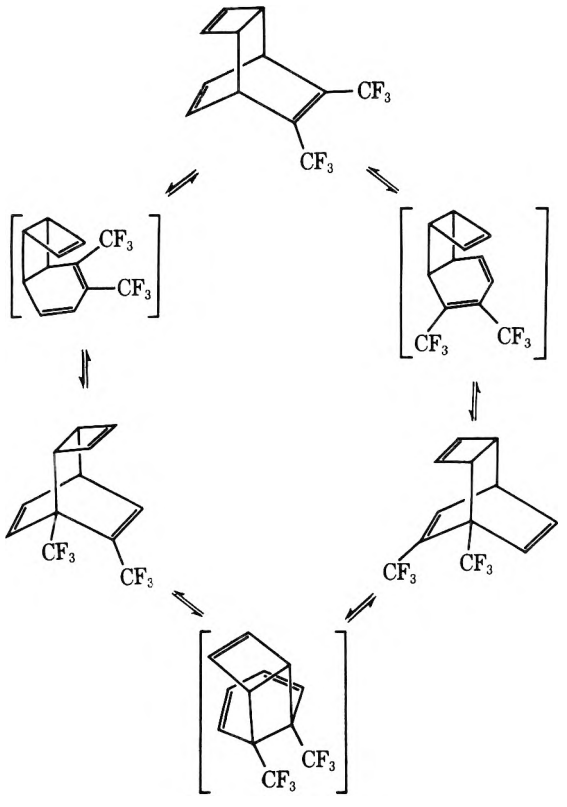
agent's thermal stability, high reactivity, volatility, and general reluctance to engage in polar or radical reactions[27] all seemed desirable. Attempted reaction at 175 °C gave very little conversion even after 7 h; however, reaction at 190–200 °C for 24 h consumed all the starting I and resulted in a mixture of three products isolable by GC, as summarized below. Of these, compound XVII was readily identifiable by its NMR spectrum.[28] The structure of XVI was strongly suggested by its mass spectrum and by its relatively short GC retention time. The identity of compound XVIII was less readily apparent. ^1H NMR spectra indicated a low symmetry structure wth five olefinic hydrogens, two of which were strongly (7 Hz) coupled to a one-proton multiplet upfield. Its ^{19}F NMR spectrum showed two quartets (J = 10 Hz), indicating the



presence of vicinal trifluoromethyl groups; both EI and CI mass spectra were strikingly similar to those of XVII. The UV spectra of XVII and XVIII were also similar. In preparing an authentic sample of XVII (from the addition of hexafluoro-2-butyne to cyclooctatetrane in a sealed tube at 180 °C), it was found that the sample contained trace impurities at the GC retention times of XVI and XVIII; increased heating (190–200 °C) produced both these products in isolable amounts. ^{1}H NMR spectroscopy now confirmed the structure of XVI, and a ^{13}C NMR spectrum that of XVIII. Carbon-13 data for all three compounds appears in Table II.

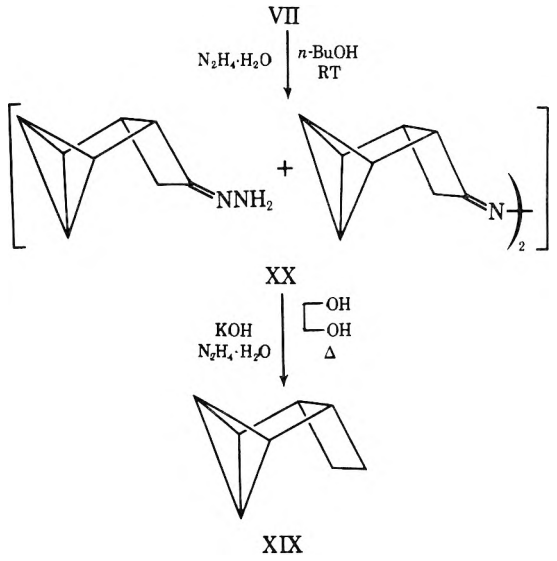
While both XVII and XVIII are stable below about 180 °C, it was found that they do equilibrate to the same mixture when heated to around 200 °C overnight. A search of the literature showed that of the many pyrolytic studies of tricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene derivatives that have been undertaken, most were carried out under very severe (300–400 °C) conditions[29] and yielded benzene, naphthalene, and/or dihydronaphthalene derivatives, and sometimes butadiene as well. A more recent study by Masamune and co-workers,[30] however, showed an analogous rearrangement, under similar conditions, of a dideuterio derivative of the parent tricyclodecatriene ("Nenitzescu's hydrocarbon"). Evidently, the equilibration of XVII and XVIII occurs via the cycle of Cope rearrangements shown in Scheme II.

Scheme II



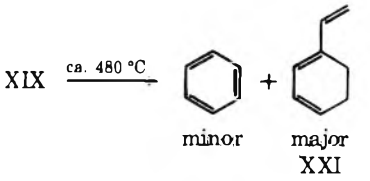
The stereochemistry shown for XVIII was assigned on assumption of the above scheme. Structures of the bracketed type are known to be unstable and to undergo rapid Cope rearrangement on gentle heating,[31] so it is not remarkable that they were not found in the mixture. On a purely statistical basis, one would expect XVII and XVIII to occur in a 1:2 mixture at equilibrium; in actuality, the ratio is about 1:6. This represents such a small energy difference that rationalization of its origin would be idle speculation.

It seems appropriate at this point to digress to the pyrolytic behavior of the parent tetracyclo[4.2.0.0^{2,4}.0^{3,5}]octane, XIX.



This compound was prepared by Wolff–Kishner reduction of the hydrazone and azine mixture (XX) obtained from VII, under conditions allowing XIX to distill into a trap as it formed. The conditions used were not entirely orthodox,[32] but the yield obtained (61% after preparative GC) was nonetheless acceptable.

Vapor-phase pyrolysis of XIX was carried out in a manner analogous to that used with I. At ca. 480 °C, XIX gave clean and complete conversion to two products; the minor one was benzene. The major one, on the basis of microhydrogenation and microozonolysis, appeared to be 1-vinylcyclohexadiene (XXI); this was confirmed by comparing its spectral proper-



ties with published NMR and IR data.[33a] Brief pyrolysis at a somewhat lower temperature (ca. 430 °C) gave a complex mixture of many products in roughly equal amounts, which were separable by preparative GC. The structures of XXII and XXIII were assigned by comparison of their NMR and IR spectra to published data;[33] that of XXIV was confirmed by its known IR spectrum and by its hydrogenation

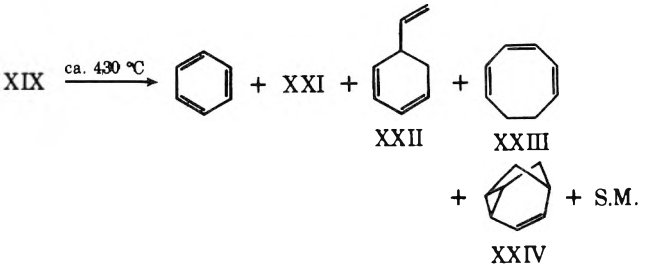
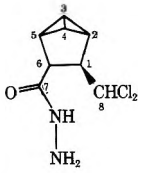
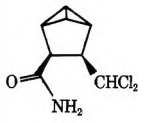
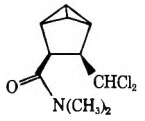


Table III. ^{13}C NMR Data on Compounds in the Tricyclo[3.1.0.0^{2,6}]hexane Series[a]

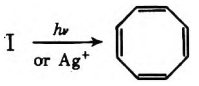
Compd	C-1	(C-2 and C-5)[b]	C-3 (syn)	C-4 (anti)	C-6	C-7	C-8[c]	Other	Solvent[d]
	46.1 (d, 145)	37.6 (d, 170)	38.3 (d, 180)	2.3 (d, 220)	4.0 (d, 220)	57.2 (d, 140)	171.0 (s)	75.4 (d, 180)		Me_2SO-d_6
	47.2	37.3	38.7[e]	2.1	3.8	57.1	173.8	73.2		Me_2SO-d_6
	42.4 (d, 130)	36.9 (d, 160)	37.6 (d, 160)	1.6 (d, 217)	3.5 (d, 214)	56.6 (d, 136)	171.4 (s)	74.0 (d, 177)	34.5, 36.4[f] (*N*-methyl)	$CDCl_3$

[a] Nonstandard numbering used to facilitate comparisons with Table I. [b] Not individually assignable. [c] Cf. ref 40. [d] Center of Me_2SO-d_6 multiplet taken as δ 39.6 relative to Me_4Si. [e] Superimposed on a peak of the solvent multiplet, but recognizable by the resulting intensity enhancement. [f] Assignment of coupling constants to the *N*-methyl groups is not definite owing to the complex appearance of this part of the coupled spectrum, but seems not inconsistent with quartets with J_{C-H} of ca. 135 Hz.

to bicyclo[3.2.1]octane.[34] In hindsight, this pyrolysis yielded few surprises. It is interesting that the reaction goes so cleanly at the higher temperature, but it has been known for several years that any of the compounds XXI, XXII, XXIII, or XXIV equilibrate above 200 °C to mixtures containing all four.[33,34] The complexity of this situation accordingly renders moot any specific discussion of how XIX comes unglued on heating.

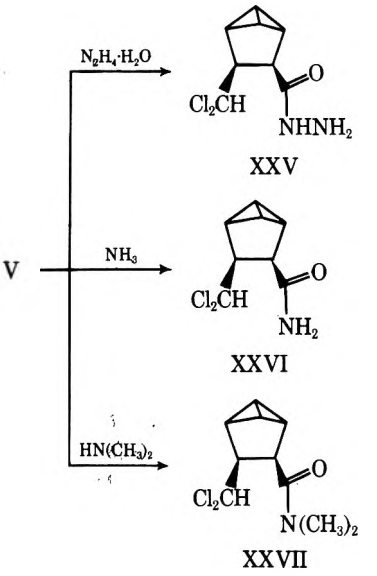
The photochemistry of I can be summarized briefly. Some sensitized irradiations through Pyrex failed to generate useful results; irradiation through quartz produced cyclooctatetraene. While photochemical conversion of I to II is an allowed process, so is II's conversion to cyclooctatetraene. The difficulty in detecting II, even if it were an intermediate in this photolysis, is therefore apparent. An attempt at trapping II by irradiation through quartz in the presence of maleic anhydride yielded only artifacts from the anhydride.

The facile reactions of small-ring compounds with transition-metal catalysts are extensively documented.[35] It seemed certain, for example, that silver ion would readily "unzip" I to form cyclooctatetraene. In fact, such treatment did result in such conversion; yields were not very high, but no other volatile products were observed even after treatment with aqueous ammonia or sodium chloride. A few other similar



reactions of I were also examined. Cuprous chloride in dimethyl sulfide/hexane left I unaffected even after 3 days at room temperature. Benzylideneacetoneiron tricarbonyl,[36] which has been used as a trapping reagent for labile dienes,[37] failed to react with I in hexane at room temperature. In benzene at 65 °C overnight, it completely destroyed the starting olefin, but no volatile products were found in solution or were liberated by oxidation of the residue with ceric ammonium nitrate. μ-Dichlorotetraethylenedirhodium(I)[38] reacted rapidly in benzene at room temperature, again to consume I without the generation of other volatile material. The use of transition metals appeared increasingly less interesting and was terminated at this point.

Finally, some attempts to study further reactions of the dichloro ketone (V) led us to a brief examination of active metal reduction and Wolff–Kishner reduction conditions. Reaction of V with hydrazine hydrate in butanol[39] or, more cleanly, in glyme gave a high yield of crystalline product whose elemental analysis, CI mass spectrum, and ^{13}C NMR spectrum (Table III)[10,40] conclusively showed it to be the ring-opened hydrazide XXV. Reactions of V with ammonia and with dimethylamine gave the analogous products XXVI and XXVII.



In all three cases, the product is evidently the result of nucleophilic attack at the carbonyl, followed by ring opening and proton transfer; with nucleophiles, there is well-established precedent for this type of reaction.[7d,41] While the formation of XXV, XXVI, and XXVII represents an easy route to 3,4-disubstituted tricyclo[3.1.0.0^{2,6}]hexanes, our particular interests lay elsewhere and our foray into this field went no further.

Experimental Section

General Remarks. Melting points and boiling points are uncorrected. NMR spectra were run in $CDCl_3$ with added Me_4Si using either a Varian A-60A or a Bruker HX-90 instrument, and are reported in δ units. IR spectra were run on a Perkin-Elmer Model 257 instrument, and are reported in cm^{-1}. Mass spectra were obtained either on a Finnigan 3300 gas chromatograph/mass spectrometer or an AEI MS-902 instrument. Microanalysis was done by Galbraith Laboratories, Inc. "Nitrogen" refers to commercial "prepurified" grade. Analytical GC work was performed with a Varian 2100 instrument,

preparative GC using a Varian 200 instrument; glass columns were used throughout.

8,8-Dichlorotetracyclo[4.2.0.0^{2,4}.0^{3,5}]octan-7-one (V). After a solution of benzvalene (2.42 g, 31 mmol) in ether (ca. 55 ml) had been cooled to 0 °C under nitrogen (a dry ice condenser was used to avoid losses due to evaporation), excluding moisture, a portion (ca. 0.5 ml) of a solution of triethylamine (3.45 g, 34 mmol) in ether (5 ml) was added. Freshly distilled dichloroacetyl chloride (4.58 g, 31 mmol) was then added to the stirred solution. With the temperature being maintained at 0 °C, the remainder of the solution of triethylamine was added dropwise to the rapidly stirred mixture over a period of 30 min. After the mixture had been stirred at 0 °C for a further 2.5 h, it was kept overnight at −15 °C. It was then allowed to warm to room temperature and the precipitate of triethylammonium chloride was removed by filtration. The ether was carefully removed at ambient temperature in vacuo (water pump) and was collected at −78 °C. (Using *N,N*-dimethylformamide as internal standard, the ether distillate was shown by NMR spectroscopy to contain 460 mg of benzvalene.) There remained a dark brown residue which yielded a pale yellow distillate (48 mg) on distillation at 24 °C (0.1 mm). Further distillation at bath temperature 24–110 °C gave a colorless distillate (4.42 g), bp 51–53 °C (0.08 mm), which turned brown on being kept overnight at 0 °C under nitrogen. Redistillation gave a pale yellow liquid (4.1 g, 86% based on consumed benzvalene). GC analysis (5% phenyldiethanolamine succinate column) showed the compound to be of high purity: MS (EI) *m/e* (rel intensity) 192 (very small), 191 (very small), 190 (1), 189 (very small), 188 (1), 187 (very small), 162 (5), 161 (7), 160 (8), 159 (11), 153 (9), 127 (32), 126 (9), 125 (100), 99 ([2(= 9] (9), 89 (36), 78 (40), 73 (8), 63 (18), 52 (11), 51 (13), 50 (10). Other data appear in ref 2.

8-Chlorotetracyclo[4.2.0.0^{2,4}.0^{3,5}]octan-7-one (VI). To 19.0 g (49 mmol) of triphenyltin hydride in 20 ml of AR cyclohexane in a 250-ml flask with reflux condenser, under nitrogen, was added 8.4 g (44 mmol) of V in 10 ml of cyclohexane. A few milligrams of azobisisobutyronitrile were added and the mixture was refluxed for 0.5 h. After cooling, GC analysis (6% OV-1 column) showed that the reaction was complete. After storage at −20 °C overnight, the mixture was filtered, evaporated, and vacuum distilled to give 5.94 g (87%) of colorless liquid: bp 45–49 °C (0.1 Torr); IR (neat) 3150 vw, 3070 w, 2990 w, 1790 vs, 1380 w, 1295 w, 1120 m, 760 s, 720 cm^{-1} m; NMR δ 2.0–2.6 (m, 4 H), 3.05 (br "tr", "*J*" = 7–8 Hz, 1 H), 3.40–3.65 (m, 1 H), 4.62 (d of d, *J* = 8, 3 Hz, 1 H); MS (EI) *m/e* (rel intensity) 156 (1.5), 154 (4.5), 128 (2), 126 (7), 125 (4), 119 (18), 118 (16), 92 (8), 91 (100), 90 (16), 89 (20), 79 (6), 78 (87), 77 (17), 65 (28), 63 (21). Anal. Calcd for C_8H_7ClO: C, 62.15; H, 4.57. Found: C, 61.95; H, 4.39.

Tetracyclo[4.2.0.0^{2,4}.0^{3,5}]octan-7-one (VII). A solution of V (3.68 g, 18.4 mmol), triphenyltin hydride (15.2 g, 43 mmol), and azobisisobutyronitrile (50 mg) in AR cyclohexane (20 ml) was stirred under nitrogen at 83 °C for 1 h. Additional azobisisobutyronitrile (20 mg) was then added to the mixture, which was then stirred at 83 °C for a further 3 h. (GC analysis now showed the absence of both V and VI.) Distillation of the mixture gave three fractions, each of which was collected in a dry ice cooled receiver. The first fraction (ambient temperature, water-pump pressure) was concentrated carefully to 1.18 g by removal, at atmospheric pressure, of most of the cyclohexane through a 20-cm column packed with glass rings. GC and NMR analysis showed the presence of 0.4 g of VII. The second fraction (ambient temperature, 0.1 Torr) (0.38 g) contained 0.19 g of VII. The third fraction [bp 30–35 °C (0.1 Torr)] contained 1.90 g of almost colorless VII, contaminated by several percent of cyclohexane. The total yield of VII was thus ca. 2.3 g, or over 95%. Spectral data appear in ref 2.

Tetracyclo[4.2.0.0^{2,4}.0^{3,5}]octan-7-one *p*-Toluenesulfonylhydrazone (X). To a warm (50–60 °C) solution of 12.4 g of *p*-toluenesulfonylhydrazide (recrystallized Aldrich material) in 18 ml of absolute ethanol was added 7.1 g of VII. The resulting solution was allowed to stand at room temperature for 20 h. The resulting mass of white crystals was separated from the mother liquor by centrifugation and dried at 0.05 Torr for several hours. The yield was 13.0 g (76%). Spectral and other characterization appears in ref 2. The ^{13}C NMR spectrum ($CDCl_3$) of X included δ −1.5, 9.6, 9.9 (bicyclobutane bridge), and 161.6 and 161.8 (C-7).

Tetracyclo[4.2.0.0^{2,4}.0^{3,5}]oct-7-ene (I). Into a dry flask, under nitrogen, was injected 1.60 ml (9.5 mmol) of 2,2,6,6-tetramethylpiperidine (Aldrich, 99+%). This was followed by injection (2 min) of methyllithium in diethyl ether (4.40 ml, Foote, 5.38%; 7.2 mmol). After the vigorous bubbling had ceased, 1 ml of dry, degassed THF was injected to dissolve the resulting yellow precipitate, giving 5 ml of dark amber solution. Into a flask fitted with septum, magnetic stirrer, and vacuum/nitrogen inlet was placed 0.58 g (2.0 mmol) of X. The flask was evacuated to 0.03 Torr, then refilled with nitrogen. The solid was dissolved by injection of 3 ml of dry, degassed THF. The flask was chilled with dry ice, and 4.0 ml of base solution added (ca. 5 min); up to 2.0 ml, the base color faded to yellow, but then remained dark. After 10 min, the flask was allowed to warm to room temperature, and stirring was continued for a further 8 h. The flask was chilled with dry ice and 5 ml of water was injected dropwise; the mixture rapidly turned from very dark to yellow. The mixture was diluted with a few milliliters of *n*-pentane and the organic phase was separated and dried over anhydrous potassium carbonate. Analysis by GC (6% OV-1 column), using cumene as internal standard, showed ca. 50% yield of I. Further details of isolation and characterization appear in ref 2. Raman (neat, in capillary, using a Spex "Ramalog" instrument, using the 19 435-cm^{-1} line of an Ar laser; calibration of scale from the 1649-cm^{-1} stretch of cyclohexene) included 3140 s, 3120 s, 3050 vs, 2950 s, 1550 s, 1170 cm^{-1} vs.

Reaction of X with Methyllithium in Ether. X (0.51 g, 1.77 mmol) was placed in a 50-ml flask with magnetic stirrer and nitrogen/vacuum/septum adapter. The solid was dried by gentle warming under vacuum, and the flask then filled with nitrogen. Anhydrous ether (15 ml) was injected, and stirring begun to give a white suspension. An ice bath was placed around the flask, and 2.3 ml of methyllithium in ether (Ventron, 2.0 M) was injected (10 min). After 10 more min, the ice bath was removed. After 18 h, the brown suspension was treated with 15 ml of water. The turbid yellow aqueous layer was syringed away from the clear yellow ether layer, and the wash was repeated. After drying over ptassium carbonate, transferral to another flask, and slow evaporation to less than 1 ml (through a 6-in. Vigreux column), benzene (0.100 ml) was added as internal standard. NMR analysis showed about 40% yield of 7-methyltetracyclo[4.2.0.0^{2,4}.0^{3,5}]octane (XI) and a much smaller amount (possibly 10%) of I. These were collected from preparative GC (6% SE-30 column; the peak for XI was ca. three times the area of that for I), and XI was characterized: IR (vapor, 10-cm cell) 3160 vw, 3070 m, 2980 s, 2960 s, 2890 w, 1450 w, 1380 w, 1120 w, 775 cm^{-1} m; NMR complex pattern from δ 1.0–2.3, showing a three-proton doublet at 1.08 (*J* = 6 Hz) and strong broadened "singlets" at 1.85 and 2.15; MS (EI) *m/e* (rel intensity) 120 (3), 106 (1), 105 (10), 92 (6), 91 (13), 79 (14), 78 (100), 77 (15), 52 (10), 51 (14), 41 (9); MS (CI) *m/e* 135 (M + 15, 3), 121 (7), 119 (16), 107 (6), 105 (30), 93 (52), 91 (29), 80 (8), 79 (100), 78 (19).

Vapor-Phase Pyrolysis of I. A 1-cm o.d. Pyrex tube, packed with 20 cm of small Pyrex rings (washed with aqueous ammonia, then dried), was placed in a vertical tube furnace, topped with a septum, and with a small trap and outlet to vacuum at the bottom. The apparatus was evacuated (ca. 0.03 Torr) and a bleed valve, improvised from a 10-μl syringe needle, used to provide a 2–5 Torr nitrogen pressure to sweep samples through the tube. Injections of 0.1 ml of I in pentane (7 mg/ml) were passed through the tube and collected in the cold (liquid nitrogen) trap at the outlet. After 5 min, the system was filled with nitrogen, the trap allowed to warm to room temperature, and the contents analyzed. The sole significant product of the pyrolyses was cyclooctatetraene, as shown by coinjection with an authentic sample on 6% Carbowax 20M, 6% OV-1, and 10% QF-1 columns, and by comparison of the product's mass spectrum with that of authentic cyclooctatetraene. Pyrolyses were carried out at several temperatures ranging from 260 °C (<10% conversion) to ca. 450–500 °C (complete conversion). In no case was any discoloration of the column observed.

Reaction of I with *N*-Phenyltriazolinedione at 140 °C. In a Pyrex tube containing a small stirring bar were placed 110 mg (1.06 mmol) of I, 350 mg (2.0 mmol) of triazolinedione, and 3 ml of chloronaphthalene (Eastman, vacuum distilled). The tube was chilled and sealed under vacuum, then heated in a bath of refluxing xylene for 52 h in the dark. After cooling, the tube was opened and the contents were removed. After evaporation (high vacuum, gentle warming), the dark solid product was subjected to preparative TLC (silica gel, ether) to give the fractions listed below. (1) R_f 0: the mass spectrum of this dark, immobile fraction indicated the presence of diadduct(s), and this fraction was not characterized further. (2) R_f 0.1, ca. 10 mg of yellowish solid. The mass spectrum indicated this to be a 1:1 adduct; NMR showed the *N*-phenyl moiety. (3) R_f 0.45, 126 mg (44%) of material identified as XII by the near-perfect match of its IR spectrum, NMR spectrum (90 MHz), and melting point to those of an authentic sample.[22] (4) R_f 0.8, ca. 10 mg of yellowish solid; NMR and mass spectra were obtained. This fraction was later shown to be XIII by comparison with a pure sample obtained and characterized in a later experiment.

Deuteration of I. Single Treatment. I (150 mg) in 1.2 ml of anhydrous ether was dripped into 4 ml of 1.6 M *n*-butyllithium in hexane (Aldrich) at room temperature under nitrogen, and stirred for 1 h. The

Table IV

Initial spectrum	Final spectrum	Shift, ppm
1.86 (broadened s, 3 H)	2.7 (d, $J \simeq 5$ Hz, 1 H)	0.8
	5.4 (d, $J \simeq 6$ Hz, 2 H)	3.5
3.01 (d, $J \simeq 7$ Hz, 1 H)	5.7 (d, $J \simeq 7$ Hz)	2.7
4.15 (broadened s, 2 H)	8.2 (s)	4.1
5.68 ("tr", $J \simeq 7$ Hz, 1 H)	6.2 ("tr", $J \simeq 7$ Hz)	0.5
6.25 (m, 1 H)	6.7 ("tr", $J \simeq 7$ Hz)	0.4
7.4 (m, 5 H, aromatic)	7.8 (m, 3 H)	0.4
	12.9 (d, $J \simeq 7$ Hz, 2 H)	5.5

flask was then chilled in dry ice, and 1.0 ml of deuterium oxide was injected dropwise; the dry ice was then removed. The water was pipetted from the flask, and the remaining solution was dried over anhydrous potassium carbonate. Preparative GC (6% SE-30 column) gave ca. 100 mg of hydrocarbon. NMR of this indicated ca. 33% deuteration of the bicyclobutane bridgehead (positions 3 and 4); it also showed ca. 10% contamination by *n*-octane (from the butyllithium).

Deuteration of I. Repeated Treatment. I (0.251 g, 2.4 mmol) in 1.2 ml of anhydrous ether was placed in a dry, nitrogen-filled 25-ml flask with a magnetic stirrer and a septum/nitrogen inlet. *n*-Butyllithium (1.6 M in hexane, 2.5 ml, 4.0 mmol) was injected and the solution was left to stir at room temperature for 3 h. The flask was chilled in dry ice and 0.075 ml (4.2 mmol) of deuterium oxide injected. The dry ice was then removed, and after 15 min 4.0 ml (6.4 mmol) of *n*-butyllithium in hexane was injected. After 5.5 h more, the flask was again chilled, and 0.110 ml of deuterium oxide (6.1 mmol) was injected. The dry ice was removed, and 5.0 ml (8.0 mmol) of *n*-butyllithium in hexane injected. After a final 12-h wait, the flask was chilled again and 1.0 ml of deuterium oxide injected dropwise. Potassium carbonate was added after several minutes to take up excess moisture; preparative GC gave 0.164 g of material. NMR analysis showed this to be a mixture of 0.10 g of deuterated I and 0.06 g of *n*-octane. Integration of the NMR spectrum showed that the former was 75% deuterated at the 3 and 4 positions.

Reaction of 3,4-Dideuteriotetracyclo[4.2.0.0^{2,4}.0^{3,5}]oct-7-ene with *N*-Phenyltriazolinedione at 140 °C. This reaction was carried out as previously described, using 0.10 g of deuterated I (75% in the 3 and 4 positions) and 330 mg of triazolinedione. Reaction was continued for 24 h, and the product, deuterated XII, was isolated as before, and in the same yield: NMR δ 2.05 (4.5 H), 5.1 (2 H), 7.5 (5 H); at 90 MHz, the central two-proton signal shows as a triplet, J = 3 Hz; MS (EI) *m/e* (rel intensity) 282 (21), 281 (100), 280 (40), 120 (44), 119 (57), 118 (20), 106 (24), 105 (47), 104 (30), 93 (42), 92 (32), 91 (32). Shift reagent experiment: 24 mg of compound, in 0.3 ml of $CDCl_3$, was treated with weighed increments of solid "resolve-Al EuFOD" (Aldrich) until the "b" (see Discussion) proton set was clearly separated from the "a" set (40 mg of shift reagent). At this point, the spectrum was δ 2.5 (2 H), 2.8 (2.5 H), 7.9 (2 H), 7.1 (3 H), 10.0 (2 H). Confirmation of the first two signals as the respective sets noted above was accomplished by an identical experiment using undeuterated XII.

Reaction of I with *N*-Phenyltriazolinedione in Benzene at 23 °C. I (48 mg, 0.46 mmol) in 1.2 ml of benzene was added to 122 mg (0.7 mmol) of triazolinedione in a tube with a small stirring bar. The mixture was closed and allowed to stir at room temperature in the dark for 24 h. Preparative TLC gave two fractions, as listed below: (1) 58 mg (46%) of XII; (2) 8 mg (6%) of solid, mp 180–200 °C (201–204 °C after recrystallization from hexane/chloroform; IR and NMR spectra were virtually unchanged by this however). IR (KBr) 3100 vw, 3080 w, 3030 vw, 1775 m, 1705 vs, 1630 w, 1595 w, 1560 w, 1500 m, 1415 s, 1360 w, 1320 w, 1275 w, 1255, 1235 w, 1140 m, 1070 m, 775 m, 750 m, 720 cm^{-1} m. For NMR (taken as a 3% solution in $CDCl_3$, with total added "Resolve-Al EuFOD" of 0, 2, 7, 12, 18, 26, and 36 mg), see Table IV. MS (EI) *m/e* (rel intensity) 280 (12), 279 (78), 227 (10), 177 (18), 160 (24), 119 (82), 118 (42), 117 (92), 104 (26), 103 (44), 91 (100), 90 (58), 78 (44), 77 (45). High-resolution MS calcd for $C_{16}H_{13}N_3O_2$, 279.1008; found, 279.1012. On the basis of this data, the structure XII was assigned to this compound.

Pyrolysis of I in the Presence of Hexafluoro-2-butyne. This experiment was carried out using a manifold of known volume. Into a 0.5-in. o.d. heavy-wall Pyrex tube (ammonia washed, then dried) were transferred, under vacuum by liquid nitrogen trapping, 0.104 g (1.0 mmol) of I and 0.36 g (2.2 mmol) of hexafluoro-2-butyne (Peninsular Chemical Research, Inc. This reagent came in a cylinder under pressure. Fitting the cylinder with an additional valve adapted to a glass joint allowed small increments of gas to be introduced into the manifold via the two valves). The tube (8-in. section) was sealed under vacuum, padded with glass wool, and placed inside a copper pipe which in turn was heated in a tube furnace to 190–200 °C for 24 h. The tube was then cooled in dry ice, opened, and allowed to warm to room temperature (in the hood). The weight of brown oil obtained was 0.288 g; GC analysis of the mixture showed three major components (approximate ratio, in order of retention time, of 0.2:1:1), and a few small peaks at longer retention time. The products were identified by matching their properties with those of more thoroughly characterized samples prepared from cyclooctatetraene. The first component was identified as XVI by its CI mass spectrum and its GC behavior. The other two components were isolated by preparative GC (6% SE-30 column). This gave 55 mg of the second component, which was identified as XVII by its ^{1}H NMR spectrum, its IR spectrum, and its EI and CI mass spectra; the ^{19}F NMR noted under the full characterization was also taken on this sample. The third component was isolated in 56-mg amount, and identified as XVIII by the same series of spectral methods; the ^{19}F NMR and the proton decoupling experiment noted below were also performed on this sample.

Preparation of 1,2-Bis(trifluoromethylbenzene) (XVI), 7,8-Bis(trifluoromethyl)tricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene (XVII), and 1,8-Bis(trifluoromethyl)tricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene (XVIII). Cyclooctatetraene (0.5 ml, 4.4 mmol) was placed in a 0.5-in. o.d. heavy-walled Pyrex tube, and an equal volume of hexafluoro-2-butyne was transferred in under vacuum. The tube was sealed and the mixture then heated to ca. 200 °C for 24 h. Preparative GC gave the three products, as described below. (1) 0.112 g (11%), identified as XVI: IR (neat) includes 1310 s, 1160 s, 1125 cm^{-1} s; NMR symmetrical multiplet (collapsed A_2B_2 pattern) centered on δ 7.73; MS (EI) *m/e* (rel intensity) 214 (45), 195 (38), 164 (18), 145 (100), 125 (14), 95 (16), 75 (26), 69 (15), 50 (19); MS (CI) 215 (2.4), 214 (3.9), 196 (19), 195 (100), 194 (18), 193 (5). (2) 0.345 g (30%), identified as XVII: IR (neat) 1670 m, 1360 m, 1315 s, 1295 vs, 1250 s, 1185 vs, 1150–1140 vs, 1030 m, 1010 m, 780 m, 710 cm^{-1} m; NMR matched that previously reported;[28] ^{19}F NMR 45 ppm from $CFCl_3$ capillary (s); MS (EI) *m/e* (rel intensity) 227 (3), 196 (3), 195 (5), 178 (3), 177 (11), 145 (12), 128 (9), 77 (4), 75 (8), 53 (6), 52 (100), 51 (14), 50 (10); MS (CI) *m/e* (rel intensity) 295 (M + 29, 2), 268 (4), 267 (28), 266 (4), 248 (23), 247 (93), 246 (12), 228 (12), 227 (31), 183 (5), 93 (5), 79 (4), 67 (16), 53 (14), 52 (100), 51 (27), 50 (10); UV (isooctane) end absorption (ϵ_{210} 700), λ_{max} 221 nm (ϵ 700). (3) 0.459 g (39%), characterized as XVIII: IR (neat) 3140 vw, 3070 w, 3000 vw, 2960 w, 1645 w, 1595 w, 1555 vw, 1360 m, 1330 s, 1285 s, 1180 vs, 1160–1150 s, 1055 m, 1030 m, 1015 m, 775 m, 740 w, 695 cm^{-1} m; ^{1}H NMR δ 2.8 (narrow m, 2 H), 3.55 (m, 1 H), 6.1 (broadened s, 2 H), 6.45 (m, 3 H, containing a one-proton doublet, J = 7 Hz), 6.8 (d, J = 7 Hz, 1 H); a decoupling experiment showed that the multiplet at δ 3.55 was coupled to the multiplet at δ 2.8 and to the doublets at δ 6.45 and 6.8; ^{19}F NMR 46 and 51 ppm from $CFCl_3$ capillary (equal quartets, J = 10 Hz); MS (EI) *m/e* (rel intensity) 227 (2), 197 (2), 196 (2), 195 (3), 177 (6), 151 (3), 145 (7), 128 (5), 75 (5), 69 (2), 53 (4), 52 (100), 51 (8), 50 (6); MS (CI) *m/e* (rel intensity) 295 (M + 29) (2), 268 (2), 267 (12), 249 (3), 248 (33), 247 (100), 246 (13), 228 (9), 227 (21), 81 (5), 79 (3), 67 (5), 53 (9), 52 (57), 51 (16), 50 (6); UV (isooctane) end absorption (ϵ_{210} 1100), λ_{max} 223 nm (ϵ 1100), λ_{max} 271 nm (ϵ 80). Anal. Calcd for $C_{12}H_8F_6$: C, 54.14; H, 3.03. Found: C, 53.94; H, 2.95.

Thermal Equilibration of XVII and XVIII. A sample of each isomer (ca. 30 mg) was sealed under vacuum into its own Pyrex tube, and both tubes were heated to 200 °C for 24 h. The NMR spectrum of each mixture was then taken and the two spectra were found to be nearly identical. From the integration, the XVIII:XVII ratio was about 6:1. Analysis by GC confirmed the near identity of the mixtures, and gave a similar ratio of XVIII to XVII. The GC trace also showed a peak at shorter, and two peaks at longer retention time than either starting material; from the NMR, these (minor) products appeared to be aromatics, but were not characterized further.

Tetracyclo[4.2.0.0^{2,4}.0^{3,5}]octane (XIX). In a 50-ml flask with magnetic stirring bar were placed 1.18 g of VII, 17 ml of AR 1-butanol, and 1.0 ml of 99% "hydrazine hydrate" (Baker). The flask was stoppered and stirring continued for 16 h; then the mixture was evaporated to give 1.23 g of a colorless, viscous mixture of hydrazone and azine (XX): IR (neat) 3360 w (broad), 3220 (broad), 3130 vw, 3060 w, 2970 m, 1685 m, 1615 w, 1400 w, 1110 m, 745 cm^{-1} s; NMR δ 1.8–3.3 (m) and 4.82 (s, removable by D_2O), in area ratio 12:1; ^{13}C NMR complex, but included δ −1.7 (d, 215), 8.7 and 8.9 (d, 210), 152.4 and 169.6 (s). Used for the reduction was a 50-ml flask with stirring bar and fitted with adapters leading to a trap cooled in ice. In the flask were placed 1.23 g of mixed hydrazone and azine, 13 ml of AR ethylene glycol, 1.5 g of potassium hydroxide, and 0.7 ml of hydrazine hydrate. After the hy-

droxide was dissolved by gentle warming and stirring, the apparatus was completed as noted, and the flask was heated by an oil bath to 180–185 °C for 2 h, after which two layers were visible in the trap. The flask was then brought to 200–210 °C for 2 h, by which time very little additional material was distilling over. After brief cooling, 2 ml of *n*-pentane was added to the pot and distilled over to rinse out droplets still in the adapters. The lower layer was pipetted from the trap, and the pentane solution dried over anhydrous potassium carbonate. Preparative GC (6% SE-30 column) gave 0.632 g of unpleasant-smelling, colorless XIX (61% from VII): IR (vapor, 10-cm cell) 3170 vw, 3060 m, 2960 s, 2870 w, 1440 w, 1380 w, 1290 w, 1230 w, 1165 w, 1120 m, 745 cm^{-1} s; NMR δ 1.2–2.4, complex m, containing two major, roughly equal "peaks" at 1.85 and 2.15; MS (EI) *m/e* (rel intensity) 106 (21), 105 (11), 104 (6), 103 (7), 92 (3), 91 (41), 79 (21), 78 (100), 77 (25), 65 (10), 52 (12), 51 (21), 50 (11), 41 (6); MS (CI) *m/e* (rel intensity) 107 (15), 105 (28), 93 (6), 91 (12), 80 (6), 79 (100), 78 (10). Anal. Calcd for C_8H_{10}: C, 90.50; H, 9.50. Found: C, 89.69; H, 9.68. For ^{13}C NMR data, see Table I.

Pyrolysis of XIX, ~480 °C. The apparatus used in this experiment was a modified version of that used for the vapor-phase pyrolysis of I. The pyrolysis tube and the trapping arrangement were the same, but the column was topped by an apparatus allowing a capillary containing the reactant to be opened under vacuum by rotating a stopcock. The furnace was heated to ca. 480 °C, a sealed capillary containing ca. 30 mg of XIX was placed in the apparatus, and the whole apparatus was then evacuated (0.05 Torr). The trap was cooled in liquid nitrogen and the capillary was opened. After 5 min, the apparatus was filled with nitrogen, the trap was allowed to warm to room temperature, and the small amount of yellow, foul-smelling liquid product was separated by preparative GC (6% SE-30 column) into its two components. The first component was identified as benzene by its NMR and mass spectra. The second was identified as XXI by its IR and NMR spectra.[33a] The identity of XXI was confirmed by its conversion to ethylbenzene on treatment with hydrogen and 10% Pd/C catalyst, and by its conversion to dimethyl succinate by ozonolysis (−78 °C, methanol/ether) followed by oxidation (hydrogen peroxide/formic acid, brief reflux) and subsequent diazomethane treatment. From the NMR spectrum of the crude mixture, the molar ratio of benzene to XXI was 1:2.7.

Pyrolysis of XIX, ~430 °C. Apparatus and method were the same as for the higher temperature reaction, except that the furnace was set to ca. 430 °C and ca. 40 mg of XIX was used. GC analysis of the product showed six components, in about equal amounts (proportions varied significantly in the two times that this experiment was carried out, but all were present in isolable amounts both times). Preparative GC gave the components, which are listed in order of retention time (6% SE-30 column). NMR and IR were obtained of all, in $CDCl_3$ solution: (1) identified as benzene; (2) identified as XXII by comparing its NMR and IR spectra with published descriptions;[33] (3) identified as starting XIX; (4) on the basis of its IR spectrum and its hydrogenation (ether, 0 °C, 1 atm, 1 h, 10% Pd/C catalyst) to bicyclo[3.2.1]octane,[34] this fraction was identified as XXIV; (5) identified as XXI; (6) identified as XXIII by its IR and NMR spectra.[33]

Irradiation of I through Quartz. A solution of I in hexane (1 ml, containing several milligrams of I) was placed in a quartz tube fitted with a stopcock, along with 10 μl of 0.1% 2,6-di-*tert*-butyl-4-methylphenol in pentane. After four freeze–pump–thaw cycles at ca. 0.01 Torr, the tube was filled with nitrogen and the stopcock closed. The sample was irradiated at ca. 20 °C for 5.5 h using a 450-W Hanovia mercury lamp. After irradiation, the yellow, foul-smelling solution was analyzed by GC, which showed a roughly 1:1 mixture of I and a product whose retention time matched that of cyclooctatetraene on both a 6% OV-1 and a 6% Carbowax 20M column. The identities both of recovered I and of the product were also confirmed by their mass spectra.

Treatment of I with Silver Ion. Solutions of silver tetrafluoroborate (D. F. Goldsmith Chemical and Metal Corp.) and of silver perchlorate (Alpha) were made up both in acetone and in THF, to ca. 0.04 M concentration. To 0.2-ml portions of these solutions were added 1-drop portions of I in $CDCl_3$ (containing 1–2 mg of I), and the mixture was analyzed by GC (6% OV-1 column) after 1, 15, and 30 min. At 30 min, the mixture was quenched by addition of 1 ml of saturated aqueous sodium chloride, and the organic layer again analyzed. In all cases, there was observed rapid formation of a small to moderate proportion of a single product with retention time identical with that of cyclooctatetraene.

(4-Dichloromethyl)-3-tricyclo[3.1.0.0^{2,6}]hexanecarboxylic Acid Hydrazide (XXV). To 1.437 g (7.6 mmol) of V in 50 ml of glyme was added 0.50 ml (10 mmol) of hydrazine hydrate, with stirring. After 1.5 h of stirring at room temperature, the resulting slurry was evaporated, then dried at 0.1 Torr overnight to give 1.618 g (96%) of cream-colored, finely crystalline solid. This substance was stable indefinitely in the solid state, but soon turned brown in Me_2SO solution; when heated, it turned black in the range 100–200 °C, without melting. IR (KBr) 3340 s, 3050 w, 2940 w, 1625 vs, 1525 m, 1390 w, 1325 w, 1265 m, 1225 w, 1195 w, 1130 w, 1065 w, 1010 w, 940 w, 885 w, 800 w, 770 m, 730 cm^{-1} m; NMR (Me_2SO-d_6) 2.0–2.35 (m, 4 H), 2.35–2.65 (m, 2 H), 3.3–5.1 (broad, 3 H), 5.9–6.3 (symmetrical m, 1 H); MS (CI) *m/e* (rel intensity) 251 (1) and 249 (2) (M + 29), 225 (5), 224 (3), 223 (28), 222 (5), 221 (43), 188 (3), 187 (32), 186 (10), 185 (100), 149 (9), 137 (8), 133 (7), 127 (8), 125 (7), 121 (8), 95 (4), 91 (18), 79 (4). Anal. Calcd for $C_8H_{10}N_2Cl_2O$: C, 43.46; H, 4.56; N, 12.67; Cl, 32.07. Found: C, 42.49; H, 4.46; N, 13.30; Cl, 31.80. For ^{13}C NMR data, see Table III.

(4-Dichloromethyl)-3-tricyclo[3.1.0.0^{2,6}]hexanecarboxamide (XXVI). Into a dry, nitrogen-filled 50-ml three-necked flask with septum, dry ice cold finger condenser topped with a stopcock, and an inlet tube were condensed a few milliliters of ammonia. Anhydrous ether (20 ml) was injected, followed by 0.447 g (2.52 mmol) of V in 1 ml of ether (dropwise over 1 min). After 1 h, a stream of nitrogen was passed through the flask until the solvent had evaporated, leaving a white deposit. This was dried overnight at 0.1 Torr at room temperature to give 0.38 g (73%) of product: mp 123–124.5 °C dec; IR (KBr) 3400 s, 3190 m, 2860 vw, 1650 vs, 1620 m/s, 1430 m, 1295 m, 1285 m, 1265 w, 1220 w, 1140 w, 1125 m, 980 w, 805 w, 760 m, 745 cm^{-1} m; NMR (Me_2SO-d_6) δ 2.1–2.4 (m, 4 H), 2.62 (broadened s, 1 H), 2.71 (broadened s, 1 H), 6.23 (pentuplet, J = 5 Hz, 1 H), 6.8 (br, 1 H), 7.4 (br, 1 H); ms (CI) *m/e* (rel intensity) 210 (6), 209 (3), 208 (31), 207 (4), 206 (49), 172 (34), 170 (100), 134 (9), 127 (20), 122 (20), 91 (46), 79 (10); MS (EI) *m/e* (rel intensity) 172 (1), 170 (3), 127 (16), 125 (43), 123 (20), 122 (82), 92 (6), 91 (57), 90 (7), 89 (18), 85 (17), 83 (27), 80 (10), 79 (98), 78 (16), 77 (35), 65 (19), 63 (15), 52 (13), 51 (17), 44 (100). Anal. Calcd for $C_8H_9Cl_2NO$: C, 46.62; H, 4.40; Cl, 34.41; N, 6.80. Found: C, 46.81; H, 4.42; Cl, 34.62; N, 6.86.

***N,N*-Dimethyl-(4-dichloromethyl)-3-tricyclo[3.1.0.0^{2,6}]hexanecarboxamide (XXVII).** A dry, 50-ml, three-necked flask was set up with cold finger condenser with bubbler outlet, septum/stopcock inlet, stopper, and magnetic stirrer. After flushing with nitrogen, the flask was chilled in dry ice and the condenser filled with dry ice. Several milliliters of dimethylamine (Matheson) were condensed in via the stopcock; this was withdrawn as completely as possible with a chilled syringe, and 2 ml was returned to the flask. Next, 15 ml of anhydrous ether was injected and stirring commenced. V (0814 g, 2.32 mmol) was syringed in (5 min), then after another 5 min the dry ice bath was removed and the solution allowed to come to room temperature. After 4 h at room temperature, the light yellow solution was evaporated to give 1.01 g of light yellow oil (99%). IR, NMR, and GC analysis indicated that starting V was absent. The product turned black and viscous at room temperature after a few days in chloroform-*d* solution; GC analysis (6% OV-1 column) was unsuccessful. IR (neat) 3140 w, 3050 w, 2990 w, 2950 m, 1660 s, 1490 m, 1410 m, 1395 m, 1255 w, 1145 m, 1115 m, 760 m, 735 cm^{-1} m; NMR δ 1.90–2.55 (m, 4 H), 2.55–3.39 (m, 2 H), 2.91 (s, 3 H), 3.10 (s, 3 H), 5.95 (d, J = 9 Hz, 1 H); MS (CI) *m/e* (rel intensity) 238 (10), 237 (8), 236 (62), 235 (18), 234 (100), 233 (11), 200 (28), 199 (12), 198 (85), 180 (23), 162 (23), 150 (22), 72 (89). For ^{13}C NMR data, see Table III.

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Registry No.—I, 35434-65-2; V, 54220-48-3; VI, 61076-11-7; VII, 54220-49-4; VIII, 61076-12-8; VIII mesylate, 61076-13-9; X, 54220-50-7; XI, 61117-20-2; XII, 30114-59-1; XIII, 61104-53-8; XVI, 433-95-4; XVII, 59905-85-0; XVIII, 61076-14-0; XIX, 36328-44-6; XX hydrazone, 61076-15-1; XX azine, 61076-16-2; XXV, 61076-17-3; XXVI, 61076-18-4; XXVII, 61076-19-5; benzvalene, 659-85-8; dichloroacetyl chloride, 79-36-7; *N*-phenyltriazolinedione, 4233-33-4; hydrazine hydrate, 10217-52-4; ammonia, 7664-41-7; dimethylamine, 124-40-3; *p*-toluenesulfonylhydrazide, 1576-35-8; hexafluoro-2-butyne, 692-50-2.

References and Notes

(1) (a) Cornell University; (b) University of Adelaide.
(2) G. E. Gream, L. R. Smith, and J. Meinwald, *J. Org. Chem.*, **39**, 3461 (1974).
(3) H. E. Zimmerman and L. R. Sousa, *J. Am. Chem. Soc.*, **94**, 834 (1972).

(4) (a) P. J. van Vuuren, R. J. Fletterick, J. Meinwald, and R. E. Hughes, *J. Am. Chem. Soc.*, **93,** 4394 (1971); (b) P. J. van Vuuren, Ph.D. Dissertation, Cornell University, 1970; (c) M. S. Baird and C. B. Reese. *Tetrahedron Lett.*, 2895 (1976).
(5) (a) T. J. Katz, E. J. Wang, and N. Acton, *J. Am. Chem. Soc.*, **93,** 3782 (1971); (b) T. J. Katz, R. J. Roth, N. Acton; and E. Carnahan, preprint of procedure submitted to *Organic Syntheses*.
(6) (a) M. Christl, *Angew. Chem.*, **85,** 666 (1973); (b) M. Christl and G. Bruntrup, *Chem. Ber.*, **107,** 3908 (1974).
(7) (a) W. T. Brady, *Synthesis,* 415 (1971), and references cited therein; (b) L. Ghosez, R. Montaigne, A. Roussel, H. Vanlierde, and R. Mollet, *Tetrahedron,* **27,** 615 (1971); (c) M. Rey, S. Roberts, A. Dieffenbacher, and A. S. Dreiding, *Helv. Chim. Acta,* **53,** 417 (1970); (d) T. R. Potts and R. E. Harmon, *J. Org. Chem.,* **34,** 2792 (1969); (e) H. C. Stevens, D. A. Reich, D. R. Brandt, K. R. Fountain, and E. J. Gaughan, *J. Am. Chem. Soc.*, **87,** 5257 (1965); (F(P. R. Brook, A. J. Duke, and J. C. R. Duke, *J. Chem. Soc. D,* 574 (1970).
(8) (a) T. J. Katz and N. Acton, *J. Am. Chem. Soc.*, **95,** 2738 (1973); (b) R. J. Roth and T. J. Katz, *ibid.*, **94,** 4770 (1972); (c) T. J. Katz and K. C. Nicolaou, *ibid.*, **96,** 1948 (1974).
(9) (a) J.-M. Conia and J.-L. Ripoll, *Bull. Soc. Chim. Fr.*, 768 (1963); (b) F. V. Brutcher, Jr., T. Roberts, S. J. Barr, and N. Pearson, *J. Am. Chem. Soc.*, **78,** 1507 (1956).
(10) M. Christl, *Chem. Ber.*, **108,** 2781 (1975).
(11) S. H. Grover, D. H. Marr, J. B. Stothers, and C. T. Tan, *Can. J. Chem.*, **53,** 1351 (1975).
(12) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley, New York, N.Y., 1972.
(13) (a) H. G. Kuivila and O. F. Beumel, Jr., *J. Am. Chem. Soc.*, **83,** 1246 (1961); (b) D. J. Carlsson and K. U. Ingold, *ibid.*, **90,** 7047 (1968); (c) G. M. L. Cragg, *J. Chem. Soc. C,* 1829 (1970).
(14) A mesylate was also prepared from VIII; its solvolytic properties have been briefly examined but have proven complex and somewhat irreproducible to date.
(15) A recent extensive review: R. H. Shapiro, *Org. React.*, **23,** 405 (1975).
(16) H. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *J. Am. Chem. Soc.*, **95,** 3662 (1973).
(17) (a) J. Meinwald and F. Uno, *J. Am. Chem. Soc.*, **90,** 800 (1968); (b) R. H. Shapiro and J. H. Duncan, *Org. Synth.*, **51,** 66 (1971).
(18) B. Shrader, *Angew. Chem., Int. Ed. Engl.*, **12,** 884 (1973).
(19) H. Iwamura, K. Morio, and T. L. Kunii, *Chem. Commun.*, 1408 (1971).
(20) (a) W. G. Dauben and R. L. Cargill, *Tetrahedron,* **12,** 186 (1961); (b) O. L. Chapman, D. J. Pasto, G. W. Borden, and A. A. Griswold, *J. Am. Chem. Soc.*, **84,** 1220 (1962).
(21) (a) R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *J. Chem. Soc. C,* 1905 (1967); (b) R. C. Cookson, S. S. Gupta, I. D. R. Stevens, and C. T. Watts, *Org. Synth.*, **51,** 121 (1971); (c) R. Huisgen, W. E. Konz, and U. Schegg, *Angew. Chem., Int. Ed. Engl.*, **11,** 715 (1972).
(22) L. A. Paquette, D. R. James, and G. H. Birnberg, *J. Am. Chem. Soc.*, **96,** 7454 (1974). We wish to thank Professor Paquette for sending us the authentic sample of XII.
(23) (a) H. E. Zimmerman, G. L. Grunewald, R. M. Paufler, and M. A. Sherwin, *J. Am. Chem. Soc.*, **91,** 2330 (1969); (b) E. N. Marvell and J. Seubert, *Tetrahedron Lett.*, 1333 (1969).
(24) R. C. Cookson, J. Dance, and J. Hudec, *J. Chem. Soc.*, 5416 (1964).
(25) J. Meinwald, C. Swithenbank, and A. Lewis, *J. Am. Chem. Soc.*, **85,** 1880 (1963).
(26) (a) M. Pomerantz, R. N. Wilke, G. W. Gruber, and U. Roy, *J. Am. Chem. Soc.*, **94,** 2752 (1972); (b) C. R. Watson, Jr., R. M. Pagni, J. R. Dodd, and J. E. Bloor, *ibid*, **98,** 2551 (1976).
(27) P. G. Gassman and K. T. Mansfield, *J. Am. Chem. Soc.*, **90,** 1517 (1968).
(28) R. S. H. Liu and C. G. Krespan, *J. Org. Chem.*, **34,** 1271 (1969).
(29) (a) M. Avram, G. Mateescu, and C. D. Nenitzescu, *Chem. Ber.*, **90,** 1857 (1967); (b) C. E. Berkoff, R. C. Cookson, J. Hudec, and R. O. Williams, *Proc. Chem. Soc., London,* 312 (1961); (c) C. D. Nenitzescu, M. Avram, I. I. Pogany, G. D. Mateescu, and M. Farcasiu, *Acad. Repub. Pop. Rom., Stud. Cercet. Chim.*, **11,** 7 (1963); *Chem. Abstr.*, **60,** 6764*h* (1964); (d) W. v. E. Doering and J. W. Rosenthal, *J. Am. Chem. Soc.*, **88,** 2078 (1966).
(30) H. H. Westberg, E. N. Cain, and S. Masamune, *J. Am. Chem. Soc.*, **91,** 7512 (1969).
(31) E. Vedejs, *Chem. Commun.*, 536 (1971).
(32) H. O. House, "Modern Synthetic Reactions", 2d ed, W. A. Benjamin, Menlo Park, Calif., 1972, Chapter 4, and references cited therein.
(33) (a) W. R. Roth and B. Peltzer, *Justus Liebigs Ann. Chem.*, **685,** 56 (1965); (b) M. St.-Jacques and R. Prud'homme, *Tetrahedron Lett.*, 4833 (1970); (c) A. C. Cope, A. C. Haven, Jr., F. L. Ramp and E. R. Trumbull, *J. Am. Chem. Soc.*, **74,** 4867 (1952).
(34) W. v. E. Doering and W. R. Roth, *Tetrahedron,* **19,** 715 (1963).
(35) (a) R. Pettit, H. Sugahara, J. Wristers, and W. Merk, *Discuss. Faraday Soc.*, **47,** 71 (1967); (b) W. Merk and R. Pettit, *J. Am. Chem. Soc.*, **89,** 4788 (1967); (c) G. Zon and L. A. Paquette, *ibid.*, **96,** 5478 (1974); (d) P. G. Gassman and R. R. Reitz, *ibid.*, **95,** 3057 (1973); (e) M. Sakai, H. Yamaguchi, H. H. Westberg, and S. Masamune, *ibid.*, **93,** 1044 (1971); (f) K. C. Bishop III, *Chem. Rev.*, **76,** 461 (1976).
(36) J. Howell, B. Johnson, P. Josty, and J. Lewis, *J. Organomet. Chem.*, **39,** 329 (1972).
(37) G. Scholes, C. Graham, and M. Brookhart, *J. Am. Chem. Soc.*, **96,** 5665 (1974).
(38) R. D. Cramer, *Inorg. Chem.*, **1,** 722 (1962).
(39) A. Schönberg, A. E. K. Fateen, and A. E. M. A. Sammour, *J. Am. Chem. Soc.*, **79,** 6020 (1957).
(40) G. Miyajima and K. Takahashi, *J. Phys. Chem.*, **75,** 331 (1971).
(41) (a) L. Ghosez, R. Montaigne, and P. Mollet, *Tetrahedron Lett.*, 135 (1966); (b) P. D. Bartlett and T. Ando, *J. Am. Chem. Soc.*, **92,** 7518 (1970); (c) V. R. Fletcher and A. Hassner, *Tetrahedron Lett.*, 1071 (1970).

Analogues of Sparteine. 3. Synthesis and Conformational Studies of Some 2,3-Substituted 7-Methyl-3,7-diazabicyclo[3.3.1]nonanes

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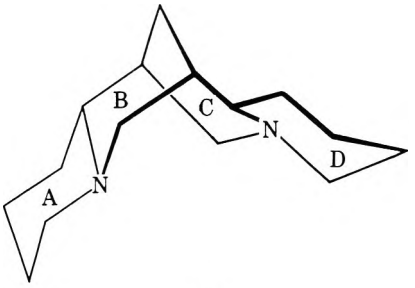
Three 3,7-disubstituted 3,7-diazabicyclo[3.3.1]nonanes having 2-exo alkyl substituents (**4a–c**) were found to adopt boat conformations with respect to the rings bearing the 2 substituents. The first two compounds were synthesized by addition of Grignard reagents to aldimmonium ion **5**, the last by similar addition to aldimine **10** followed by introduction of the N-3 benzyl group. Evidence in favor of the configurational assignments was obtained from the IR and NMR spectra, and in the case of **4a**, by comparison of its spectral and physical properties with those of its epimer (**8**). The conformational preference of **4a–c** was compared to that of other 3,7-diazabicyclo[3.3.1]-nonanes and to that of the alkaloid sparteine (**1**).

By various approaches, the C rings of sparteine (**1**) and α-isosparteine (**2**) have been shown to prefer the boat and chair conformations, respectively.[1] Together, the B and C rings of these alkaloids constitute the 3,7-diazabicyclo[3.3.1]-nonane (bispidine) moiety (**3**). Interest in the structure of this and other bicyclo[3.3.1]nonanes has centered mainly on variants at the 3,7 and 9 positions,[2] with less attention focused on variants at the 2 position.



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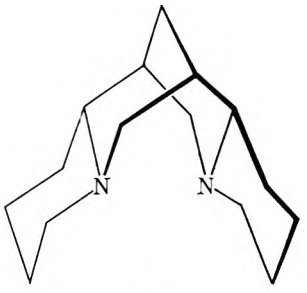

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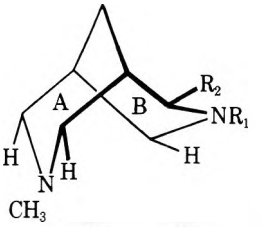
N,N'-Dimethylbispidine (**3**, R = CH_3) has been shown to exist in a double-chair conformation, qualitatively similar to that of the inner rings of **2**, based on NMR spectral features, physical properties (dipole moment, basicity), and on LCAO–MO calculations.[3] Our attention was directed toward the influence of 2-alkyl substituents on the conformation of this ring system. It was anticipated that 2-exo alkyl systems (**4**),[4] being configurationally similar to **1**, would adopt chair–boat conformations similar in respect to the inner rings of **1**. In this paper, we describe synthetic routes which furnished several 2-alkyl derivatives of **3**, and some conformational features of these compounds.

Results and Discussion

Oxidation of **3** (R = CH_3) followed by reaction of the resulting aldimmonium ion (**5**) with methylmagnesium iodide

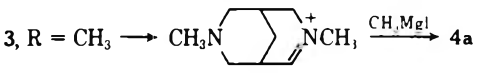
3



	R_1	R_2
4a	CH_3	CH_3
b	CH_3	i-C_3H_7
c	CH_2Ph	CH_3

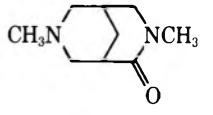
had been expected to give **4a** (Scheme I). However, oxidation of *N,N'*-dimethylbispidine with excess mercuric acetate in

Scheme I



5

5% aqueous acetic acid[5] gave 71% of a waxy solid that had strong IR absorption at 6.10 μ and a molecular ion of *m/e* 168.1261 in its mass spectrum. From these spectral features, we concluded that the product was bicyclic lactam **6**, rather than **5**.[4] Oxidation of other cyclic diamines to lactams under these conditions has been reported.[6] Treatment of **3** (R =



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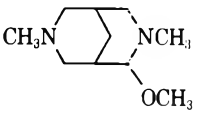

7

CH_3) as before, except using 33% acetic anhydride in acetic acid as solvent, furnished **5**, which was isolated (31%) as the diperchlorate salt. It exhibited C=N$^+$ absorption at 5.90 μ in its IR spectrum,[5a] and a broad signal at 8.97 ppm,[1c] due to the presence of the HC=N$^+$ group, in its NMR spectrum. Conversion of **5** to its free base in the presence of methanol gave the *N,O*-acetal **7** as evidenced by spectral features. Its NMR spectrum had an OCH_3 singlet and an NCHO doublet centered at 3.30 and 3.90 ppm, respectively, and no signals at lower field. Its IR spectrum had no bands in the C=N$^+$ region. Treatment of **5** with excess methylmagnesium iodide (Scheme I) gave a product (89%) tentatively assigned as that of exo addition (**4a**). Its NMR spectrum displayed one CCH_3 doublet centered at 1.00 ppm, signifying the presence of a single diastereomer. In order to substantiate this configurational assignment, the endo diastereomer (**8**) was required for comparison.

Reaction of **6** with excess methylmagnesium iodide in re-

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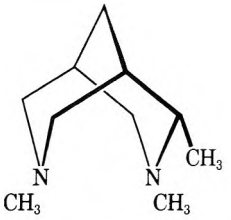
† Professor Smissman died on July 14, 1974.



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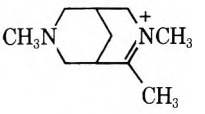


9

fluxing ether, followed by treatment of an ethereal solution of the base with excess perchloric acid, furnished ketimmonium salt **9** (40%) which had a characteristic C=N$^+$ band at 5.90 μ in its IR spectrum. Sodium borohydride reduction of **9** in water gave 98% of a single diastereomer **8** as evidenced by the appearance of a single CCH_3 doublet centered at 1.10 ppm in its NMR spectrum. Inspection of molecular models of **9** indicated much less hinderance to exo relative to endo nucleophilic addition. This, along with the known[7] sensitivity of sodium borohydride to steric factors, was the basis for the *endo*-2-methyl configurational assignment.

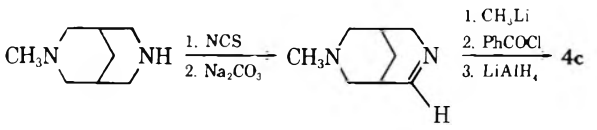
Compound **8** had a GLC retention time of 1.39 relative to **4a.** Also, **8** and **4a** differed in their IR spectral "fingerprint" regions, NMR spectra, and melting points as dihydrobromide salts. By deduction, we concluded that **4a** was the 2-exo isomer, and that addition of Grignard reagents to **5** proceeded stereospecifically. Since **4b** was prepared in the same manner as **4a** (Scheme I), it too was assigned the 2-exo configuration.[4]

Information regarding the conformations of the 2-alkyl substituents of **4a,b** and **8** was provided by inspection of the respective IR and NMR spectra. The NMR spectrum of each compound exhibited signals between 2.60 and 3.10 ppm which integrated for three protons (Table I). Protons in this region of the NMR spectra of related compounds have been postulated to be gauche to the nitrogen lone pairs, with other N- and C-aliphatic protons appearing upfield from these.[8] This suggested an equatorial orientation of the 2-alkyl groups in each of these compounds. Comparison of the IR spectra of *N,N'*-dialkylbispidines (**3**)[9] with those of **4a,b** and **8** indicated considerable similarity in regard to appearance and intensity of Bohlmann (trans) bands, centered at ca. 3.6 μ. The intensity of these has been shown to be proportional to the number of C–H bonds anticoplanar to the nitrogen lone pairs.[10] This indicated that **3, 4a, 4b,** and **8** all had the same number of these bonds, and that the alkyl groups in the last three were equatorial, in agreement with the NMR spectral findings.

In order to substantiate further the equatorial conformational assignment of the 2-exo alkyl substituents in **4a,b,** we wished to prepare the *N*-benzyl analogue (**4c**) for NMR spectral analysis. In the related *N*-benzyl-2-alkylpiperidines, the benzylic methylene protons appear as a singlet if the 2-alkyl substituent is axial, and as an AB quartet if it is equatorial.[11,12]

Compound **4c** was prepared as shown in Scheme II. Oxidation of *N*-methylbispidine with *N*-chlorosuccinimide[13]

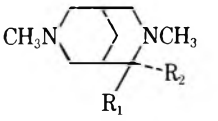
Scheme II



10

followed by treatment of the unstable *N'*-chloro intermediate with base gave a product thought to be aldimine **10,** as the monoperchlorate salt in 67% yield. While this product had the expected elemental composition, it lacked spectral features characteristic of the presence of an aldimine moiety. When it was converted to the free base, it exhibited a one-proton multiplet centered at 7.86 ppm (HC=N)[14] and absorbance at 6.00 μ (C=N) in its NMR and IR spectra, respectively. This suggested that the initially isolated salt was nonmonomeric, but that the free base was monomer **10.** Other features in the above spectra and in the mass seectrum of the free base were consistent with this structural assignment. In contrast to **10,** monocyclic aldimines **11** and **12** have been shown to exist

Table I. NMR Spectral Features of *N,N'*-Dimethylbispidine and 2-Alkyl Derivatives[a]



Compd	R_1	R_2	CCH_3, δ	NCH_3, δ	Protons gauche to N[b]
3	H	H		2.15, 2.15	4
4a	CH_3	H	1.00 (d, J = 6 Hz)	2.08, 2.17	3
4b	i-C_3H_7	H	0.77, 0.88 (d, J = 6 Hz)	2.08, 2.12	3
8	H	CH_3	1.10 (d, J = 6 Hz)	2.11, 2.11	3

[a] Spectra were taken using benzene as solvent. Chemical shifts are in parts per million relative to internal tetramethylsilane. [b] Calculated from the relative integrated intensity of the spectrum between 2.60 and 3.10 ppm.[8]

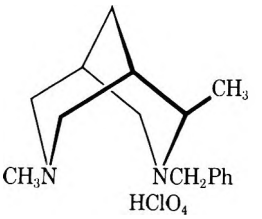
11 12

predominantly and exclusively as trimers, respectively.[13b,15]

Treatment of **10** with methyllithium, followed by benzoylation of the resulting secondary amine and subsequent reduction of the benzamide with lithium aluminum hydride, gave **4c** (Scheme II). The low overall yield (6%) of this sequence was due primarily to the difficulty encountered in reduction of the benzamide—this proceeded in only 17% yield.[16] Other approaches to the synthesis of **4c** proved even less satisfactory.

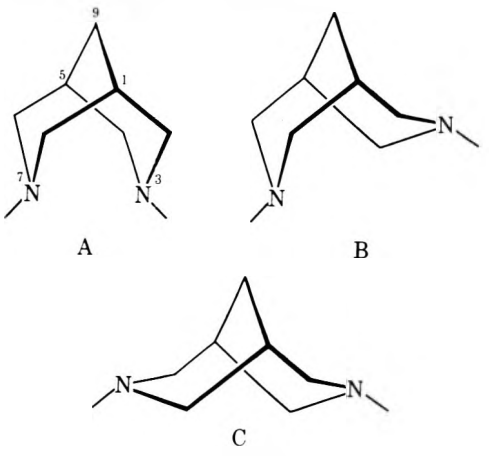
The NMR spectrum of **4c** monoperchlorate exhibited a singlet at 3.77 ppm, representative of the *N*-benzylic methylene protons. The lack of observable nonequivalence of these protons signified an axial orientation of the 2-methyl group.[11] In addition, this indicated that **4c** resulted from exo addition of methyllithium to **10,** since the ring system of this salt was assumed to adopt the double chair conformation (Chart I).

Chart I. Conformation of 4c Monoperchlorate

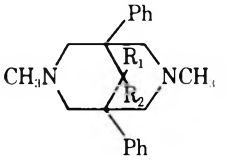


(The inner rings of **1** monoperchlorate have been shown to adopt a similar conformation.[17]) Conversion of **4c** monoperchlorate to the free base caused the *N*-benzylic methylene protons to appear as an AB quartet in the NMR spectrum, which indicated that the 2-methyl group was now equatorial.[11]

Conformation of the Ring Systems in 4a–c. The 3,7-diazabicyclo[3.3.1]nonane (bispidine) ring system may assume any of three nondistorted orientations (A–C). Its 3,7-dimethyl



derivative (**3**, R = CH_3) has been shown to exist as A.[3] However, structural modifications of this system have been found to alter this preference. Its 9-phenyl-9-hydroxy derivative has been shown to exist in the chair–boat form (B), on the basis of strong transannular hydrogen bonding seen in its IR spectrum.[2c] The 1,5-diphenyl derivatives (**13a,b**) have also been



	R_1	R_2
13a	(=O)	
b	H	OH

postulated to prefer this conformation, based on spectral and dipole moment studies.[18] The spectral evidence described above indicated that the 2-exo-alkyl groups in **4a–c** were all equatorial. Thus, the 2-substituted ring of each of these compounds exists in the boat conformation, and either B or C may represent their ring systems. Of these, B appears to be favored owing to unfavorable steric interactions present in C; however, the spectral characteristics we observed do not rule out the presence of the latter conformer.

Assuming that B represents the preferred conformer of **4a–c**, these compounds are not only configurationally similar to the inner rings of (±)-sparteine, but are qualitatively similar to them conformationally.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (IR) were taken on a Beckman IR 33 spectrophotometer. Nuclear magnetic resonance spectra (NMR) were obtained using a Varian T-60 spectrometer with tetramethylsilane as internal standard. Electron impact mass spectra (EIMS) were recorded using a Varian CH5 spectrometer, at 70 eV. The chemical ionization mass spectrum (CIMS) was obtained using a Finnegan 1015 spectrometer with isobutane as ionizing gas. Elemental analyses were obtained on a Hewlett-Packard 185, C, H, N analyzer, and from Midwest Microlab, Inc., Indianapolis, Ind. Analytic gas–liquid chromatography (GLC) was performed with a F & M 810 gas chromatograph using flame ionization detection; carrier gas helium (30 ml/min); detector gases hydrogen (55 ml/min), compressed air (250 ml/min); columns 6 ft × 0.125 in. stainless steel containing Dowfax 9N9 KOH supported on 80–100 mesh acid-washed DMCS-treated HP Chromosorb G; instrument temperatures, injection port (210 °C), detector (225 °C), oven (125–170 °C isothermal).

General Methods. All reactions involving air-sensitive reagents were carried out under dry nitrogen. Workup of organic extracts: solutions of products were dried with anhydrous sodium sulfate, filtered, and concentrated at a rotary evaporator using a Buchler water aspirator (10–40 mm) at water bath temperatures of 40 °C or less. Free bases were prepared from salts by partitioning them between ether and 10% aqueous sodium hydroxide. Ethanol was added to increase the rate of equilibration in the case of water-insoluble salts.

***N*-Methylbispidine** and ***N,N'*-dimethylbispidine** were obtained as described previously.[9]

3,7-Dimethyl-3-azonia-7-azabicyclo[3.3.1]non-2-ene (5). To 100 ml of cold 33% v/v acetic anhydride in glacial acetic acid were added 1.3 g (8.4 mmol) of *N,N'*-dimethylbispidine and 10 g (31 mmol) of mercuric acetate. The solution was heated to 40 °C for 5 min, then allowed to stand for 96 h at room temperature. The suspension was filtered and the filtrate was saturated with hydrogen sulfide, filtered, and concentrated at the oil pump. The residual viscous yellow oil was dissolved in 25 ml of chloroform, and the solution cooled in ice and equilibrated with 20 ml of ice-cold 20% aqueous sodium hydroxide. The aqueous phase was extracted three more times with 30-ml portions of cold chloroform. The combined extracts were concentrated, leaving a light yellow oil. This was dissolved in ether, cooled, and treated with excess aqueous ethanolic perchloric acid. The diperchlorate salt separated from alcohol as white crystals: 1.30 g (31%); mp 251–253 °C dec; IR (KBr) 3.23 (s), 3.34 (w), 3.55 (w), 5.90 (s, C=N⁺), 6.85 (s), 9.22 μ (s, ClO_4^-); NMR (D_2O) δ 2.20 (t, *J* = 2 Hz, 2, CH_2 bridge) 3.01 (s, 6, $^+NCH_3$), 4.67 (s, 2, HDO), 8.97 (m, $W_{1/2}$ = 9 Hz, 1, HC=N⁺).

Anal. Calcd for $C_9H_{18}Cl_2N_2O_8$: C, 30.61; H, 5.14; N, 7.93. Found: C, 30.84; H, 4.80; N, 7.21.

Reactivity of 5. A. With Methanol. The perchlorate salt of **5** (100 mg) was converted to the base by partition between 30 ml of alcohol-free chloroform and 3 ml of 15% aqueous sodium hydroxide. The concentrated residue was dissolved in 5 ml of methanol, the solution reduced to dryness, the residue taken up in 5 ml of benzene, and this solution reduced to dryness at the oil pump. This afforded methyl acetal **7** as a yellow oil: NMR (CD_3OD) δ 2.11 and 2.33 (s, 6, NCH_3), 3.30 (s, OCH_3), 3.88 (d, *J* = 2 Hz, 1, carbinolamine CH), 1.30–3.10 (10, remaining protons).

B. With Grignard Reagents. 2-*exo*,3,7-Trimethyl-3,7-diazabicyclo[3.3.1]nonane (4a) was made by addition of 0.35 g (1 mmol) of **5** diperchlorate to 1 ml of a cold (−20 °C) 2.7 M solution of methylmagnesium iodide in ether. After stirring for 24 h at room temperature, the excess Grignard reagent was destroyed with 30% aqueous ammonium chloride. The mixture was treated with excess 20% aqueous potassium fluoride and centrifuged. The supernatant was decanted, made strongly basic with 20% aqueous sodium hydroxide (5 ml), and extracted with four 15-ml portions of ether. The combined ethereal extracts were worked up to give 0.15 g (89%) of a colorless liquid: IR (neat) 3.40, 3.58, 7.84, 8.10, 8.70, 9.05, 9.26, 9.52, 9.76 μ; NMR (Table I); EIMS *m/e* 168 (M), 58 (B). Treatment of a cold ether solution of this base with a 24% solution of hydrobromic acid in aqueous acetone afforded the dihydrobromide salt as a white powder which separated from alcohol–acetone as white plates, mp 266–270 °C dec.

Anal. Calcd for $C_{10}H_{22}Br_2N_2$: C, 36.38; H, 6.72; N, 8.48. Found: C, 36,54; H, 6.75; N, 8.22.

The free base was prepared from a portion of this salt: GLC (130 °C) retention time 5.6 min, ca. 100% purity.

2-*exo*-Isopropyl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonane (4b) was prepared by addition of a suspension of 1.3 g (3.7 mmol) of **5** diperchlorate in 5 ml of dry tetrahydrofuran to 8 ml of a stirred 1.25 M solution of isopropylmagnesium bromide in tetrahydrofuran. The mixture was stirred and refluxed for 42 h and cooled, and the excess Grignard reagent destroyed as above. The solvent was removed in vacuo. To the residue was added 5 ml of water. The mixture was adjusted to pH 7 by addition of 10% aqueous hydrochloric acid, treated with 20% aqueous potassium fluoride, and centrifuged. The supernatant was made strongly basic by addition of sodium hydroxide pellets and extracted with four 10-ml portions of ether. The combined organic extracts were washed with 30 ml of fresh 1 M aqueous sodium bicarbonate and worked up to give a light amber liquid, 0.3 g, GLC (140 °C) 88% purity. This was dissolved in 10 ml of ether, cooled, and treated with excess ethereal hydrochloric acid to precipitate 0.25 g of the crude dihydrochloride. Crystallization from alcohol–ethyl acetate afforded 0.2 g (25%) of **4b** as white crystals, mp 255–257 °C dec.

Anal. Calcd for $C_{12}H_{26}N_2Cl_2$: C, 53.53; H, 9.73; N, 10.40. Found: C, 53.14; H, 9.89; N, 10.18.

The free base was prepared from this salt as a colorless oil: IR (neat) 3.40 and 3.59 μ (s, aliphatic CH); NMR (Table I); EIMS *m/e* 196 (M), 58 (B).

3,7-Dimethyl-3,7-diazabicyclo[3.3.1]nonan-2-one (6). To 70 ml of cold 5% aqueous acetic acid was added 2.2 g (14.3 mmol) of *N,N'*-dimethylbispidine and 18.2 g (57.2 mmol) of mercuric acetate. The solution was heated at 47 °C for 6 h, during which time a copious white precipitate of mercurous acetate formed. The mixture was saturated with hydrogen sulfide, filtered, and concentrated at the oil

pump. The residue was dissolved in 16 ml of ice-cold 20% aqueous sodium hydroxide, and extracted with four 16-ml portions of chloroform. The combined extracts were concentrated to give 1.7 g (71%) of a waxy, yellowish solid: mp 62–64 °C; IR (KBr) 3.38 (s), 3.57 (s), 6.10 μ (s, NC=O); NMR (CCl_4) δ 2.10 (s, 3, NCH_3), 2.85 (s, 3, $CONCH_3$), 1.50–3.50 (remaining protons); EIMS *m/e* 168 (M) 58 (B), M 168.1261 (calcd for $C_9H_{16}N_2O$, 168.1314); CIMS *m/e* (rel intensity) 169 (qm, 100), 71 (14).

Anal. Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.51; H, 9.71; N, 16.67.

2,3,7-Trimethyl-3-azonia-7-azabicyclo[3.3.1]non-2-ene (9). A solution of 2.0 g (11.9 mmol) of **6** in 15 ml of dry benzene was added to an ice-cold 1.8 M solution of methylmagnesium iodide in ether. The mixture was stirred, refluxed for 43 h, and cooled, and excess Grignard reagent was removed (see above). The ether was decanted from precipitated solids. The precipitate was treated with excess 20% aqueous potassium fluoride and centrifuged. The supernatant was made strongly basic with 20% aqueous sodium hydroxide and the resulting mixture (15 ml) was extracted with four 15-ml portions of chloroform. Workup of the combined extracts furnished 1.0 g (45%) of a yellow oil which darkened readily on exposure to air: NMR ($CDCl_3$) δ 2.15 (s, 3, NCH_3), 2.30 (s, 3, CCH_3), 2.40 (s, 3, NCH_3), 1.30–3.30 (10, remaining protons). To 60 mg of this oil dissolved in 5 ml of ether was added excess aqueous ethanolic perchloric acid. The product was recrystallized three times from ethanol to give yellow needles: mp 223–225 °C dec; IR (KBr) 5.97 (s, $C{=}N^+$), 9.17 μ (s, ClO_4^-).

Anal. Calcd for $C_{10}H_{20}Cl_2N_2O_8$: C, 32.71; H, 5.49; N, 7.63. Found: C, 32.43; H, 5.42; N, 7.59.

2-*endo*,3,7-Trimethyl-3,7-diazabicyclo[3.3.1]nonane (8). To a solution of 0.95 g (6.2 mmol) of **9** in 25 ml of water was added 0.5 g (13 mmol) of sodium borohydride. After stirring for 24 h, the suspension was extracted with three 50-ml portions of ether. The combined extracts were concentrated to give 0.9 g (98%) of a colorless, mobile liquid, NMR (Table I). This was dissolved in 20 ml of acetone and treated with an ice-cooled solution of 25% hydrobromic acid in water–acetone. The white precipitate was filtered, washed with acetone, and crystallized from ethanol–acetone to give 1.1 g of the dihydrobromide salt: mp 251–253 °C dec; EIMS *m/e* 168 (M), 58 (B).

Anal. Calcd for $C_{10}H_{22}Br_2N_2$: C, 36.38; H, 6.72; Br, 48.42; N, 8.48. Found: C, 36.12; H, 6.86; Br, 48.68; N, 8.42.

The free base was prepared from a portion of this salt: GLC (130 °C) retention time 7.8 min; ca. 100% purity; IR (neat) 3.39, 3.58, 7.84, 8.77, 9.26, 9.57, 9.80 μ.

7-Methyl-3,7-diazabicyclo[3.3.1]non-2-ene (10). To a solution of 1.1 g (7.85 mmol) of *N*-methylbispidine in 40 ml of dry ether was added 1.1 g (7.85 mmol) of *N*-chlorosuccinimide. The suspension was stirred at room temperature for 24 h. About 5 ml of ethanol was added and the solution was concentrated. The residue was dissolved in 5 ml of ethanol, and 2 g of anhydrous sodium carbonate was added. The suspension was stirred for 0.5 h and then filtered. The filtrate was cooled in ice and treated with excess 35% perchloric acid in ethanol–water. The resulting fine white precipitate was filtered, yielding 1.25 g (67%) of the monoperchlorate: mp 232–233 °C dec; IR (KBr) 3.25, 3.31, 3.37, 6.7, 9.22 μ (s, ClO_4^-); NMR (Me_2SO-d_6) δ 1.92 (m, 2, CH_2 bridge), 2.82 (m, 2, bridgehead CH), 3.35 (s, 3, NCH_3), 3.52 (m, 7, remaining protons).

Anal. Calcd for $C_8H_{15}ClN_2O_4$: C, 40.26; H, 6.33; N, 11.73. Found: C, 40.39; H, 6.40; N, 11.60.

The salt (0.202 g, 0.85 mmol) was suspended in 10 ml of methanol, and sufficient Bio-Rad AG2-X8, 50–100 mesh (OH^-) was added to dissolve the product. The mixture was then placed on a 4-g column of the above resin and eluted with 50 ml of methanol. The eluent was concentrated and residual solvent was removed azeotropically with benzene, in vacuo. This left a low-melting white solid: IR (neat) 3.39 and 3.57 (s, aliphatic CH), 5.90 μ (s, C=N); NMR (CD_3OD) δ 1.48 (m, 2, CH_2 bridge), 3.50 (m, 2, $CNCH_2$), 7.7 (m, 1, HC=N), 1.62–3.30 (remaining protons); EIMS *m/e* 138 (M), 44 (B).

3-Benzyl-2-*exo*-7-dimethyl-3,7-diazabicyclo[3.3.1]nonane (4c). To a suspension of 0.55 g (4 mmol) of aldimine **10** in 7 ml of dry tetrahydrofuran at 0 °C was added 4.4 ml of a 1.36 M solution of methyllithium in ether. The stirred solution was maintained at 0–5 °C. GLC analysis (140 °C) indicated the reaction to be 80% complete 0.5 h after completion of addition. Over the next 0.5 h, the reaction suspension was allowed to warm to room temperature, and then the excess methyllithium was destroyed with saturated aqueous ammonium chloride. The product was worked up in ether and 20% aqueous sodium hydroxide affording 0.53 g (86%) of a colorless oil: NMR (C_6H_6) δ 1.23 (d, J = 7 Hz, 3, CCH_3), 1.98 (s, 3, NCH_3); EIMS *m/e* 154 (M) 58 (B). Treatment of 0.33 g (2.1 mmol) of this with benzoyl chloride under previously described conditions[9] afforded 0.23 g (42%) of the benzamide, IR (neat) 6.13 μ (s, NC=O). This was dissolved in 5 ml of dry tetrahydrofuran and added dropwise to a saturated solution of lithium aluminum hydride in 3 ml of tetrahydrofuran. The solution was stirred and refluxed for 21 h, then cooled, and excess hydride was destroyed by addition of 30% aqueous ammonium chloride. The suspension was filtered and the insolubles were washed well with tetrahydrofuran. The filtrate and washings were combined and concentrated. The residue was dissolved in 10 ml of ether. The solution was washed once with 5 ml of 5% aqueous sodium hydroxide, cooled, and treated with excess aqueous ethanolic perchloric acid. The monoperchlorate salt separated from methanol–water, and then alcohol, as light orange needles: 0.053 g (17%); mp 160.5–161.5 °C; NMR (CD_3COCD_3) δ 1.00 (d, J = 6 Hz, 3 CCH_3), 1.70–2.27 (m, 4, CH_2 bridge and bridgehead CH), 2.80 (s, 3, NCH_3), 2.92–3.63 (m, 7, NCH_2), 3.77 (s, 2, $NCH_2C_6H_5$), 7.42 (m, 5, C_6H_5).

Anal. Calcd for $C_{16}H_{25}ClN_2O_4$: C, 55.73; H, 7.31; N, 8.12. Found: C, 55.56; H, 7.39; N, 7.90.

The free base was obtained from the monoperchlorate as a light yellow oil: NMR (C_6D_6) δ 0.93 (d, J = 6 Hz, 3, CCH_3), 1.17–1.75 (m, 4, CH_2 bridge and bridgehead CH), 2.18 (s, 3, NCH_3), 2.03–3.97 (m, 7, NCH_2), 3.39 (d, J = 14 Hz, 1, $NCH_2C_6H_5$), 3.65 (d, J = 14 Hz, 1, $NCH_2C_6H_5$), 6.98–7.58 (m, 5, C_6H_5); EIMS *m/e* 244 (M), 58 (B); GLC (170 °C) retention time 12.5 min, >95% purity.

Acknowledgments. The assistance of Mr. R. Drake, Mr. J. Haug, and Ms. K. Widiger in obtaining mass spectral and elemental analysis data is gratefully acknowledged. This research was sponsored by training grant GM 1341 from the National Institutes of Health, Department of Health, Education, and Welfare.

Registry No.—**3** (R = CH_3), 14789-33-4; **4a**, 61267-75-2; **4a** di-HBr, 61267-76-3; **4b**, 61267-77-4; **4b** di-HCl, 61267-78-5; **4c**, 61267-79-6; **4c** monoperchlorate, 61267-80-9; **5**, 61267-81-0; **5** diperchlorate, 61267-82-1; **6**, 61267-83-2; **7**, 61267-92-3; **8**, 61267-84-3; **8** di-HBr, 61267-85-4; **9** diperchlorate, 61267-87-6; **10**, 61267-88-7; **10** monoperchlorate, 61267-89-8; **10** 2-methyl derivative, 61267-90-1; **10** 2-methyl-3-benzoyl derivative, 61267-91-2; methyl iodide, 74-88-4; isopropyl bromide, 75-26-3; *N*-methylbispidine, 58324-99-5; *N*-chlorosuccinimide, 128-09-6; methyllithium, 917-54-4; benzoyl chloride, 98-88-4.

References and Notes

(1) (a) N. J. Leonard, P. D. Thomas, and V. W. Gash, *J. Am. Chem. Soc.*, **77**, 1552 (1955) (b) F. Bohlmann, D. Schumann, and C. Arndt, *Tetrahedron Lett.*, 2705 (1965); (c) M. Wiewiórowski, O. E. Edwards, and M. D. Bratek-Wiewiórowska, *Can. J. Chem.*, **45**, 1447 (1967); (d) M. Wiewiórowski and L. Lompa-Krzymień, *Rocz. Chem.*, **44**, 1219 (1970); (e) A. S. Sadykov, F. G. Kamayev, V. A. Korenevsky, V. B. Leont'ev, and Yu. A. Ustynyuk, *Org. Magn. Reson.*, **4**, 837 (1972).

(2) (a) N. S. Zefirov and S. V. Rogozina, *Russ. Chem. Rev.* (*Engl. Transl.*), **42**, 190 (1973); (b) N. S. Zefirov, *ibid.*, **44**, 196 (1975); (c) E. E. Smissman and P. C. Ruenitz, *J. Med. Chem.*, **19**, 184 (1976).

(3) (a) J. E. Douglass and T. B. Ratliff, *J. Org. Chem.*, **33**, 355 (1968); (b) M. R. Chakrabarty, R. L. Ellis, and J. L. Roberts, *ibid.*, **35**, 541 (1970).

(4) The *absolute* configurations of all chiral bicyclic compounds reported here have been assigned arbitrarily.

(5) (a) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, **77**, 439 (1955); (b) N. J. Leonard, R. W. Fulmer, and A. S. Hay, *ibid.*, **78**, 3457 (1956); (c) N. J. Leonard, L. A. Miller, and P. D. Thomas, *ibid.*, **78**, 3463 (1956).

(6) (a) H. Möhrle and S. Mayer, *Arch. Pharm.* (*Weinheim, Ger.*), **306**, 209 (1973); (b) E. B. Sanders, J. F. DeBardeleben, and T. S. Osdene, *J. Org. Chem.*, **40**, 2848 (1975).

(7) (a) W. G. Dauben, G. L. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956); (b) L. A. Paquette and P. C. Storm, *ibid.*, **92**, 4295 (1970).

(8) F. Bohlmann, D. Schumann, and H. Schulz, *Tetrahedron Lett.*, 173 (1965); see also ref 1b.

(9) E. E. Smissman and P. C. Ruenitz, *J. Org. Chem.*, **41**, 1593 (1976).

(10) R. T. LaLonde, C. F. Wong, and K. C. Das, *J. Am. Chem. Soc.*, **95**, 6342 (1973), and references cited therein.

(11) Determination of conformational requirements for observable magnetic nonequivalence of benzylic methylene protons in *N*-benzyl-2-alkylpiperidines and related compounds: (a) R. K. Hill and T. H. Chan, *Tetrahedron*, **21**, 2015 (1965); (b) R. E. Lyle, J. J. Thomas, and D. A. Walsh in "Conformational Analysis", G. Chiurdoglu, Ed., Academic Press, New York, N.Y., 1971, pp 157–164; (c) R. E. Lyle and J. J. Thomas, *Tetrahedron Lett.*, 897 (1969).

(12) For a review of the subject of chemical shift nonequivalence of geminal groups in NMR spectra, see W. B. Jennings, *Chem. Rev.*, **75**, 307 (1975).

(13) (a) M. F. Grundon and B. E. Reynolds, *J. Chem. Soc.*, 3898 (1963); (b) M. F. Grundon and B. E. Reynolds, *ibid.*, 2445 (1964).

(14) R. E. Ireland, M. I. Dawson, S. C. Welch, A. Hagenbach, J. Bordner, and B. Trus, *J. Am. Chem. Soc.*, **95**, 7829 (1973).

(15) (a) D. W. Fuhlhage and C. A. VanderWerf, *J. Am. Chem. Soc.*, **80**, 6249

(1958); (b) C. Schöpf, H. Arm, and H. Krimm, *Chem. Ber.*, **84**, 690 (1951); (c) however, the monomer **12** (R = H) has been isolated as a salt: G. Adam, *Chem. Ber.*, **101**, 1 (1968).
(16) We had expected this reduction to proceed more readily, since under these conditions the related *N*-benzoyl-*N'*-*n*-butylbispidine gave 83% of the respective *N*-benzyl derivative.[9]
(17) (a) J. Skolik, M. Wiewiórowski, and P. J. Krueger, *J. Mol. Struct.*, **5**, 461 (1970); (b) T. E. Borowiak, N. G. Bokii, and Y. T. Struchkov, *Zh. Strukt. Khim.*, **14**, 387 (1973); *Chem. Abstr.*, **79**, 24503y (1973).
(18) P. Scheiber and K. Nádor, *Acta Chim. Acad. Sci. Hung.*, **84**, 193 (1975).

Syntheses and Spectral Properties of Substituted Imidazolidones and Imidazolines

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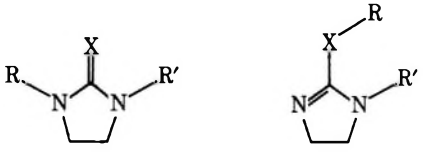
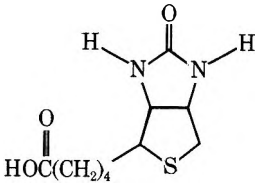
A series of substituted imidazolidones and imidazolines were synthesized as potential model compounds for the coenzyme, biotin. The syntheses and mass, infrared, ^{1}H NMR, and ^{13}C NMR spectral properties for these substrates are described. The ^{1}H NMR spectra for the acetyl substituted imidazolidones and imidazolidinethiones exhibited a characteristic downfield shift for the acetyl methyl proton (ca. δ 2.50 and 2.80, respectively). Surprisingly, the ^{1}H NMR spectra for the acyl substituted thioimidazolines consistently showed a singlet for the ethylene unit rather than the expected AA'BB' pattern. Verification of this unusual accidental equivalence in the ^{1}H NMR spectra was accomplished by the use of ^{13}C NMR. The ^{13}C NMR spectra for these compounds exhibited two distinct resonances which were attributed to the different ring carbon atoms.

Substituted imidazolidones (**1**) and imidazolines (**2**) are compounds of considerable current interest both as model



1 (X = O, S) **2** (X = O, S)

substrates for biological processes[1-7] and as chemotherapeutic agents.[8-10] As part of a current project dealing with the mechanism of biotin catalysis,[1] we synthesized a series of imidazolidones (**1**) and imidazolines (**2**) as model substrates. Compounds of types **1** and **2** possess many of the unique structural features found in biotin (**3**).[11]

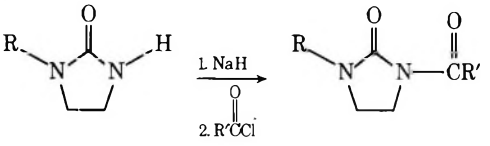


3

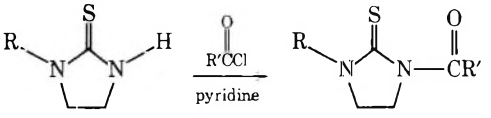
Many of the simple members of these classes of compounds have not been prepared. In this paper, we report the syntheses and characterization of these substrates, as well as a comparison of their properties to those of previously reported congeners.[12,13] Although the acyl substituted thioimidazolines prepared gave satisfactory elemental analyses, mass, and infrared spectral data, the surprising simplicity of their ^{1}H NMR necessitated a ^{13}C NMR study of these compounds. We also examined the ^{13}C NMR spectra of their counterparts, the substituted imidazolidones. The importance of ^{13}C NMR in clarifying the structural assignment of these heterocyclic molecules is outlined. In a subsequent paper, the chemistry of some of these compounds will be described.[14]

Synthesis. Tables I and II list the substrates we have prepared and pertinent infrared and ^{1}H NMR data. The majority of these substrates are new. They were prepared by a variety of synthetic routes. All new compounds gave the appropriate parent peak in the mass spectrum and satisfactory elemental analysis or high-resolution mass spectral characterization. Most of the compounds reported herein were crystalline,[15] with only the dialkyl substituted imidazolines generally being liquids.

Two general synthetic methods were adopted for the preparation of the new acyl-substituted imidazolidones and imidazolidinethiones. The imidazolidones (**9, 10, 12,** and **13**) were synthesized by the prior formation of the corresponding imidazolidone anion, followed by the addition of the acylating



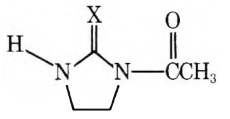
agent. By comparison, in the sulfur series (**16, 18, 19, 20, 21,** and **22**), the acylating agent was introduced to a solution containing both the imidazolidinethione and pyridine. Although the method of choice for the preparation of the substituted imidazolidones was the initial formation of the anion, these substrates could be prepared in lower yields by a method analogous to that used for the imidazolidinethiones. The re-



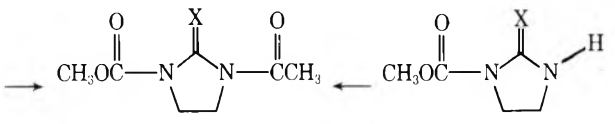
duced reactivity observed in the oxygen series appears to stem from the decreased nucleophilicity of the imidazolidone's ring carbonyl group as compared to the thione group in the imidazolidinethiones.[16] In an experiment to verify this reactivity pattern, procedures comparable to those employed in the syntheses of **18** and **21** (CH_2Cl_2, reflux) were adopted for the preparation of **8** and **12**. Even though the reaction times were doubled in the imidazolidone series, considerably lower yields were observed for these reactions.[14]

The molecular structure assigned by us for each of these acyl substrates was the N,N'-disubstituted products rather than the isomeric N,O- or N,S-substituted imidazolines.

Support for this assignment stems from a variety of sources, the foremost being (1) literature precedent,[1,4,12,13,17] (2) the correlation of spectral absorptions with structure, (3) the synthesis and characterization of alternate isomers (cf. **8** vs. **27**, **9** vs. **28**, **18** vs. **32**, and **19** vs. **37**), and (4) the subsequent derivatization of some of these substrates.[1,14] Additional chemical support for N,N′ disubstitution pattern stems from the syntheses of **12** and **21**. In these cases, the diacylated compounds (**12** and **21**) could be easily prepared from the corresponding *N*-acetyl (**5** and **15**) or the *N*-carbomethoxy (**6** and **16**) derivatives.



5, X = O
15, X = S

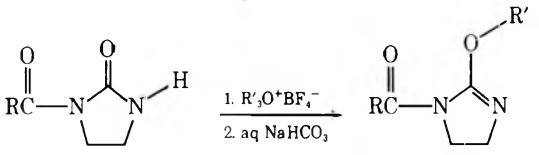


12, X = O
21, X = S

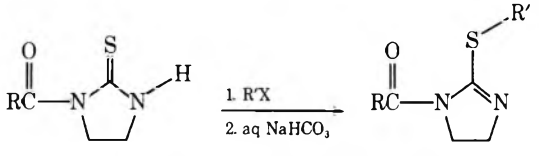
6, X = O
16, X = S

Although no mechanistic studies were conducted, analogy with previous work suggests two likely possibilities.[4,12,13,17] One involves the initial formation of the oxygen or sulfur bound imidazoline, followed by a Chapman-type rearrangement[16,18-22] to the N,N′-disubstituted product, while the other involves direct acylation of one of the ring nitrogen atoms of the imidazolidone or imidazolidinethione. Of these two mechanisms, the former has enjoyed the widest support.[16,18-22]

The *O*-alkyl-*N*-acylimidazolines (**27**, **28**, and **29**) were prepared by the addition of either trimethyloxonium[23] or triethyloxonium fluoroborate[24] (Meerwein salts) to a solution containing the starting acyl imidazolidone. When less reactive alkylating agents, alkyl halides, were used in place of the Meerwein salts, only the starting acyl imidazolidones were recovered ($CHCl_3$, 40 °C, 5 days).[14]

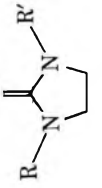


Syntheses of the corresponding substituted thioimidazolines were generally accomplished by one of two methods. Unlike the preparation of the acyl imidazolines, the acyl imidazolidinethiones readily underwent direct S-alkylation with the alkyl halides, to give the desired products (**32**, **37**, **38**, and **43**). These results are in accord with the reactivity pattern



previously observed for these substrates.[16] Alternatively, these compounds (**34**, **35**, **39**, **40**, **41**, **42**, and **43**) were prepared by the introduction of the alkylating agent to a solution containing both the starting substrate and triethylamine. In the cases where both methods were utilized, the second method gave slightly higher yields.[1,14,25] Comparison of the experimental yields for the S-alkylation of *N*-acetylimidazoli-

Table I. Summary of Selected Physical and Spectral Properties of the Substituted Imidazolidones



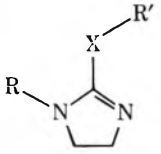
No.	X	R	R′	Bp,[a] °C	Mp,[a] °C	IR data[b]			¹H NMR data[c]			
						X=C–N	O=NCR	Other	NCH_3	$-CH_2CH_2-$	$-\overset{O}{\overset{\|}{C}}CH_3$	$-\overset{O}{\overset{\|}{C}}OCH_3$
4	O	H	CH_3[d]		114–115			1690, 1510	2.75	3.40		
5	O	H	O=CCH$_3$[e]		176–180	1750	1645			3.25–4.14	2.50	
6	O	H	O=COCH$_3$[f]		179–180		1750	1640		3.23–4.07		3.80
7	O	CH_3	CH_3[g]	106–108 (17 mm)		1710[h]			2.75	3.25		
8	O	CH_3	O=CCH$_3$[i]		78–81	1730	1670		2.80	3.20–3.95	2.40	
9	O	CH_3	O=COCH$_3$		56–59	1720	1760	1805	2.81	3.20–3.95		3.80
10	O	CH_3	O=COCH$_2$CH$_3$	128 (0.30 mm)		1720	1760	1800	2.82	3.20–4.00		
11	O	O=CCH$_3$	O=CCH$_3$[i]		126–127	1750, 1760[i]	1700, 1710[i]			3.80	2.52	
12	O	O=CCH$_3$	O=COCH$_3$		143–145	1715	1695, 1750			3.82	2.48	3.85
13	O	O=COCH$_3$	O=COCH$_3$		233–239	1785	1760			3.85		3.95
14	S	H	CH_3[j]		131.5–132	1510, 1520			3.12	3.52–3.77		
15	S	H	O=CCH$_3$[i]		165–167	1530	1650			3.38–4.41	2.85	
16	S	H	O=COCH$_3$[k]		156–158		1750	1675		3.37–4.32		3.82
17	S	CH_3	CH_3[l]		108–110	1510			3.13	3.60		

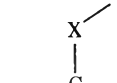
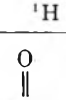
Ph. 5 April 1978

18	S	CH_3	$O{=}CCH_3$	81–82	1520	1665		3.22	3.40–4.25	2.80		
19	S	CH_3	$O{=}COCH_3$	111–112.5	1515	1745		3.17	3.44–4.23		3.82	
20	S	$O{=}CCH_3$	$O{=}CCH_3$[i]	87–89	1470	1685			3.95	2.77		
21	S	$O{=}CCH_3$	$O{-}COCH_3$	95–97		1690, 1760	1710		4.05	2.84	3.87	
22	S	$O{=}COCH_3$	$O{=}COCH_3$	198–199.5		1735, 1765			3.97		3.80	

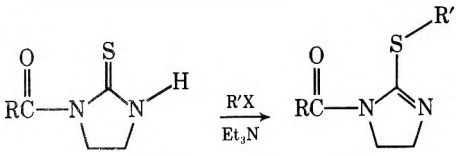
[a] Boiling and melting points are uncorrected. [b] Infrared peak position recorded in cm^{-1} vs. the 1601-cm^{-1} band in polystyrene and were taken in KBr disks unless otherwise noted. [c] ^1H NMR chemical shift value (δ) recorded vs. Me_4Si in $CDCl_3$. [d] Reference 40. [e] Reference 17. [f] Reference 4. [g] A. B. A. Jansen and P. J. Stokes, *J. Chem. Soc.*, 4909 (1962). [h] Infrared taken in $CHCl_3$ in matching cells. [i] Reference 12. [j] Reference 41. [k] Reference 1. [l] L. Maier, *Helv. Chim. Acta*, **53**, 1417 (1970).

Table II. Summary of Selected Physical and Spectral Properties of the Substituted Imidazolines



						IR data[b]			^1H NMR data[c]					
No.	X	R	R′	Bp,[a] °C	Mp,[a] °C			Other	NCH_3	$-CH_2CH_2-$			$-XCH_3$	$-XCH_2-$
23	O	H	CH_3[d]		86–87	1625		1601		3.59			3.81	
24	O	H	CH_2CH_3[d]		50–51	1635				3.62				4.24 (q, J = 7.0)
25	O	CH_3	CH_3	127–128		1640[e]		1505	2.65	3.07–3.70			3.80	
26	O	CH_3	CH_2CH_3	71 (25 mm)		1635[f]			2.63	3.20–3.72				4.20 (q, J = 7.5)
27	O	$O{=}CCH_3$	CH_3		39–42	1645	1680			3.42–4.12	2.28		3.93	
28	O	$O{=}COCH_3$	CH_3		79–82	1650	1740			3.63–4.10		3.77	3.95	
29	O	$O{=}COCH_3$	CH_2CH_3		67–70	1655	1760			3.40–4.08		3.76		4.33 (q, J = 7.0)
30	S	H	CH_3[d]		102–107	1560				3.24–4.17			2.49	
31	S	CH_3	CH_3	31 (0.15 mm)		1590[e]			2.75	3.08–3.94			2.49	
32	S	$O{=}CCH_3$	CH_3		112–113.5	1580	1670			3.97	2.18		2.40	
33	S	$O{=}CCH_3$	CH_2CH_3		56.5–58.5	1580	1670			3.92	2.18			2.87 (q, J = 7.5)
34	S	$O{=}CCH_3$	$CH_2CH{=}CH_2$	130 (0.2 mm)		1590[e]	1680			3.98	2.20			3.55–3.75 (m)
35	S	$O{=}CCH_3$	$CH_2Ph(p\text{-}F)$		138–139	1585	1670			3.92	2.18			4.20
36	S	$O{=}CCH_3$	$CH_2C(=O)Ph$[g]		149–149.5	1575	1670	1670		3.90	2.18			4.48
37	S	$O{=}COCH_3$	CH_3		103.5–105.5	1585	1715			3.88		3.77	2.40	
38	S	$O{=}COCH_3$	CH_2CH_3		71–73.5	1590	1710			3.84		3.73		2.97 (q, J = 7.5)
39	S	$O{=}COCH_3$	$CH_2CH{=}CH_2$	97–98 (0.19 mm)	32–33.5	1585[e]	1715			3.90		3.80		3.55–3.82 (m)
40	S	$O{=}COCH_3$	$CH_2C(=O)CH_3$		73–75	1585	1705	1705		3.82		3.75		3.79
41	S	$O{=}COCH_3$	$CH_2COOCH_2CH_3$		66–67	1600	1710	1755		3.91		3.83		3.83
42	S	$O{=}COCH_3$	$CH_2Ph(p\text{-}F)$		101.5–102	1585	1725			3.85		3.71		4.15
43	S	$O{=}COCH_3$	$CH_2C(=O)Ph$[h]		153.5–155.5	1580	1715	1670		3.87		3.78		4.54

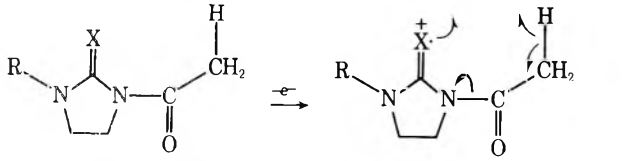
[a] Boiling and melting points are uncorrected. [b] Infrared peak positions recorded in cm^{-1} vs. the 1601-cm^{-1} band in polystyrene, and were taken in KBr disks unless otherwise noted. [c] ^1H NMR chemical shift value (δ) recorded vs. Me_4Si in $CDCl_3$. [d] G. I. Poos, J. Kleis, and C. K. Cain, *J. Org. Chem.*, **24**, 645 (1959). [e] Infrared taken neat on NaCl plates. [f] Infrared taken in CCl_4 in matching cells. [g] Reference 25. [h] Reference 1.



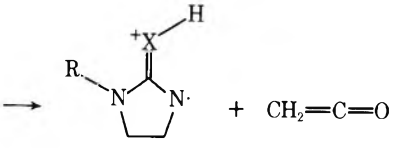
dinethione vs. that for the corresponding *N*-carbomethoxyimidazolidinethione with a variety of alkylating agents also showed that consistently higher yields were obtained for the *N*-carbomethoxy derivatives. Despite efforts to increase the conversion in the former series of compounds by increasing the reaction times, reaction temperatures, and the ratio of alkylating agent to starting material, only moderate yields were observed.[14] This reactivity pattern appears to be a reflection of the enhanced nucleophilicity of the thione group in the *N*-carbomethoxyimidazolidinethiones vs. the thione group in the *N*-acetyl compounds.

Mass Spectral Data. Each substituted acyl imidazolidone and imidazoline gave a discernible parent peak in the mass spectrum (ionization voltage 70 eV). Two distinct modes of cleavage emerge upon examination of the fragmentation patterns for these compounds.

A significant feature in the breakdown patterns for the *N*-acetyl substituted imidazolidones (**44**, X = O) (compound **12**) and imidazolidinethiones (**44**, X = S) (compounds **18**, **20**, and **21**) was the P − 42 peak. Similarly the *N*-carbomethoxy substituted imidazolidones (**46**, X = O) (compounds **9** and **13**) and imidazolidinethiones (**46**, X = S) (compounds **16**, **19**, **21**, and **22**) gave a characteristic P − 58 fragment. Both of these

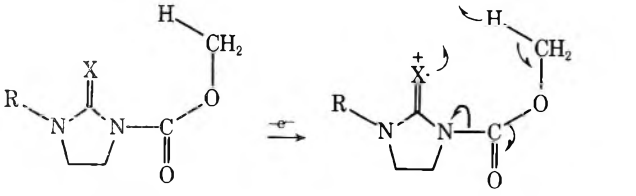


44 (X = O,S)

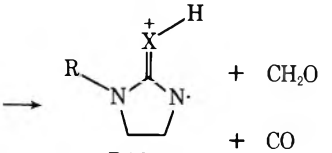


P-42

45



46 (X = O,S)

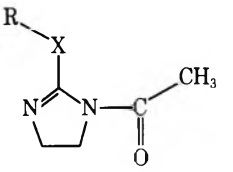


P-58

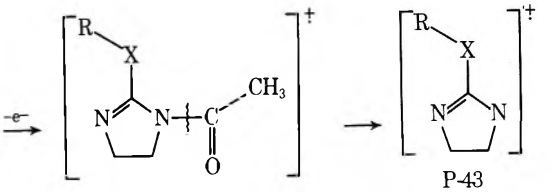
47

peaks can be rationalized in terms of a McLafferty type rearrangement[26,27] of the starting molecular ion to give **45** and **47**, respectively.

This pattern was not observed in the *N*-acyl substituted imidazolines and thioimidazolines. Instead the *N*-acetyl derivatives (**48**) (compounds **27**, **32**–**35**) gave a diagnostic peak at P − 43, while the *N*-carbomethoxy substrates (**50**) (compounds **28**, **29**, **37**–**39**) gave rise to a peak at P − 59. Cleavage of the bond adjacent to the ring with loss of O=CCH$_3$ and O=COCH$_3$, respectively, accounts for these peaks.[26,27]

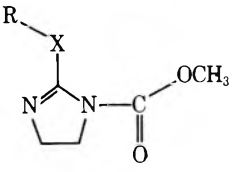


48 (X = O,S)

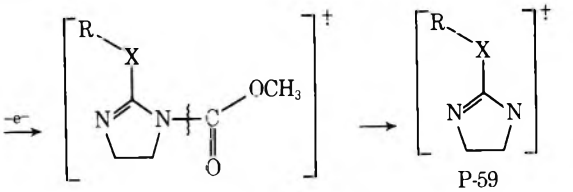


P-43

49



50 (X = O,S)



P-59

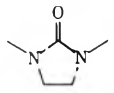
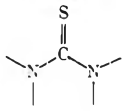
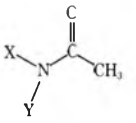
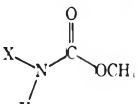
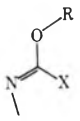
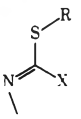
51

The composite set of mass spectral data for all newly prepared acyl substituted imidazolidones and imidazolines reveals that exceptions do exist to these generalizations. The mass spectral data provide helpful but not conclusive evidence for structure.

Infrared Spectral Data. The infrared group frequencies which have been reported for thioureas, ureas, and cyclic derivatives are sketchy.[28,29] Furthermore, the examples which have been cited do not reveal an invariant set of frequencies. We have constructed the following table (Table III) to summarize the literature values found in Bellamy,[28,29] Nakanishi,[30] and our work. We also note the number of cases observed in our study for each structural type. Even though a substantial number of examples agree with expectation, we have recorded enough exceptions that we feel these frequencies are not unique diagnostic tools. For example, **4** and **6** do not exhibit the expected urea carbonyl band at ca. 1720 cm^{-1},[30] but instead show enolic absorptions at 1690 and 1640 cm^{-1}, respectively. Compounds **9** and **10** exhibit extra strong absorptions in the carbonyl region at 1805 and 1800 cm^{-1}, respectively. Compound **16** is characterized by a 1675-cm^{-1} band, a feature for which we have no explanation. Finally, we could not confidently find the three sets of bands abscribed to thioureas.[29] In most cases the high-frequency absorption was easily observed, but every assignment of the lower frequency bands we attempted to make was ambiguous.

Our experience with the interpretation of the infrared spectra of these 40 compounds leads us to the following generalizations. The cyclic imine band characteristic of compounds in Table II exhibits a reliable infrared absorption at 1655–1600 cm^{-1} (X = O) and 1605–1560 cm^{-1} (X = S), and is useful in structure elucidation. In contrast, the ring carbonyl and thione frequencies for the substituted imidazolidones and

Table III. Summary of Selected Infrared Group Frequencies

Functional group	Lit. values, cm^{-1}	Obsd values, cm^{-1}	No. of observations
	1720[a]	1750–1712	7
	1570–1395[b] 1420–1260 1140– 940	1530–1470	6
	1650[a,c]	1710–1645	14
	1740–1690[a] 1736–1700[c]	1765–1705	18
	1665[b]	1655–1600	7
	1611[b]	1605–1560	14

[a] Reference 30. [b] Reference 29. [c] Reference 28.

imidazolidinethiones are much less reliable and do not provide a conclusive demonstration of the absence or presence of these functional groups.

Magnetic Resonance Data. ^{1}H NMR. We routinely recorded ^{1}H NMR spectra of all the compounds in this study, in order to characterize the structure unambiguously. Unfortunately, this expectation was not realized. The chemical shift for the protons of the substituted imidazolidones and imidazolidinethiones are recorded in Table I. The *N*-methyl, the *N*-carbomethoxymethyl, and the ring ethylene protons all exhibited chemical shifts in regions previously assigned.[31,32] The ethylene pattern was an AA′BB′ spin system for the asymmetric substituted compounds and was an A_4 singlet for the symmetric substituted compounds. In three instances (compounds **4, 12,** and **21**) the near equivalence of the substitution on the two nitrogens gave rise to accidental equivalence of the ring ethylene protons.

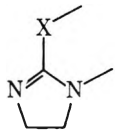
The consistent appearance of the *N*-acetyl methyl group at ca. δ 2.50 in the substituted imidazolidones and ca. δ 2.80 in the sulfur analogues was at lower field than we anticipated.[31,32] Greenhalgh and Weinberger[13] have noted downfield shifts in a related series of compounds, and have explained the observations in terms of anisotropy and of selective population of a particular conformer. Whatever the cause, we note that the *N*-acetyl imidazolidones exhibit a diagonistic peak at δ 2.40–2.52, and the *N*-acetyl imidazolidinethiones at δ 2.75–2.85.[33]

The chemical shifts of N-substituted imidazolines and thioimidazolines can be identified by correlation charts.[31,32] Indeed the *N*-methyl, *N*-carbomethoxymethyl, and even the *N*-acetyl methyl resonances occur at the expected values.

The chemical shifts of the ethylene protons agree well with previous correlation charts.[31,32] As expected, the oxygenated compounds of Table II exhibited the AA′BB′ spectra that are required by their symmetry. Thus we were astonished by the simple single absorption for the ring ethylene protons that was invariably observed for the *N*-acetyl- and *N*-carbomethoxythioimidazolines. The highly asymmetric substitution patterns for these compounds cannot be easily reconciled with accidental degenerate $-CH_2CH_2-$ resonances. The use of a variety of solvents ($CDCl_3$, CD_3CN, $C_6H_5NO_2$) did not lift the degeneracy. In one case (compound **37**) the effect of benzene-d_6 caused the singlet to become a perceptibly more complicated pattern [δ 3.25–3.53 (m, 4 H)]. Varying the temperature of the NMR sample of compound **37** between −40 and 30 °C did not lift the degeneracy.

Our inability to alter the $-CH_2CH_2-$ singlet resonance in these classes of compounds (12 substrates) led us to consider alternative structures and/or kinetic processes which interconvert alternative structures, as well as to question the correctness of the topological description of this whole class of compounds. ^{13}C NMR, however, provides an immediate indication of whether the ^{1}H spectra require a special explanation.

^{13}C NMR. Examination of the proton decoupled ^{13}C NMR spectrum[35] of six of the *N*-acyl substituted thioimadozolines (**32, 36–38, 40,** and **43**) of Table II gave the expected number of signals for carbons bound to hydrogens. In a few cases the low intensity of the quaternary carbons precluded the confident assignment of these atoms. The key observation is the consistent appearance of two resonances in the indicated shift range, separated by ca. 6 ppm for the two carbons in the ring ethylene bridge. The identity of these two carbons was assured



53.8- 47.0-
54.5 48.6

by observing triplets, J = 144 and 142 Hz, for the resonances at δ 48.1 and 53.8 in the proton coupled spectra of compound **32.** Additionally, triplets, J = 150 and 145 Hz, occurred at δ 47.9 and 54.2 in the spectrum of compound **43.** Using these chemical shifts as references we made consistent assignments to the ethylene resonances in the remaining compounds. Under ordinary ^{13}C NMR conditions, there is no convenient observation to assign the two resonances separately, so we assign them as a set. The values recorded for the carbons of the ethylene bridge may be reversed, but the pattern of shifts makes the paired assignment certain. The consistent appearance of two ^{13}C NMR signals for the ethylene bridge verifies the structure and assures that the ^{1}H NMR results from accidental equivalence. The remaining resonances were assigned from proton coupling constants, correlation charts,[36–39] and internal consistency.

Model compounds have been reported by Jackman and Jen.[36] Their ^{13}C NMR assignments accord well with ours with a single exception. We suggest that the resonances recorded as C-4 and C-6 in their Table VIII should be reversed.

The ^{13}C NMR spectra[35] of eight of the imidazolidones (**4, 9, 13, 16–19,** and **22**) which appear in Table I were recorded. In those cases where the substituents at the two nitrogen atoms differed, two resonances for the ring ethylene carbons were noted. The assignments were made as before. We find nothing unusual in these shifts and present them without comment.

In extensions of this work, we have relied extensively upon the assignments of the chemical shift values observed in this study to provide positive identification of other analogues. The complete data set and two histograms which summarize all of the ^{13}C NMR data appear in the microfilm edition of this journal.

Experimental Section

General. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on Perkin-Elmer Model 700 and 237B spectrometers and calibrated against the 1601-cm^{-1} band of polystyrene. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Varian Associates Model T-60 and EM-390 instruments. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were determined on Bruker Models HFX-90 and WH-90, JEOL Model FX60H, and Varian Associates Models CFT-20 and XL-100-15 spectrometers. The XL-100 was equipped with a Nicolet Technology Corp. TT-100 data system.

Chemical shifts are expressed in parts per million relative to Me_4Si, and coupling constants (J values) in hertz. Spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Mass spectral (MS) data were obtained at an ionizing voltage of 70 eV on a Hitachi Perkin-Elmer Model RMU-6H mass spectrometer. High-resolution mass spectra were performed by Dr. James Hudson at the Department of Chemistry, Rice University, on a CEC21-110B double focusing magnetic sector spectrometer at 70 eV. Exact masses were determined by peak matching. Elemental analyses were obtained at Spang Microanalytical Laboratories, Ann Arbor, Mich.

The solvents and reactants were of the best commercial grade available and were used without further purification unless noted. When dry solvents were required, CH_2Cl_2 was distilled from P_2O_5, benzene was distilled and then stored over sodium, dimethylformamide was stored over sodium sulfate and then distilled from CaH_2, and anhydrous ether was stored over sodium metal. All reactions were run under nitrogen, and all glassware dried before use.

Materials. All previously reported substrates were synthesized by their literature procedures unless otherwise indicated. The physical and spectral properties observed for these compounds were generally in good agreement with the reported values.

***N*-Carbomethoxy-*N'*-methylimidazolidone (9).** NaH (50% mineral oil dispersion) (2.75 g, 0.05 mol) was washed with benzene (3 × 50 ml) and then an additional 50 ml of benzene was added. A benzene solution (250 ml) of **4**[40] (4.00 g, 0.04 mol) was slowly added (5 h), followed by 4.4 ml (0.05 mol) of methyl chloroformate. The solution was stirred for 18 h at room temperature, filtered, and evaporated in vacuo. Fractional recrystallization from Et_2O gave 3.93 g (62%) of the desired product: selected ^{13}C NMR ($CDCl_3$) 40.6, 43.2 ppm (CH_2CH_2); MS *m/e* (rel %) 158 (100), 138 (13), 113 (17), 100 (35), 99 (33), 98 (35), 70 (39).

Anal. Calcd for $C_6H_{10}N_2O_3$: C, 45.56; H, 6.37; N, 17.71. Found: C, 45.68; H, 6.27; N, 17.69.

***N*-Carboethoxy-*N'*-methylimidazolidone (10).** The preceding reaction was repeated using 1.44 g (0.03 mol) of NaH (50% mineral oil dispersion), 2.00 g (0.02 mol) of **4**,[40] and 2.9 ml (0.03 mol) of ethyl chloroformate. Distillation gave 4.58 g (67%) of a white semisolid: MS *m/e* (rel %) 172 (42), 128 (12), 99 (100), 70 (21), 56 (24).

Anal. Calcd for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.03; N, 16.27. Found: C, 48.90; H, 7.04; N, 15.81.

***N*-Acetyl-*N'*-carbomethoxyimidazolidone (12). Method A.** This compound was synthesized in 55% yield (1.02 g) from 0.62 g (0.013 mol) of NaH (50% mineral oil dispersion), 1.28 g (0.01 mol) of **5**,[17] and 1.0 ml (0.013 mol) of methyl chloroformate using the method described for the preparation of **9**. Reprecipitation of the white solid from chloroform–hexanes gave the purified product: MS *m/e* (rel %) 186 (26), 158 (40), 144 (38), 88 (100), 59 (26), 56 (26).

Anal. Calcd for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.42; N, 15.05. Found: C, 45.12; H, 5.32; N, 15.10.

***N*-Acetyl-*N'*-carbomethoxyimidazolidone (12). Method B.** Acetyl chloride (0.4 ml, 0.007 mol) was added to a stirred CH_2Cl_2 suspension (25 ml) of **6**[4] (0.72 g, 0.005 mol) and pyridine (0.4 ml, 0.005 mol). The mixture was refluxed for 48 h. The resulting solution was washed with H_2O (2 × 30 ml), dried (Na_2SO_4), and evaporated in vacuo. Reprecipitation of the white solid from chloroform–hexanes gave purified product, yield 0.37 g (40%).

***N,N'*-Dicarbomethoxyimidazolidone (13).** NaH (50% mineral oil dispersion) (4.80 g, 0.1 mol) was washed with DMF (3 × 75 ml) and an additional 20 ml of DMF was added. Imidazolidone (2.15 g, 0.025 mol) in DMF (50 ml) was then slowly added (5 h), followed by 7.0 ml (0.1 mol) of methyl chloroformate. The reaction was exothermic, and the mixture was allowed to stir at room temperature for 18 h. The mixture was filtered and the filtrate evaporated in vacuo. The yellow-brown residue was taken up in H_2O (50 ml) and continuously extracted (48 h) with CH_2Cl_2. The CH_2Cl_2 was dried (Na_2SO_4) and evaporated in vacuo. The yellow-white solid was chromatographed on a neutral alumina column (15 × 2.3 cm) using $CHCl_3$ as the eluent. The first eluted material was the desired product. The title compound was further purified by reprecipitation from chloroform–hexanes: yield 1.28 g (25%); selected ^{13}C NMR ($CDCl_3$) 39.9 ppm (CH_2CH_2); MS *m/e* (rel %) 202 (29), 158 (100), 144 (37), 113 (17).

Anal. Calcd for $C_7H_{10}N_2O_5$: C, 41.59; H, 4.99; N, 13.86. Found: C, 41.27; H, 4.85; N, 14.09.

***N*-Acetyl-*N'*-methylimidazolidinethione (18).** To a stirred CH_2Cl_2 solution (100 ml) containing **14**[41] (4.64 g, 0.04 mol) and pyridine (3.16 g, 0.04 mol), acetyl chloride (2.8 ml, 0.04 mol) was slowly added. The solution was refluxed overnight and then washed with H_2O (2 × 60 ml), dried (Na_2SO_4), and evaporated in vacuo. Purification of the desired compound was accomplished by reprecipitation from carbon tetrachloride–hexanes: yield 4.35 g (69%); selected ^{13}C NMR ($CDCl_3$) 44.3, 47.5 ppm (CH_2CH_2); MS *m/e* (rel %) 158 (100), 116 (50), 115 (27), 72 (14).

Anal. Calcd for $C_6H_{10}N_2OS$: C, 45.54; H, 6.37; N, 17.71. Found: C, 45.61; H, 6.40; N, 17.76.

***N*-Carbomethoxy-*N'*-methylimidazolidinethione (19).** The preceding reaction was repeated using 4.64 g (0.04 mol) of **14**,[41] 6.32 g (0.08 mol) of pyridine, and 60.0 ml (0.78 mol) of methyl chloroformate. The exothermic reaction was kept under control (moderate CH_2Cl_2 reflux) by adjusting the rate of addition of methyl chloroformate. Recrystallization from CCl_4 afforded 3.75 g (54%) of the desired product: selected ^{13}C NMR ($CDCl_3$) 44.5, 48.5 ppm (CH_2CH_2); MS *m/e* (rel %) 174 (100), 116 (48), 115 (24), 72 (32).

Anal. Calcd for $C_6H_{10}N_2O_2S$: C, 41.36; H, 5.79; N, 16.08. Found: C, 41.34; H, 5.66; N, 16.08.

***N*-Acetyl-*N'*-carbomethoxyimidazolidinethione (21). Method A.** Using the method described for the preparation of **18**, **21** was synthesized from 4.00 g (0.025 mol) of **16**,[1] 1.98 g (0.025 mol) of pyridine, and 2.5 ml (0.035 mol) of acetyl chloride. Purification of **21** was accomplished by reprecipitation from chloroform–hexanes: yield 4.11 g (81%); MS *m/e* (rel %) 202 (66), 160 (100), 144 (87), 102 (95), 88 (35), 74 (34), 72 (66).

Anal. Calcd for $C_7H_{10}N_2O_3S$: C, 41.57; H, 4.98; N, 13.85. Found: C, 41.68; H, 4.97; N, 13.82.

***N*-Acetyl-*N'*-carbomethoxyimidazolidinethione (21). Method B.** Using the method described for the preparation of **18**, **21** was synthesized from 0.86 g (0.006 mol) of **15**,[12] 0.95 g (0.012 mol) of pyridine, and 7.2 ml (0.093 mol) of methyl chloroformate. The exothermic reaction was kept under control (moderate CH_2Cl_2 reflux) by adjusting the rate of addition of methyl chloroformate. The solution was refluxed for 72 h. Purification of **21** was accomplished by reprecipitation from chloroform–hexanes; yield 0.75 g (60%).

***N,N'*-Dicarbomethoxyimidazolidinethione (22).** Compound **22** was synthesized in 33% yield (1.45 g) from 2.04 g (0.02 mol) of imidazolidinethione, 4.74 g (0.06 mol) of pyridine, and 23.3 ml (0.30 mol) of methyl chloroformate using the method described for the preparation of **18**. The exothermic reaction was kept under control (moderate CH_2Cl_2 reflux) by adjusting the rate of addition of methyl chloroformate. Reprecipitation from chloroform–hexanes gave purified **22**: selected ^{13}C NMR ($CDCl_3$) 44.7 ppm (CH_2CH_2); MS *m/e* (rel %) 218 (100), 160 (66), 102 (23), 88 (52), 72 (69).

Anal. Calcd for $C_7H_{10}N_2O_4S$: C, 38.52; H, 4.62; N, 12.84. Found: C, 38.70; H, 4.68; N, 12.84.

***N*-Methyl-2-methoxyimidazoline (25).** A methanolic solution (20 ml) containing *N*-methyl-2-methylthioimidazolinium hydriodide[41] (5.10 g, 0.02 mol) was added to 20 ml of a freshly prepared 2.5 N NaOMe–MeOH (0.05 mol) solution. The solution was refluxed for 24 h and filtered and then 20 ml of H_2O added. The solution was continuously extracted with CH_2Cl_2 for 18 h, and the organic layer dried (Na_2SO_4) and evaporated in vacuo. Bulb-to-bulb distillation at 55 °C (0.45 mm) gave 0.78 g (34%) of the desired compound, a clear liquid: MS *m/e* (rel %) 114 (56), 113 (42), 99 (35), 84 (12), 71 (26), 56 (100); mol wt 114.0791 (calcd for $C_5H_{10}N_2O$, 114.0793).

***N*-Methyl-2-ethoxyimidazoline (26).** The preceding reaction was repeated using an ethanolic solution (50 ml) containing 5.10 g (0.02 mol) of *N*-methyl-2-methylthioimidazolinium hydriodide[41] and 20 ml (0.05 mol) of 2.5 N NaOEt–EtOH solution. Distillation gave 1.64 g (64%) of the desired compound, a clear liquid: selected ^{13}C NMR ($CDCl_3$) 48.9, 53.6 ppm (CH_2CH_2); MS *m/e* (rel %) 128 (100), 114 (12), 99 (71), 87 (25).

Anal. Calcd for $C_6H_{12}N_2O$: C, 56.22; H, 9.44; N, 21.86. Found: C, 56.25; H, 9.51; N, 21.84.

***N*-Acetyl-2-methoxyimidazoline (27).** To 0.64 g (0.005 mol) of **5**,[17] 1.11 g (0.0075 mol) of trimethyloxonium fluoroborate[23] in CH_3NO_2 (7 ml) was slowly added. The solution was heated at 35 °C for 18 h, and then Et_2O (20 ml) added causing the separation of an oil. The supernatant layer was decanted off, and the remaining oil dried

in vacuo. CH_2Cl_2 (10 ml) was then added, and the mixture neutralized with aqueous 5% $NaHCO_3$ (10 ml). The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The desired product was further purified by sublimation (40 °C, 0.1 mm) to yield 0.81 g (29%) of white crystals; MS *m/e* (rel %) 142 (2), 113 (39), 99 (36), 56 (100).

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.55; H, 7.15; N, 19.57.

***N*-Carbomethoxy-2-methoxyimidazoline (28).** The preceding reaction was repeated using 1.44 g (0.01 mol) of **6**[4] and 2.96 g (0.02 mol) of trimethyloxonium fluoroborate.[23] After the addition of aqueous 5% $NaHCO_3$ (20 ml) the CH_2Cl_2–H_2O mixture was continuously extracted (~8 h) with CH_2Cl_2. The organic layer was then dried (Na_2SO_4) and evaporated in vacuo, and the title compound further purified by two successive sublimations (30 °C, 0.05 mm) to give 0.36 g (11%) of white crystals: selected ^{13}C NMR ($CDCl_3$) 47.6, 47.7 ppm (CH_2CH_2); MS *m/e* (rel %) 158 (80), 143 (10), 127 (15), 99 (19), 71 (43), 56 (100).

Anal. Calcd for $C_6H_{10}N_2O_3$: C, 45.56; H, 6.37; N, 17.71. Found: C, 45.58; H, 6.44; N, 17.57.

***N*-Carbomethoxy-2-ethoxyimidazoline (29).** To 0.72 g (0.005 mol) of **6**,[4] 1.90 g (0.01 mol) of triethyloxonium fluoroborate[24] in CH_2Cl_2 (50 ml) was slowly added. The solution was refluxed for 18 h, then washed with aqueous 5% $NaHCO_3$ (2 × 20 ml) and H_2O (20 ml). The CH_2Cl_2 solution was dried (Na_2SO_4) and evaporated in vacuo. The desired compound was purified by sublimation (35 °C, 0.05 mm) to yield 0.48 g (78%) of white crystals: MS *m/e* (rel %) 172 (44), 144 (72), 143 (26), 113 (39), 88 (100).

Anal. Calcd for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.03; N, 16.27. Found: C, 48.74; H, 7.10; N, 16.27.

***N*-Acetyl-2-methylthioimidazoline (32).** The preceding reaction was repeated using 5.76 g (0.04 mol) of **15**[12] and 5.0 ml (0.08 mol) of MeI. The reaction solution was refluxed for 72 h, during which time the *N*-acetyl-2-methylthioimidazolinium hydriodide salt precipitated out. The salt was collected and then neutralized using the procedure described above. Purification was accomplished by reprecipitation from carbon tetrachloride–hexanes: yield 2.43 g (38%); selected ^{13}C NMR ($CDCl_3$) 48.1 (t, $J_{^{13}C-H}$ = 144 Hz), 53.8 ppm (t, $J_{^{13}C-H}$ = 142 Hz) (CH_2CH_2); MS *m/e* (rel %) 158 (47), 143 (98), 116 (82), 115 (56), 87 (100), 72 (47).

Anal. Calcd for $C_6H_{10}N_2OS$: C, 45.54; H, 6.37; N, 17.71. Found: C, 45.55; H, 6.28; N, 17.59.

***N*-Acetyl-2-ethylthioimidazoline (33).** Using the method described for the preparation of **29, 33** was synthesized from 1.44 g (0.01 mol) of **15**[12] and 2.09 g (0.011 mol) of triethyloxonium fluoroborate.[24] The reaction mixture was allowed to stand at room temperature overnight. The desired compound was purified by reprecipitation from chloroform–hexanes: yield 1.51 g (88%); MS *m/e* (rel %) 172 (17), 157 (7), 144 (72), 143 (29), 129 (33), 102 (100), 101 (19), 97 (48), 72 (41), 70 (33).

Anal. Calcd for $C_7H_{12}N_2OS$: C, 48.81; H, 7.02; N, 16.27. Found: C, 48.63; H, 6.93; N, 16.13.

***N*-Carbomethoxy-2-methylthioimidazoline (37).** Compound **37** was synthesized in 61% yield (5.32 g) from 8.00 g (0.05 mol) of **16**[1] and 6.3 ml (0.10 mol) of MeI using the method described for the preparation of **29.** The reaction mixture was refluxed for 72 h. The desired product was purified by reprecipitation from carbon tetrachloride–hexanes: NMR ($CDCl_3$) δ 2.40 (s, 3 H), 3.77 (s, 3 H), 3.88 (s, 4 H) (the three peaks remained singlets at −40 °C); (CD_3CN) δ 2.32 (s, 3 H), 3.68 (s, 3 H), 3.80 (s, 4 H); ($C_6H_5NO_2$) δ 2.43 (s, 3 H), 3.84 (s, 7 H); (C_6D_6) δ 2.32 (s, 3 H), 3.25–3.53 (m, 4 H), 3.42 (s, 3 H); selected ^{13}C NMR ($CDCl_3$) 47.7, 54.1 ppm (CH_2CH_2); MS *m/e* (rel %) 174 (100), 115 (66), 87 (47), 72 (64).

Anal. Calcd for $C_6H_{10}N_2O_2S$: C, 41.36; H, 5.79; N, 16.08. Found: C, 41.33; H, 5.76; N, 16.10.

***N*-Carbomethoxy-2-ethylthioimidazoline (38).** Using the method described for the preparation of **29, 38** was synthesized from 4.80 g (0.03 mol) of **16**[1] and 4.8 ml (0.06 mol) of EtI. The reaction was refluxed for 72 h. The product was purified by sublimation (55 °C, 1.0 mm) to yield 3.24 g (57%) of product: selected ^{13}C NMR ($CDCl_3$) 47.0, 53.9 ppm (CH_2CH_2); MS *m/e* (rel %) 188 (17), 160 (100), 155 (30), 129 (43), 102 (42), 72 (57), 70 (43), 59 (30).

Anal. Calcd for $C_7H_{12}N_2O_2S$: C, 44.66; H, 6.43; N, 14.88. Found: C, 44.45; H, 6.26; N, 14.79.

***N*-Methyl-2-methylthioimidazoline (31).** *N*-Methyl-2-methylthioimidazolinium hydriodide[41] (3.00 g, 0.012 mol) was dissolved in 50 ml of an aqueous 1 N NaOH (0.05 mol) solution and immediately extracted with CH_2Cl_2 (5 × 20 ml). The organic layer was dried (Na_2SO_4), evaporated in vacuo, and distilled to give a clear liquid, yield 0.63 g (40%): MS *m/e* (rel %) 130 (100), 105 (28), 100 (18), 87 (77), 72 (97), 56 (70); mol wt 130.0562 (calcd for $C_5H_{10}N_2S$, 130.0565).

***N*-Acetyl-2-allylthioimidazoline (34).** To a stirred CH_2Cl_2 solution containing **15**[12] (2.88 g, 0.02 mol) and Et_3N (8.08 g, 0.08 mol), 7.0 ml (0.08 mol) of allyl bromide was slowly added. The solution was gently refluxed for 330 h, then consecutively washed with aqueous 5% $NaHCO_3$ (2 × 50 ml) and H_2O (50 ml) and dried (Na_2SO_4). The CH_2Cl_2 layer was evaporated in vacuo, leaving an approximate 50:50 ratio of starting material to product. The mixture was triturated with hexanes (100 ml) and then filtered. The remaining residue was placed in a Soxhlet extractor and extracted with hexanes. The hexanes layer was filtered, combined with the initial hexanes layer, and evaporated in vacuo to give 1.66 g (45%) of the desired compound. The product was further purified by distillation: MS *m/e* (rel %) 184 (37), 182 (36), 169 (41), 141 (100), 70 (35).

Anal. Calcd for $C_8H_{12}N_2OS$: C, 52.14; H, 6.57; N, 15.21. Found: C, 52.19; H, 6.56; N, 15.23.

***N*-Acetyl-2-*p*-fluorobenzylthioimidazoline (35).** The preceding reaction was repeated using 2.88 g (0.02 mol) of **15**,[12] 8.08 g (0.08 mol) of Et_3N, and 9.0 ml (0.075 mol) of 4-fluorobenzyl chloride. The residue was triturated with hexanes (100 ml) and then the remaining solid was recrystallized from hot hexanes: yield 2.52 g (50%); MS *m/e* (rel %) 252 (100), 210 (61), 209 (50), 177 (22), 144 (61), 70 (21).

Anal. Calcd for $C_{12}H_{13}FN_2OS$: C, 57.12; H, 5.19; N, 11.10. Found: C, 57.01; H, 5.23; N, 11.18.

***N*-Carbomethoxy-2-allylthioimidazoline (39).** Using the method described for the preparation of **34, 39** was synthesized from 3.20 g (0.02 mol) of **16**,[1] 4.04 g (0.04 mol) of Et_3N, and 3.5 ml (0.04 mol) of allyl bromide. The solution was refluxed for 168 h. The remaining oil was distilled to yield 3.00 g (75%) of **39:** MS *m/e* (rel %) 200 (59), 185 (100), 141 (19), 72 (56).

Anal. Calcd for $C_8H_{12}N_2O_2S$: C, 47.98; H, 6.04; N, 13.99. Found: C, 47.92; H, 6.16; N, 14.01.

2-(1′-Carbomethoxy-2′-imidazoline-2′-thiyl)ethyl Acetate (41). Compound **41** was synthesized in 22% yield (2.15 g) from 6.40 g (0.04 mol) of **16**,[1] 8.08 g (0.08 mol) of Et_3N, and 5.3 ml (0.048 mol) of ethyl chloroacetate using the method described for the preparation of **34.** The solution was refluxed for 72 h. Recrystallization of the remaining oil with hexanes (1000 ml) gave purified **41:** MS *m/e* (rel %) 246 (63), 201 (46), 173 (54), 160 (100), 113 (24), 102 (43), 72 (96), 70 (73), 59 (63), 56 (59).

Anal. Calcd for $C_9H_{14}N_2O_4S$: C, 43.89; H, 5.73; N, 11.38. Found: C, 43.98; H, 5.64; N, 11.41.

***N*-Carbomethoxy-2-*p*-fluorobenzylthioimidazoline (42).** Using the method described for the preparation of **34, 42** was synthesized from 3.20 g (0.02 mol) of **16**,[1] 4.04 g (0.04 mol) of Et_3N, and 4.5 ml (0.0375 mol) of 4-fluorobenzyl chloride. The solution was gently refluxed for 72 h. The crude product was recrystallized from hot hexane: yield 3.75 g (70%); MS *m/e* (rel %) 268 (100), 235 (14), 180 (10), 63 (25).

Anal. Calcd for $C_{12}H_{13}FN_2O_2S$: C, 53.72; H, 4.88; N, 10.44. Found: C, 53.81; H, 4.79; N, 10.44.

1-(1′-Carbomethoxy-2′-imidazoline-2′-thiyl)-2-propanone (40). To a stirred CH_2Cl_2 solution (250 ml) containing **16**[1] (4.96 g, 0.031 mol) and Et_3N (6.57 g, 0.065 mol), 4.8 ml of distilled chloroacetone (0.06 mol) was added all at once. The solution was allowed to stand at room temperature for 72 h, and then washed with aqueous 5% $NaHCO_3$ (2 × 100 ml) and H_2O (100 ml), and dried (Na_2SO_4). An additional 100 ml of CH_2Cl_2 was added to the organic layer and the whole solution was diluted to 1000 ml with hexanes. The solution was then concentrated in vacuo to 200 ml, causing a red-brown oil to rapidly drop out of solution. The oil was separated and the remaining solution was refrigerated overnight, resulting in the precipitation of 2.45 g (37%) of the desired product. A sample for elemental anaylsis was prepared by sublimation (60 °C, 0.2 mm): selected ^{13}C NMR ($CDCl_3$) 47.8 (t, $J_{^{13}C-H}$ = 155 Hz), 54.0 ppm (t, $J_{^{13}C-H}$ = 140 Hz) (CH_2CH_2); MS *m/e* (rel %) 216 (29), 201 (98), 199 (100), 115 (54), 72 (63), 70 (48).

Anal. Calcd for $C_8H_{12}N_2O_3S$: C, 44.43; H, 5.59; N, 12.96. Found: C, 44.41; H, 5.60; N, 13.00.

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61076-71-9; **13**, 26407-92-1; **14**, 13431-10-2; **15**, 5391-52-6; **16**, 59863-98-8; **17**, 13461-16-0; **18**, 60546-76-1; **19**, 60546-78-3; **20**, 5391-53-7; **21**, 61076-72-0; **22**, 61076-73-1; **23**, 28118-54-9; **24**, 61076-74-2; **25**, 61076-75-3; **26**, 61076-76-4; **27**, 61076-77-5; **28**, 61076-78-6; **29**, 61076-79-7; **30**, 20112-79-2; **31**, 52839-23-3; **32**, 60546-75-0; **33**, 61076-80-0; **34**, 61076-81-1; **35**, 61076-82-2; **36**, 60498-94-4; **37**, 60546-77-2; **38**, 61076-83-3; **39**, 61076-84-4; **40**, 61076-85-5; **41**, 61076-86-6; **42**, 61076-87-7; **43**, 59863-93-3; methyl chloroformate, 79-22-1; ethyl chloroformate, 541-41-3; acetyl chloride, 75-36-5; imidazolidone, 120-93-4; imidazolidinethione, 96-45-7; *N*-methyl-2-methylthioimidazolinium HI, 61076-89-9; *N*-acetyl-2-methylthioimidazolinium HI, 61076-88-8; MeI, 74-88-4; allyl bromide, 106-95-6; 4-fluorobenzyl chloride, 352-11-4; ethyl chloroacetate, 105-39-5; chloroacetone, 78-95-5; *N*-methylethylenediamine, 109-81-9; ethyl carbonate, 105-58-8.

Supplementary Material Available. The complete experimental procedures employed for the preparation of all new compounds, the physical and spectral properties observed for all compounds, as well as two histograms summarizing extensive ^{13}C NMR data for the compounds reported herein (18 pages). Ordering information is given on any current masthead page.

References and Notes

(1) H. Kohn, *J. Am. Chem. Soc.*, **98**, 3690 (1976).
(2) R. F. Pratt and T. C. Bruice, *J. Am. Chem. Soc.*, **94**, 2823 (1972); R. F. Pratt and T. C. Bruice, *Biochemistry*, **10**, 3178 (1971).
(3) M. Caplow and M. Yager, *J. Am. Chem. Soc.*, **89**, 4513 (1967); M. Caplow, *ibid.*, **87**, 5774 (1965).
(4) H. J. Schaeffer and P. S. Bhargava, *J. Pharm. Sci.*, **51**, 1116 (1962); **53**, 137 (1964).
(5) J. Knappe and F. Lynen, *Colloq. Ges. Physiol. Chem.*, **74**, 265 (1963).
(6) J. Knappe, *Int. Congr. Biochem., Proc., 6th*, **32**, 355 (1965).
(7) Y. Akasaki and A. Ohno, *J. Am. Chem. Soc.*, **96**, 1957 (1974).
(8) For reviews, see (a) W. T. Comer and A. W. Gomoll, "Medicinal Chemistry", Part II, 3d ed, A. Burger, Ed., Wiley-Interscience, New York, N.Y., 1970, Chapter 39, p 1019; (b) J. N. Delgado and E. I. Isaacson, ibid., Chapter 52, p 1386; (c) A. Krentzberger, *Prog. Drug Res.*, **11**, 356 (1968).
(9) H. Kohn, B. A. Kohn, M. L. Steenberg, and J. P. Buckley, *J. Med. Chem.*, **20**, 158 (1977).
(10) J. L. Marx, *Science*, **191**, 57 (1976).
(11) (a) J. Moss and M. D. Lane, *Adv. Enzymol.*, **35**, 321 (1971); (b) J. Knappe, *Annu. Rev. Biochem.*, **39**, 757 (1970); (c) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms", Vol. II, W. A. Benjamin, New York, N.Y., 1966, Chapter 11; see also these references for a review of the earlier literature.
(12) J. G. Roberts, *J. Chem. Soc.*, 176 (1964).
(13) R. Greenhalgh and M. A. Weinberger, *Can. J. Chem.*, **43**, 3340 (1965).
(14) H. Kohn, J. H. Arceneaux, and M. J. Cravey, unpublished results.
(15) Unlike their parent compounds, the substitution of sulfur for the oxygen at the central carbonyl position of the acyl substituted imidazolidones did not always raise the melting point of the substrate.[16] Most of the newly prepared acyl substituted thioimidazolines, however, did melt higher than their imidazoline counterparts.
(16) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds", Vol. 1, W. A. Benjamin, New York, N.Y., 1965, Chapter 6, p 233.
(17) H. K. Hall and A. K. Schneider, *J. Am. Chem. Soc.*, **80**, 6409 (1958).
(18) J. W. Schulenberg and S. Archer, *Org. React.*, **14**, 1 (1965), and references cited therein.
(19) C. G. McCarty, "The Chemistry of the Carbon-Nitrogen Double Bond", S. Patai, Ed., Interscience, New York, N.Y., 1970, Chapter 9, p 363, and references cited therein.
(20) A. F. Hegarty and T. C. Bruice, *J. Am. Chem. Soc.*, **92**, 6561, 6568, 6575 (1970); A. F. Hegarty, R. F. Pratt, T. Giudici, and T. C. Bruice, *ibid.*, **93**, 1428 (1971); T. C. Bruice and A. F. Hegarty, *Proc. Natl. Acad. Sci. U.S.A.*, **65**, 805 (1970).
(21) A. E. Dixon and J. Taylor, *J. Chem. Soc.*, **117**, 720 (1920).
(22) D. Y. Curtin and L. L. Miller, *Tetrahedron Lett.*, 1869 (1965).
(23) H. Meerwein, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 1096.
(24) Reference 23, p 1080.
(25) C. J. Sharpe, R. S. Shadbolt, A. Ashford, and J. W. Ross, *J. Med. Chem.*, **14**, 977 (1971).
(26) F. W. McLafferty, "Interpretation of Mass Spectra", 2d ed, W. A. Benjamin, New York, N.Y., 1973, Chapter 4, p 40.
(27) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day, San Francisco, Calif., 1967, Chapters 4, 9, 15.
(28) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules", Wiley, New York, N.Y., 1958; see also this reference for a review of the earlier literature.
(29) L. J. Bellamy, "Advances in Infra-red Group Frequencies", Methuen, London, 1968, and references cited therein.
(30) K. Nakanishi, "Infra-red Absorption Spectroscopy", Holden-Day, San Francisco, Calif., 1969.
(31) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2d ed, Pergamon Press, Elmsford, N.Y., 1969; see in particular Part 3, p 159.
(32) N. F. Chamberlain and J. J. R. Reed, "The Analytical Chemistry of Sulfur and Its Compounds", Part 3, J. H. Karchmer, Ed., Wiley-Interscience, New York, N.Y., 1971, p 287.
(33) This unusual resonance has already been used to advantage in examining the thermal rearrangement of *N*-acetyl-2-allythioimidazoline (**34**) to the isomeric *N*-acetyl-*N*′-allylimidazolidinethione. In this case the acetyl resonances appeared at δ 2.20 and 2.81, respectively.[34]
(34) H. Kohn and J. H. Arceneaux, unpublished results.
(35) These spectra were obtained using a variety of spectrometers as noted in Figures 1 and 2. It is gratifying that the reproducibility from spectrometer to spectrometer was within the experimental error of the measurements.
(36) L. M. Jackman and T. Jen, *J. Am. Chem. Soc.*, **97**, 2811 (1975).
(37) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, and references cited therein.
(38) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, and references cited therein.
(39) H. O. Kalinowski and H. Kessler, *Angew. Chem., Int. Ed. Engl.*, **13**, 90 (1974).
(40) J. G. Frick, B. A. Kottis, and J. D. Reid, *Text. Res. J.*, **29**, 314 (1959).
(41) A. F. McKay and M. E. Kreling, *J. Org. Chem.*, **22**, 1581 (1957).

A Short Synthesis of Aromatic Analogues of the Aranotins

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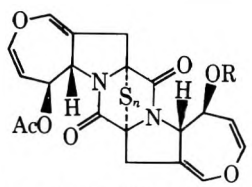
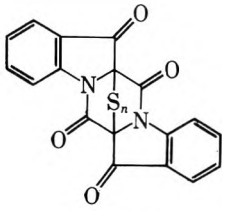
Various pyrazino[1,2-*a*:4,5′-*a*′]diindoles have been synthesized corresponding in structure to the diketopiperazine type dimers of indole- and indoline-2-carboxylic acids. 7,14-Dihydroxy-6*H*,13*H*-pyrazino[1,2-*a*:4,5-*a*′]diindole-6,13-dione reacted with sulfur monochloride and pyridine to give epidithio and epitrithio derivatives. These are aromatic analogues of the aranotins. The structure of the epitrithio derivative was verified by single-crystal x-ray crystallography. The space group is $P_{2_1}P_{2_1}P_{2_1}$ with pertinent cell data as follows: a = 9.199 (4), b = 13.846 (4), c = 13.248 (3) Å, and Z = 4.

The aranotins are a small group of sulfur-bridged diketopiperazines produced by the fungal species *Arachniotus aureus* and *Aspergillus terreus*.[1] The compounds have elicited attention from chemotherapists because of their antiviral activity which is observed in both in vivo and in vitro testing.[2]

Aranotin (**1**) and acetylaranotin (**2**, also known as LL-S88$_{(1)}$) are naturally occurring members of the group. Compounds **3** and **4** are partially synthetic members obtained by chemical modifications of acetylaranotin.[3] Since the dihydrooxepin rings may not be crucial to the biological activity of this series,[4] a synthesis of some aromatic analogues was initiated and led



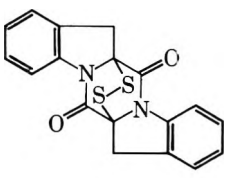
1, n = 2; R = H (aranotin)
2, n = 2; R = Ac (acetylaranotin)
3, n = 3; R = Ac
4, n = 4; R = Ac



5, n = 2
6, n = 3

to a short and easy synthesis of the analogues **5** and **6**.

The simplest aromatic analogue would be structure **7** and the bisindolodiketopiperazines **8**, **9**, and **10** were prepared as potential synthetic precursors to **7**.



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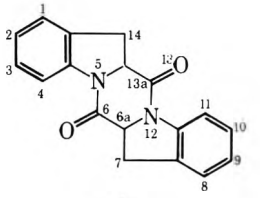

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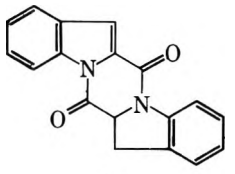

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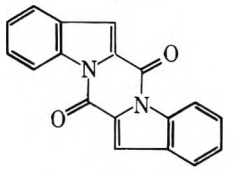

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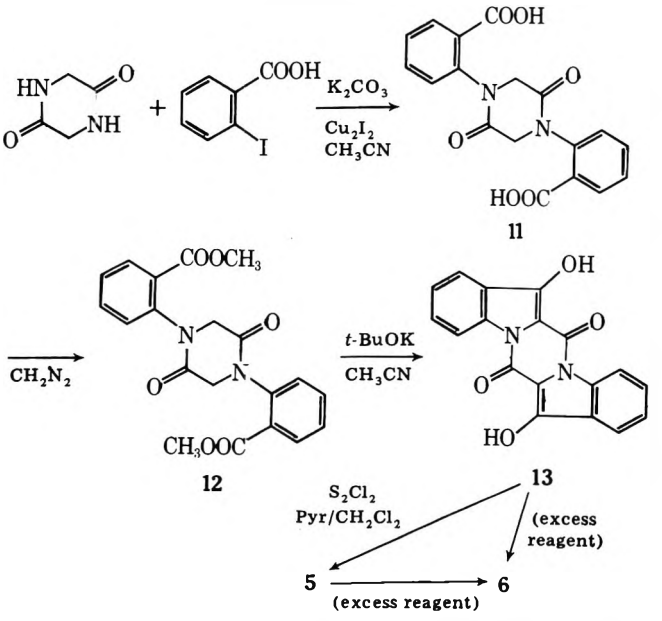
We were unable to obtain **7** from any of these three compounds[5] and proceeded to a synthesis of the slightly more complex analogues **5** and **6** as shown in Scheme I. The methods used to obtain **8**, **9**, and **10** are outlined in Scheme II.

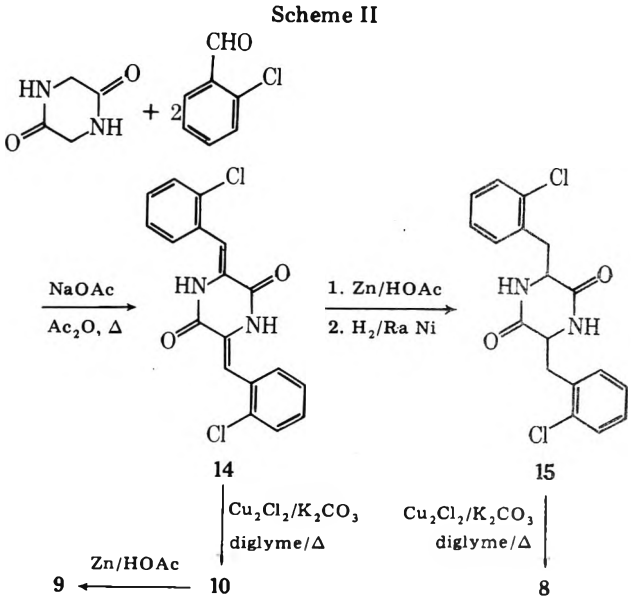
Scheme I



The syntheses described in Schemes I and II take advantage of the C_2 symmetry property of the products. By selecting the central diketopiperazine ring as the starting material, the synthetic steps proceed as dual transformations.

The copper-catalyzed nucleophilic substitution reaction leading to compound **11** has a precedent in the synthesis of dehydrogliotoxin reported by Kishi and co-workers.[6] Although the yield in this step was only 32%, substantial quantities of **11** could be prepared quite conveniently. The yields in the subsequent steps were quite good. The diacetate of **13** could be obtained directly from **11** by heating it with sodium acetate

Scheme II



and acetic anhydride, but the yield of **13** from hydrolysis of its diacetate was very poor compared with that obtained from the Dieckmann route shown.

The direct introduction of a disulfide bridge into a diketopiperazine using sulfur monochloride was reported for a simpler case.[7] The yield was only 17% and a mixture of di- and tetrasulfides was obtained. In the present case, the conversion of **13** to **5** proceeded in 65% yield and pure product was obtained by a simple recrystallization. When a large excess of sulfur monochloride was used, the trisulfide **6** was obtained in slightly lower yield. The intermediacy of the disulfide in the formation of the trisulfide can be inferred from the fact that **5** gave **6** when treated with more sulfur monochloride. Both compounds were tested for antiviral activity in mice using influenza-A2, coxsacki, and Semliki forest viruses but no activity was observed.

The structures of **5** and **6** were in agreement with the spectral and analytical data. In particular the mass spectra of both compounds contained M^+ peaks. Their NMR spectra, however, contained only aromatic proton signals and provide no proof for the assigned structures. In order to remove any equivocation about these structural assignments, we decided to take advantage of the propensity which compound **6** showed to produce well-formed crystals and carried out an x-ray crystallographic structure determination. The results are presented in Figure 1 and Tables I and II.

Two ancillary results of the x-ray crystallographic investigation of **6** deserve comment. One is that the crystal examined consisted of a single enantiomer as would be expected for space group $P_{2_12_12_1}$ indicating that the individual crystals had resolved spontaneously during crystallization. The second, possibly related result is that the sulfur bridge is unsymmetrical, not only in conformation but in C–S and S–S distances. The differences in these bond lengths (Table II) are well outside the 3σ error associated with them. The origin of this distortion may be either a crystal lattice effect or the result of an interaction between the central sulfur atom and the proximal benzene ring.

Syntheses of Compounds 8, 9, and 10. The Sasaki procedure[8] for condensing benzaldehydes with glycine anhydride was used to prepare compound **14**. Contrary to Sasaki's report, however, we found that these bisbenzylidenediketopiperazines were only *partially* reduced with zinc in boiling acetic acid. The resulting dihydro compound from **14** was further reduced to **15** with hydrogen and Raney nickel in acetic acid. This two-step reduction sequence was superior to direct catalytic reduction of **14** because of its very poor solubility.

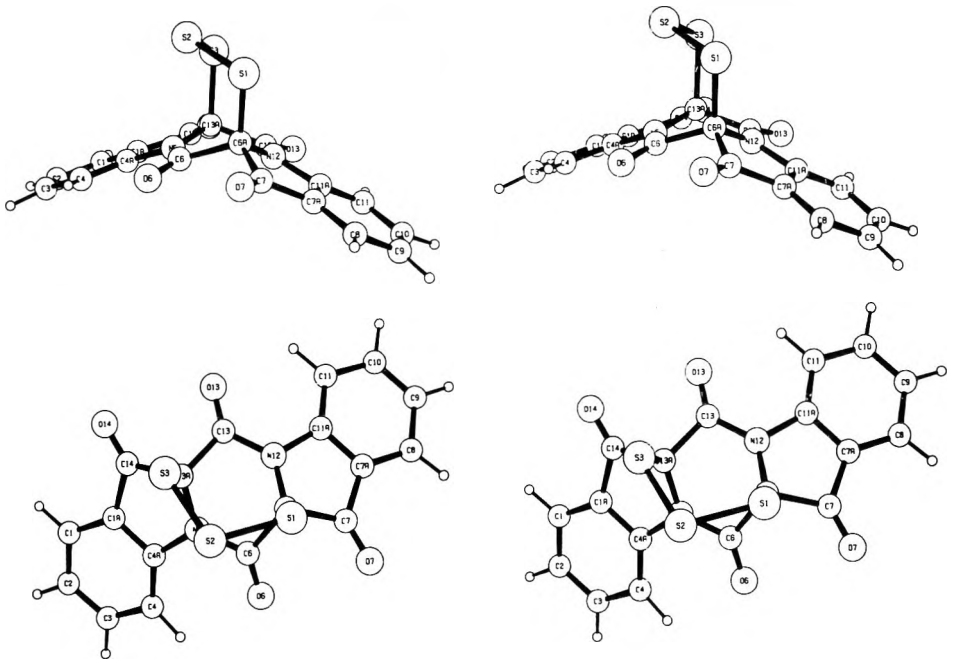


Figure 1. Stereoscopic drawings of compound **6**. The thermal ellipsoids for all nonhydrogen atoms are scaled to the 50% inclusion level. The hydrogen atoms are shown as spheres.

Table I. Crystal Data for 6

Space group	$P2_12_12_1$
a	9.199 (4)
b	13.846 (4)
c	13.248 (3)
Z	4
d_{calcd}	1.611
μ(Cu Kα), cm^{-1}	40.06

Table II. Bridge Bond Lengths and Angles for 6

S_1–C_{6A}	1.806 Å
S_3–C_{13A}	1.916 Å
S_1–S_2	2.069 Å
S_2–S_3	2.018 Å
S_2–S_1–C_{6A}	101°
S_1–S_2–S_3	105°
S_2–S_3–C_{13A}	101°

Double cyclizations via copper-catalyzed intramolecular substitution reactions were carried out on both **14** and **15** giving **10** and **8**, respectively, as shown in Scheme II. As with the bisbenzylidenediketopiperazines, the bisindolo compound **10** was reduced only to the dihydro level with zinc in acetic acid, giving compound **9**.

Compound **8** has been prepared previously by dimerization of ethyl indoline-2-carboxylate[5] and the reported melting point and NMR data are similar to those obtained from a sample prepared according to Scheme II. Neither route permits an assignment of stereochemistry. Nor can a distinction between the cis (with C_2 symmetry) and trans (with S_2 symmetry) isomers be made on the basis of the NMR spectra.

Experimental Section[9]

1,4-Bis(*o*-carboxyphenyl)-2,5-piperazinedione (11). A mixture of glycine anhydride (11.4 g, 0.1 mol), *o*-iodobenzoic acid (51 g, 0.205 mol), cuprous iodide (10 g, 0.052 mol), potassium carbonate (50 g, 0.36 mol), and acetonitrile (500 ml) was stirred at reflux under argon for 16 h. After cooling, the mixture was poured into water and filtered through Celite. The filtrate was acidified with dilute aqueous HCl, causing a gummy precipitate to form. Ether was added and the mixture stirred to give a cleaner precipitate. This was filtered, washed with water and ether, then air dried to give 11.5 g (32.5%) of crude compound **11** (single spot on TLC). A sample for analysis was recrystallized from ethanol/ether, giving colorless crystals with mp 279–281 °C: IR (Nujol) 3400, 2600, 2500, 1725, 1645, 1610, 1585 cm^{-1}; NMR (Me_2SO-d_6) 4.4 (s, broad, 4 H), 6.6 (s, broad, exchanged with D_2O), 7.6 ppm (aromatic H); mass spectrum *m/e* 336 and 354 (M^+, 100%).

Anal. Calcd for $C_{18}H_{14}N_2O_6$: C, 61.02; H, 3.98; N, 7.91. Found: C, 61.03; H, 4.17; N, 8.01.

1,4-Bis(*o*-carbomethoxyphenyl)-2,5-piperazinedione (12). The diacid **11** (4.0 g) gradually dissolved in reagent grade methanol (300 ml) during 45 min of boiling. After cooling, freshly prepared diazomethane in ether was added in portions until the yellow color persisted and TLC analysis showed that esterification was complete. The solution was filtered through Celite and stripped of solvent under reduced pressure. The crystalline residue was triturated with ether, collected, and air dried to give 3.95 g (91.5%) of colorless crystals. An analytical sample from methylene chloride/ether had mp 166–168 °C: IR (Nujol) 1715, 1660, 1590, and 1570 cm^{-1}; NMR ($CDCl_3$) 3.94 (s, 6 H), 4.47 (s, 4 H), and 7.3–8.3 ppm (m, 8 H); mass spectrum *m/e* 350 and 382 (M^+, 100%).

Anal. Calcd for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.56; H, 4.90; N, 7.48.

7,14-Dihydroxy-6*H*,13*H*-pyrazino[1,2-*a*:4,5-*a'*]diindole-6,-13-dione (13). Compound **12** (3.75 g, 0.0098 mol) in acetonitrile (100 ml) was stirred at reflux while potassium *tert*-butoxide (3.75 g, 0.033 mol) was added in portions. The resulting orange slurry was heated at reflux for an additional 1.5 h and then poured into water. The resulting clear solution was acidified with 3 N HCl and the fine yellow precipitate was collected on Whatman no. 42 filter paper. After washing with water and ether and then air drying, 2.87 g (92%) of pale yellow powder was obtained. A sample for analysis prepared by vacuum sublimation changed to fine needles above 250 °C but did not melt up to 320 °C. The sample had IR (Nujol) 3300, 1685, 1670, 1625, 1600 and 1575 cm^{-1}; mass spectrum *m/e* 318 (M^+, 100%). An NMR spectrum was precluded by poor solubility.

Anal. Calcd for $C_{18}H_{10}N_2O_4$: C, 67.93; H, 3.17; N, 8.80. Found: C, 67.82; H, 3.33; N, 8.75.

6a,13a-Epidithio-6a,7,13a,14-tetrahydro-6*H*,13*H*-pyrazino-[1,2-*a*:4,5-*a'*]diindole-6,7,13,14-tetraone (5). A suspension of compound **13** (2.0 g, 0.0063 mol) in methylene chloride (160 ml) was stirred vigorously while pyridine (4 ml, 0.05 mol) was added. Sulfur monochloride (1.2 ml, 2 g, 0.015 mol) was added slowly dropwise giving a clear yellow solution. After 10 min of stirring, the solution was washed with 0.6 N HCl (200 ml), dried, filtered, and concentrated under reduced pressure using a water bath at 35 °C. Crystals began to form when the volume was reduced to ca. 100 ml. Further concentration to ca. 50 ml by boiling was followed by storage in the freezer for 2 h. The crude product (1.68 g) was collected, washed with cold methylene chloride, and dried. Recrystallization from methylene

chloride gave 70 mg of insoluble starting material and 1.56 g (65%) of pure product in two crops of tiny, pale yellow needles. The recrystallized product decomposed without melting above 300 °C: IR (Nujol) 1730 and 1600 cm^{-1} (1745 and 1600 cm^{-1} in $CHCl_3$); NMR ($CDCl_3$) 7.3–8.4 ppm (m, aromatic H); mass spectrum *m/e* 64 (100%), 316, 318, and 380 (M^+).

Anal. Calcd for $C_{18}H_8N_2O_4S_2$: C, 56.83; H, 2.12; N, 7.36, S, 16.86. Found: C, 56.86; H, 2.29; N, 7.39; S, 16.57.

6a,13a-Epitrithio-6a,7,13a,14-tetrahydro-6*H*,13*H*-pyrazino-[1,2-*a*:4,5-*a'*]diindole-6,7,13,14-tetraone (6). A suspension of compound **13** (500 mg, 1.57 mmol) in methylene chloride (40 ml) was treated with pyridine (1 ml) and stirred for 10 min. Sulfur monochloride (0.9 ml, 1.5 g, 0.011 mol) was added all at once and the resulting solution was boiled gently for 15 min. It was then washed with 0.6 N HCl, dried, filtered, and concentrated to ca. 20 ml by boiling. After scratching with a seed crystal and chilling, the product which separated was collected, washed with cold methylene chloride, and air dried to give 380 mg (58%) of the epitrisulfide as a light yellow solid. Recrystallization from methylene chloride with charcoal treatment while in solution gave pale yellow crystals which decomposed without melting at 255 °C. The product had IR (KBr) 1747, 1700, and 1595 cm^{-1} (the neat solid has strong Raman bands at 1760, 1710, 1610, 630, and 490 cm^{-1}); NMR ($CDCl_3$/Me_2SO-d_6) 7.3–8.8 ppm (m, aromatic H); mass spectrum *m/e* 64, 96, 316 (100%), 318, and 412 (M^+).

Anal. Calcd for $C_{18}H_8N_2O_4S_3$: C, 52.42; H, 1.96; N, 6.79; S, 23.32. Found: C, 52.13; H, 2.00; N, 6.65; S, 23.20.

3,6-Bis(*o*-chlorobenzylidine)-2,5-piperazinedione (14). A mixture of glycine anhydride (114 g, 1 mol), o-chlorobenzaldehyde (310 g, 2.2 mol), sodium acetate (330 g, 4 mol), and acetic anhydride (520 g, 5.1 mol) was stirred and heated in an oil bath at 140–145 °C for 5 h. The reaction mixture was left to cool with stirring overnight and water was then added in 50-ml portions causing a vigorous reaction. After dilution to ca. 2 l., the black precipitate was collected and washed with water. This material was suspended in ethanol and heated on the steam bath with occasional swirling. It was then filtered and washed repeatedly with methylene chloride until a light yellow filter cake remained. After drying, the product weighed 176 g (49%). A sample recrystallized from CH_2Cl_2/EtOH decomposed without melting above 300 °C: IR (Nujol) 3250, 1700, and 1650 cm^{-1}; mass spectrum *m/e* 323 (100%) and 358 (M^+). Poor solubility precluded an NMR spectrum.

Anal. Calcd for $C_{18}H_{12}Cl_2N_2O_2$: C, 60.19; H, 3.37, Cl, 19.73; N, 7.80. Found: C, 30.57; H, 3 55; Cl, 19.93; N, 7.88.

3,6-Bis(*o*-chlorobenzyl)-2,5-piperazinedione (15). A mixture of compound **14** (25 g) and zinc dust (60 g) in glacial acetic acid (1 l.) was stirred at reflux for 16 h, during which the yellow starting material disappeared. A small amount of water was added carefully to the hot mixture to dissolve the precipitated zinc salts. The excess zinc was filtered and the filtrate concentrated by evaporation under reduced pressure. The colorless product was obtained in quantitative yield by precipitation with cold water followed by collecting, washing with water, and air drying. The product has IR (Nujol) 3200, 1690 and 1640 cm^{-1}. The NMR ($CDCl_3$/Me_2SO-d_6) spectrum has vinyl H singlets at 4.70 and 6.61 ppm showing the product to be a mixture (ca. 1:1) of cis and trans geometrical isomers:[10] mass spectrum *m/e* 325 (100%) and 360 (M^+, very weak). Without further characterization, this dihydro isomer mixture (5 g) was dissolved in hot glacial acetic acid (150 ml), treated with ca. 2 g of Raney nickel, and shaken under 60 psi of H_2 for 50 h. The catalyst was filtered and the filtrate diluted with water. The product was collected, washed with water, and air dried to give 4.3 g (85%) of colorless crystals. A sample recrystallized from acetic acid/ether had mp 220–222 °C; IR (Nujol) 3200, 3050, and 1680 cm^{-1}; NMR ($CDCl_3$/Me_2SO-d_6/D_2O) 2.61 (dd, H_A), 3.17 (dd, H_B), 4.10 (dd, H_X), J_{AB} = 14, J_{AX} = 8, J_{BX} = 5 Hz, 7.30 (aromatic H), and 7.90 (NH, seen before adding D_2O); mass spectrum *m/e* 327 (M − Cl, 100%).

Anal. Calcd for $C_{18}H_{16}Cl_2N_2O_2$: C, 59.52; H, 4.44; Cl, 19.52; N, 7.71. Found: C, 59.77; H, 4.65; Cl, 19.26; N, 7.70.

6a,7,13a,14-Tetrahydro-6*H*,13*H*-pyrazino[1,2-*a*:4,5-*a'*]diindole-6,13-dione (8). A mixture of compound **15** (5 g), cuprous chloride (5 g), and anhydrous potassium carbonate (5 g) in diglyme (100 ml) was stirred and heated at reflux under argon for 20 h. The mixture was then diluted with chloroform and filtered through Celite, the solid being washed several times with hot chloroform. The filtrate was concentrated to a small volume under reduced pressure during which the product began to crystallize. After chilling, the product was collected, washed with ether, and air dried to give 1.85 g (46%) of **8** as a light tan solid. A sample for analysis was vacuum sublimed giving colorless crystals. A recrystallized sample had mp 258–260 °C (lit.[5] mp 263–265 °C): IR (Nujol) 1670 and 1605 cm^{-1}; NMR ($CDCl_3$/Me_2SO-d_6) 3.37 (dd, H_A), 3.55 (dd, H_B), 5.19 (dd, H_X), J_{AB} = 17, J_{AX} = 10, J_{BX} = 8 Hz, 7.20 (m, 6 H, aromatic), and 8.0 (m, 2 H, aromatic); mass spectrum *m/e* 90, 117 (100%), and 290 (M^+).

Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.60; H, 4.80; N, 9.75.

6*H*,13*H*-Pyrazino[1,2-*a*:4,5-*a'*]diindole-6,13-dione (10).[11] A mixture of 60 g each of compound **14**, cuprous chloride, and anhydrous potassium carbonate in diglyme (2 l.) was stirred at reflux under argon for 18 h. After cooling, the mixture was diluted with water and the solid material filtered out. This solid was washed with water and with ether and then air dried. It was then extracted with boiling *o*-dichlorobenzene (500 ml) for ca. 1 h. The mixture was filtered through a preheated fine sintered glass funnel, the liquid in the funnel being kept at >150 °C during the filtration. Additional boiling *o*-dichlorobenzene was used as needed to keep the product in solution and to wash the filter cake of copper salts. The filtrate was cooled and the product collected. The product was then suspended in methylene chloride (500 ml), filtered again, and air dried to give 35.9 g (75%) of **10** as a pale yellow powder. A sample for analysis was vacuum sublimed giving fine yellow crystals with mp 326–328 °C: IR (Nujol) 1705, 1695, 1620, 1585, and 1570 cm^{-1}; mass spectrum *m/e* 286 (M^+, 100%). An NMR spectrum was precluded by poor solubility.

Anal. Calcd for $C_{18}H_{10}N_2O_2$: C, 75.52; H, 3.52; N, 9.78. Found: C, 75.42; H, 3.60; N, 9.88.

6a,7-Dihydro-6*H*,13*H*-pyrazino[1,2-*a*:4,5-*a'*]diindole-6,13-dione (9). A mixture of compound **10** (10 g) and zinc dust (20 g) in glacial acetic acid (250 ml) was stirred at reflux for 18 h. After cooling the mixture was diluted to 1 l. with water and the suspension of the product carefully decanted from the unreacted zinc. The product was collected by filtration, washed with water and with ether, then air dried to give a quantitative yield of **9** as pale yellow powder. Recrystallization from *o*-dichlorobenzene gave 8.4 g of pale yellow crystals with mp 303–306 °C: IR (Nujol) 1720, 1645, 1600, 1580, and 1560 cm^{-1}; NMR ($CDCl_3$/Me_2SO-d_6 spectrum is weak and poorly resolved owing to low solubility) 3.50 (m, 1 H), 4.30 (m, 1 H), 5.70 (m, 1 H), 7.40 (broad, aromatic H), and 8.03 ppm (s, 1 H); mass spectrum *m/e* 115, 143, 144, and 288 (M^+, 100%).

Anal. Calcd. for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.82; H, 4.26; N, 9.72.

Crystallographic Study of 6. Yellow crystals of **6** were grown from methylene chloride. A crystal approximately 0.11 × 0.06 × 0.05 mm was mounted on a glass capillary tube with epoxy resin. The space group was found to be $P2_12_12_1$ by a combination of film and counter methods. The cell constants were found using 14 reflections on a Hilger and Watts four circle diffractometer (Cu Kα,λ = 1.54178 Å, nickel filter) to be a = 9.199 (4), b = 13.846 (4), and c = 13.248 (3) Å. Additional crystal data appear in Table I. The crystal density was measured by flotation in aqueous KI as 1.62 g/ml, in good agreement with a calculated density of 1.611 g/ml assuming four molecules in the unit cell. Intensity data were collected using a scintillation counter with pulse-height discrimination, a θ–2θ scan technique, 1°/min scan rate with four background reflections measured every 100 reflections to monitor the extent of crystal decomposition and movement. Of 2015 independent reflections measured, with $\theta < 57°$, *1231* (with $I \geq 2.5\sigma_I$) were considered significantly greater than background.

Data were corrected for Lorentz, polarization, and absorption. The structure was solved by a multiple solution procedure.[12] Nearly all nonhydrogen atoms were located on the first E map. Inclusion of these atoms in an electron density calculation located all remaining atoms. Full-matrix least-squares refinement with first isotropic, then anisotropic refinement were utilized. The positions of all hydrogen atoms were calculated and placed with a C–H bond length of 1.0 Å. Further refinement using anisotropic temperature factors for nonhydrogen atoms and hydrogen atoms at fixed positions reduced R_w ($R = [(\Sigma w|F_o| - |F_c|)^2/\Sigma wF_o^2]^{1/2}$) to 0.087. A final difference Fourier map has no significant features.

Registry No.—**5**, 61193-59-7; **6**, 61193-60-0; **8**, 50501-06-9; **9**, 61193-61-1; **10**, 58881-41-7; **11**, 61193-62-2; **12**, 61193-63-3; **13**, 61193-64-4; **14**, 7670-67-9; *trans*-dihydro-**14**, 61193-65-5; *cis*-dihydro-**14**, 61193-66-6; **15**, 7763-25-9; glycine anhydride, 106-57-0; *o*-iodobenzoic acid, 88-67-5; sulfur monochloride, 10025-67-9; o-chlorobenzaldehyde, 89-98-5.

References and Notes

(1) R. Nagarajan, L. L. Huckstep, D. H. Lively, D. C. DeLong, M. M. Marsh, and N. Neuss, *J. Am. Chem. Soc.*, **90**, 2980 (1968); R. Nagarajan, N. Neuss, and M. M. Marsh, *ibid.*, **90**, 6518 (1968); D. B. Cosulich, N. R. Nelson, and J. H. van den Hende, *ibid.*, **90**, 6519 (1968); N. Neuss, R. Nagarajan, B. B. Molloy, and L. L. Huckstep, *Tetrahedron Lett.*, 4467 (1968).

(2) P. W. Trown, H. F. Lindh, K. P. Milstrey, V. M. Gallo, B. R. Mayberry, H. L Lindsay, and P. A. Miller, *Antimicrob. Ag. Chemother.*, 225 (1968).
(3) K. C. Murdock, *J. Med. Chem.*, **17**, 827 (1974).
(4) Mammalian metabolism of 7 via an arene oxide pathway would conceivably produce an aranotin; see, for example, D. M., Jerina, H. Yagi, and J. W. Daly, *Heterocycles*, **1**, 267 (1973); D. M. Jerina and J. W. Daly, *Science*, **185**, 573 (1974).
(5) An account of another attempt to prepare **7** from **8** was found during this work: J. Yoshimura, Y. Sugiyama, and H. Nakamura, *Bull. Chem. Soc. Jpn.*, **46**, 2850 (1973).
(6) Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Am. Chem. Soc.*, **95**, 6492 (1973).
(7) T. Hino and T. Sato, *Chem. Pharm. Bull.*, **22**, 2866 (1974).
(8) T. Sasaki, *Chem. Ber.*, **54**, 163 (1921).
(9) Melting points are uncorrected. NMR spectra were recorded on a Varian T-60 instrument and are reported in parts per million from internal tetramethylsilane. Infrared and mass spectra were recorded on Perkin-Elmer 137 and CEC-110B instruments, respectively. Elemental analyses were conducted under the supervision of Dr. F. Scheidl of our microanalytical laboratory.
(10) K. W. Blake and P. B. Sammes, *J. Chem Soc. C*, 980 (1970).
(11) A synthesis of this compound from indole-2-carbonyl chloride was reported subsequent to the submission of this manuscript: R. J. Boatman and H. W. Whitlock, *J. Org. Chem.*, **41**, 3050 (1976).
(12) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).

Synthesis and Chemistry of Cyclic Sulfoximines[1]

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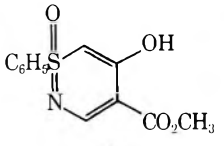
The synthesis of 1,2,4-thiadiazine 1-oxides, which are cyclic sulfoximines exemplified by **16**, **19**, **27**, and **30**, is reported. Alkylation of **16** with methyl iodide–NaH gives **20**, which in turn can be converted to **21**; **16** on treatment with triethyloxonium tetrafluoroborate gives **27**. The unsaturated but nonaromatic 1,2,4-thiadiazine 1-oxide **30** can be prepared by the action of ethyl iodide on the silver salt of **27**. That **27** and **30** are ylidic in nature is shown by their ^1H and ^{13}C NMR spectra, which are discussed, and their ability to undergo electrophilic substitution in the same manner as thiabenzene 1-oxides. The mass spectra of the various thiadiazine 1-oxides show important fragmentation pathways involving phenyl migration from sulfur to the adjacent carbon. These migrations are not important in the spectra of the open-chain intermediates.

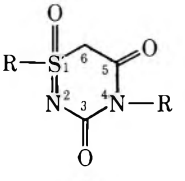
The chemistry of sulfoximines has been the focus of much attention in the past several years, and two reviews of this developing area of organosulfur chemistry have recently appeared.[3] Part of the interest in the chemistry of sulfoximines, which are capable of wide structural variations, has been concerned with the synthesis of heterocycles containing this functionality. Two arrangements are possible: (a) with the S=N moiety exocyclic to the ring, and (b) with the S=N moiety an integral part of the ring.[4] We report here the synthesis and chemistry of 1,2,4-thiadiazine 1-oxides, which are sulfoximine heterocycles that exemplify the second category.

Reported syntheses of sulfoximine heterocycles such as **1**[5] and **2**[6] have utilized an existing sulfoximine unit around which to construct a ring. Our initial synthetic goal which would provide access to the thiadiazine 1-oxide system was a diketo structure represented by **3**. The successful preparation of such

1



2



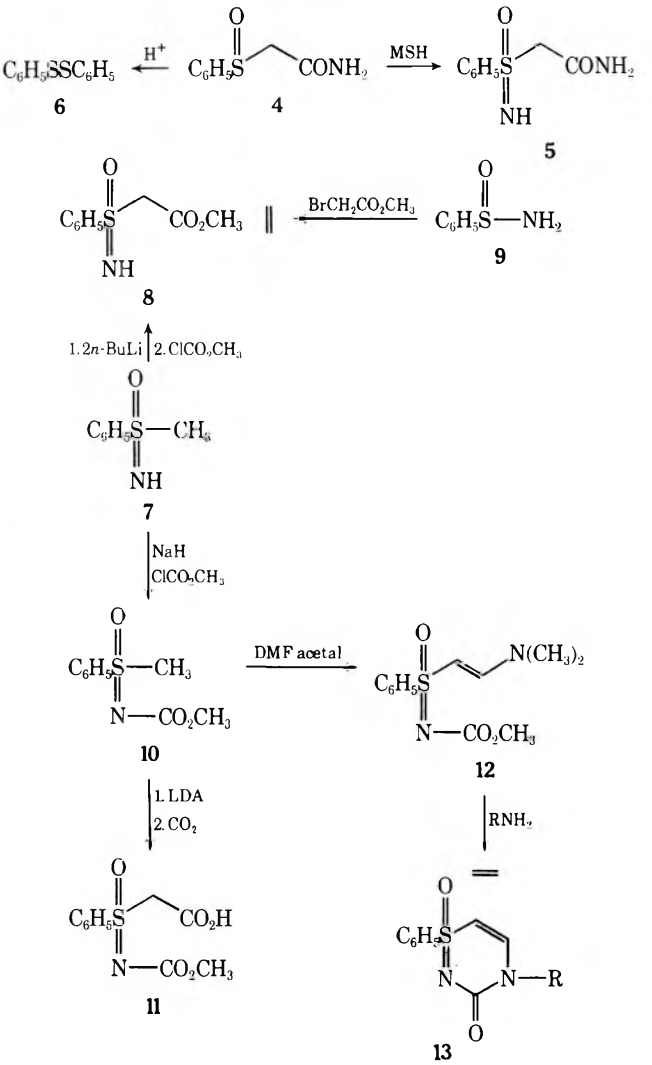
3

a dione was accomplished similarly by starting from an intact sulfoximine.

Scheme I depicts initial unsuccessful approaches. The carboxamidosulfoximine **5** was envisioned as a useful intermediate not only for the synthesis of the dione **3**, but also, by reaction with formic acid, nitrous acid, or reduction–carbonylation, for the generation of other heterocycles as well.

Attempted conversion of the corresponding sulfoxide **4**[7] to **5** by the standard reaction with hydrazoic acid[8] gave exclusively the Pummerer rearrangement product, diphenyl disulfide (**6**). Use of the versatile but unstable amino transfer reagent *O*-mesitylsulfonylhydroxylamine (MSH)[9] did provide the desired intermediate **5** but in less than acceptable yields.

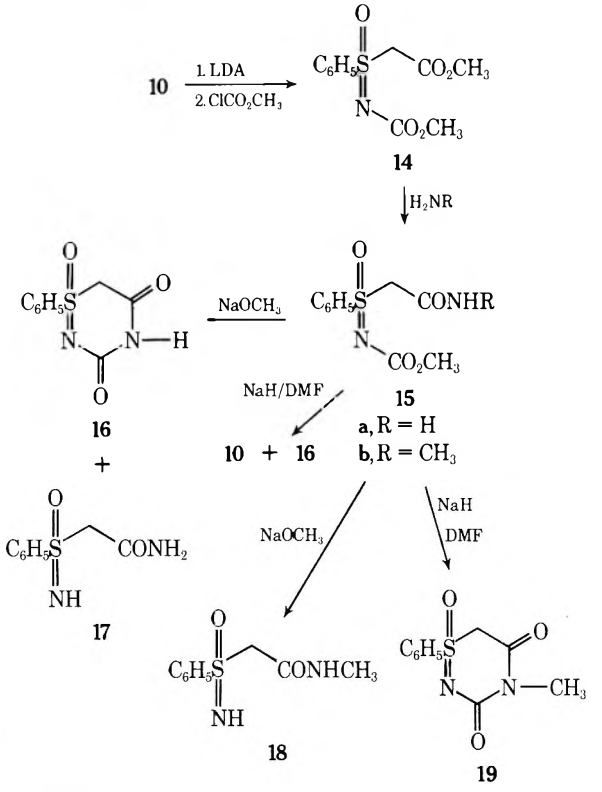
Scheme I



Some effort was made to prepare the ester **8** which would then be converted to **5.** The known and readily accessible methylphenylsulfoximine[10] **7,** on conversion to the dianion and treatment with 1 equiv of methyl chloroformate, gave little of the desired **8,** however. An attempted modification of the well-known preparation of sulfones,[11] where the sulfinamide **9** rather than sodium benzenesulfinate was reacted with methyl bromoacetate, did not yield **8.** Sulfoximine **7** was easily converted to the methoxycarbonyl derivative **10** in good yield. The anion of **10,** generated with LDA, could be carboxylated giving the free acid **11** (39%), stable toward decarboxylation, but offering no advantage over the corresponding ester prepared directly (Scheme II). Finally, later it was found that **10** could undergo condensation with DMF acetal in a manner similar to that of ketones[12] and the enaminosulfoximine **12,** a quite stable yellow solid, was formed in 50% yield. All attempts to convert **12** to **13** (R = H or alkyl) by amination with ammonia, ammonium acetate, amines, or triethyloxonium tetrafluoroborate (Meerwein reagent) followed by ammonia failed.

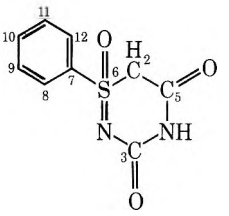
A successful approach to the thiadiazine system was devised (Scheme II) which took advantage of the ability of **10** to undergo acylation on carbon. Inverse addition of the lithio derivative of **10** to 1 equiv of methyl chloroformate gave in good yield, the ester **14,** which could be aminated with ammonia or methylamine in good yields providing the amides **15.** Cyclization of **15a** with sodium methoxide gave the 1,2,4-thiadiazinedione 1-oxide **16** in 47% yield along with 2–5% of the methanolysis product **17.**[13] Attempted cyclization of **15b** with sodium methoxide gave only the methanolysis product **18** (55%). Apparently methanolysis in this case competes effectively with cyclization with the more bulky *sec*-amide anion. When sodium hydride in DMF was employed, however, cyclization readily occurred yielding the *N*-methyl dione **19** (75%). Interestingly, when **15a** was subjected to these same conditions only a 31% yield of **16** was obtained along with a surprising 43% of **10.**[14]

Scheme II



The dione **16** (as well as **19**) is essentially nonenolic; the infrared spectrum indicates carbonyl absorption at 1705 and 1675 cm^{-1}. The NMR spectrum shows an exchangeable proton at δ 10.8 and geminal protons at δ 4.91 (J = 17 Hz), which are exchanged rapidly by D_2O in Me_2SO-d_6 or immediately if acid or base are added. The AB quartet at δ 4.91 collapses to a broad singlet at 100 °C which becomes a sharper singlet at 150 °C while the phenyl protons remain sharp and clear. On cooling to room temperature the original quartet is restored. Although no enol is detected, the collapse of the quartet on heating is consistent with chemical averaging through the enol form which becomes rapid at elevated temperature. ^{13}C NMR spectra which define **16** are seen in Chart I. In the mass spectrum of **16** a base peak of *m/e* 91 corresponding to C_7H_7 suggests a migration of the phenyl moiety from sulfur to carbon. Oae et al.[15] have reported the migration of aryl groups from sulfur to nitrogen in the mass spectra of aryl alkyl sulfoximines. This migration of phenyl to carbon appears to be electron impact induced and is characteristic of all 1,2,4-thiadiazine 1-oxides discussed in this paper. The migration was of little or no significance in the spectra of the open-chain intermediates.

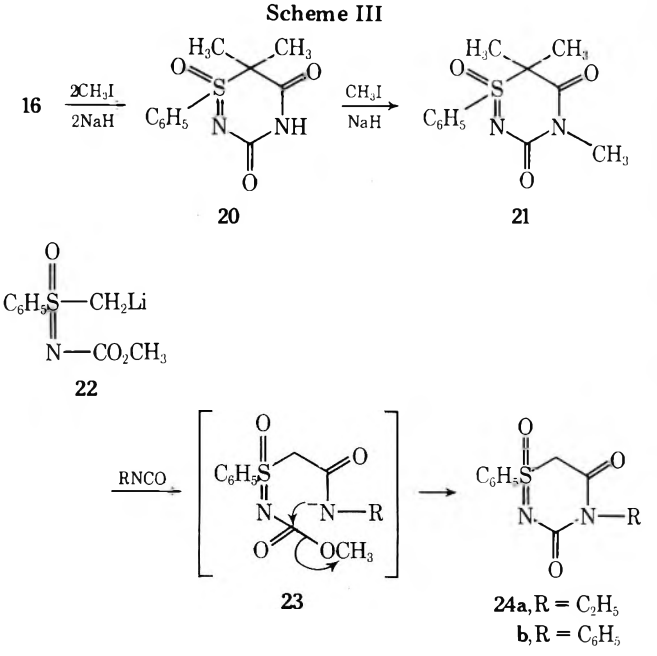
Chart I. ^{13}C **Chemical Shifts (ppm from Me_4Si) of 16 in Me_2SO-d_6**



Chemical shift, ppm	Assignment
52.8	C-6
128.2	C-9, C-11
129.8	C-8, C-12
135.3	C-7, C-10
152.3	C-3, C-5
161.5	

Alkylation of **16** is shown in Scheme III. Treatment of **16** with 1 equiv of NaH and CH_3I yielded a mixture of several major components probably due to indiscriminate alkylation at several sites. With 2 equiv of base and CH_3I a 37% yield of **20** could be isolated from a mixture. This geminally dialkylated product could be converted smoothly to the trimethyl dione **21** in 70% yield. In spite of geminal methyl groups, fragmentations of *m/e* 119, ascribable to $[C_6H_5C(CH_3)_2]^+$ resulting from phenyl migration, are seen in the spectra of **20** [25% of base peak at 125 ($C_6H_5S{\equiv}O^+$)] and **21** [100% of base peak relative to *m/e* 125 (75%)].

Scheme III



A shorter approach to N-substituted diones like **24** was attempted by acylation of the lithio derivative of **10** with

isocyanates. Cyclization was envisioned as occurring directly via **23**, a similar intermediate to the anion involved in the cyclization of **15b** to **19**, to give **24**. Indeed, **24a** and **24b** were obtained but only in very low yields and all attempts to improve this process failed.

Attention was then focused on the conversion of the dione **16** (Scheme IV) to the dichloro derivative **25**. The displacement of the halogens in **25** could then be studied, and their reductive removal to yield the basic 1,2,4-thiadiazine 1-oxide **26** attempted. All efforts to convert **16** to **25** with $SOCl_2$, $POCl_3$, etc., gave unstable yellow mixtures which eluded characterization. Reaction of **16** with 2 equiv of Meerwein reagent, in an attempt to prepare a dialkoxy version of **25** (i.e., **30**) gave a new substance in 80% yield which could be assigned the structure **27**. This new substance showed a one-proton singlet at δ 4.33 that was exchanged with NaOD and DCl. The mass spectrum indicated an M^+ peak at *m/e* 252 and a base peak at *m/e* 118 which was shown by high resolution to be C_8H_6O, most probably attributable to $C_6H_5CH{=}C{=}O$, and a second peak at *m/e* 90 corresponding to C_7H_6. The ^{13}C NMR spectrum (Chart II) showed an important peak at 59.4 ppm.

Scheme IV

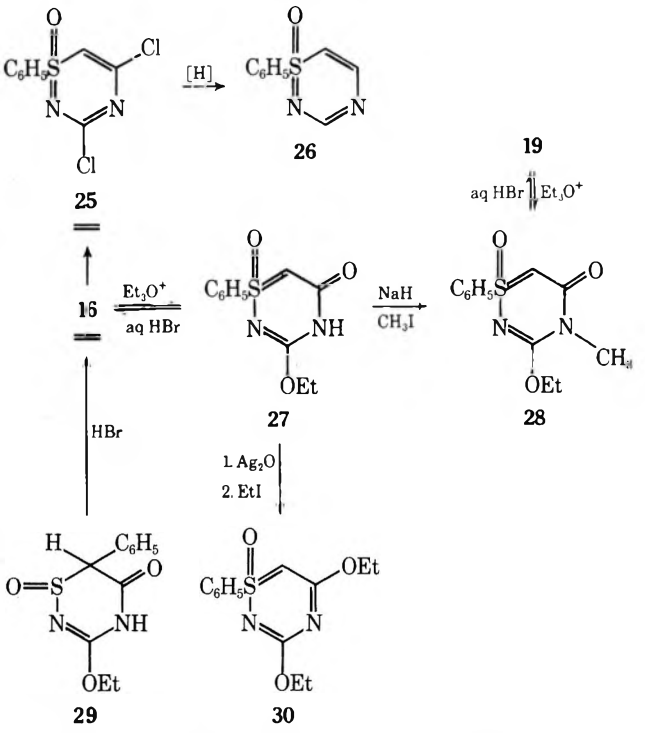
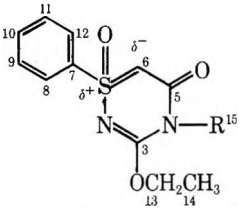


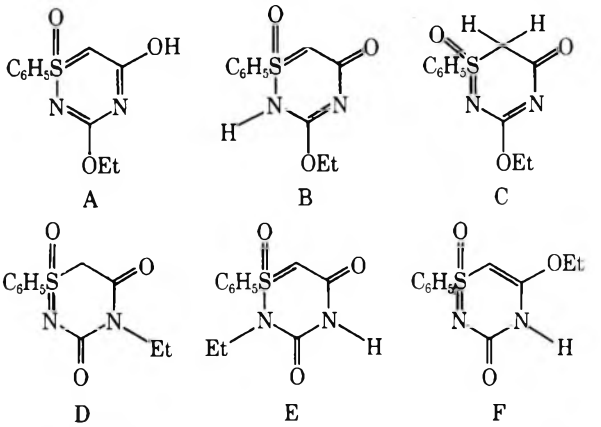
Chart II. ^{13}C Chemical Shifts (ppm from Me_4Si) of **27** and **28** in Me_2SO-d_6



Chemical shift, ppm R = H (27)	Chemical shift, ppm R = CH_3 (28)	Assignment carbon no.
13.9	13.8	14
	27.0	15
59.4	59.3	6
64.9	66.3	13
126.5	126.7	9, 11
129.3	129.2	8, 12
132.9	133.0	10
143.9	143.8	7
157.3	156.2	3, 5
159.4	157.8	

All data indicated that only one ethyl group had entered the new molecule. The indicated ylidic polarization (structure, Chart II) imparts anionic character to carbon 6, shielding it, and explains the unusually high field value for an otherwise vinylic carbon which might be expected to resonate in the 100–140-ppm range. A less plausible structure was **29** which would have resulted from a phenyl migration and change in oxidation state of sulfur during the reaction. The phenyl-bound carbon of **29** could possibly resonate in the 50–60-ppm range, and the molecule might give rise to the phenylketene fragment, *m/e* 118. The coupling constant $J_{^{13}C-H}$ for carbon 6 has a value of 179.9 Hz which should exclude any structure containing an sp^3-hybridized carbon such as in **29**. The $J_{^{13}C-H}$ for carbon 6 in **16** is 146.0 Hz. However, in order to rule out unequivocally **29** and N-alkylated possibilities shown in Chart III, a simple hydrolysis with 16% hydrobromic acid at room temperature was attempted and, indeed, **16** was isolated in 33% yield. The result of this experiment supports structure **27** and definitely rules out structure **29**, as well as D and E (Chart III). The phenyl migration seen in the mass spectrum of **27** then must occur in the spectrometer as it does with **16**, **19**, **20**, **21**, and **28**. Methylation of **27** with NaH–methyl iodide gave the same product **28**, in good yield, as that obtained from **19** and triethyloxonium tetrafluoroborate. Compound **28**, similarly, could be hydrolyzed to **19**. The methyl group of **28** is unequivocally placed on nitrogen at position 4 since **19** was derived from **15** which had been prepared from **14** and methylamine. This is important if one considers the near identity of the ^{13}C NMR spectra of **27** and **28** (Chart II) which suggests structure **27** for the Meerwein product rather than the tautomers A and B (Chart III). A chemical shift difference of 7.7 ppm between carbon 6 in **27** and in **30** (Chart IV and Scheme IV) argues against the enol tautomer A (Chart III). Carbon 6 in A should not be so dissimilar from that of **30**. Other possibilities in Chart III which may be ruled out are C (no methylene protons in the NMR spectrum) and F (it would be difficult to account for the C_8H_6O fragment and the unusually high ylidic shielding (Chart II) of carbon 6[16]).

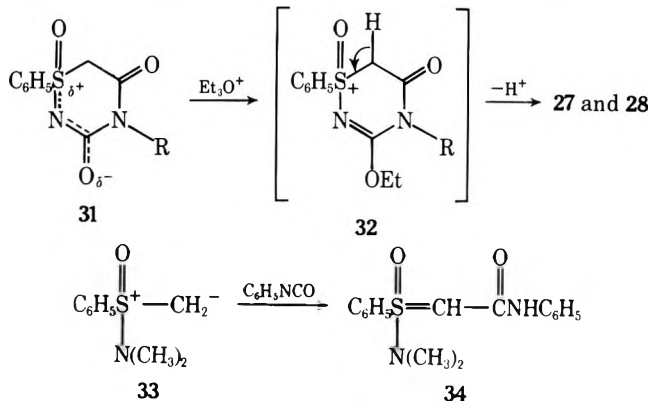
Chart III



The pathway for formation of **27** and **28** can be seen in Scheme V. Polarization of the acylsulfoximide grouping is strong (**31**) and provides as the most choice site for attack by the oxonium species the carbonyl oxygen of position 3 leading via **32** to **27** and **28**. Some precedent exists for this as shown by the acylation of the ylide **33** with phenyl isocyanate to give **34**.[10]

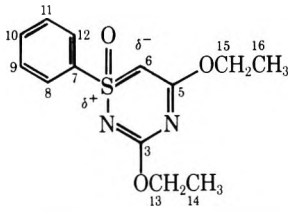
The action of the Meerwein reagent on the dimethyl dione **20** gave a mixture of several components, and in reaction with the open-chain intermediates **14** and **15** no ylidic product similar to **34** was isolated. Reaction of **27** or its sodium salt with 1 equiv of the Meerwein reagent gave a mixture of at least four major products which was not pursued. The desired product **30**, a probable component of this mixture, could be

Scheme V



prepared from **27** by first obtaining the silver salt and treating this in ether at room temperature with ethyl iodide.[17] The ^1H NMR spectrum of **30** shows two nearly identical methylenes and two identical methyls which indicates that the new ethyl group is also on oxygen and not nitrogen. This structure, as might be expected from the electronic nature of **27** and from previous reports,[5,6,18,19] shows chemical and physical properties consistent with ylidic character. The ^{13}C NMR spectrum (Chart IV) shows the ylidic anionic shielding at carbon 6 which

Chart IV. ^{13}C Chemical Shifts (ppm from Me_4Si) of 30 in Me_2SO-d_6

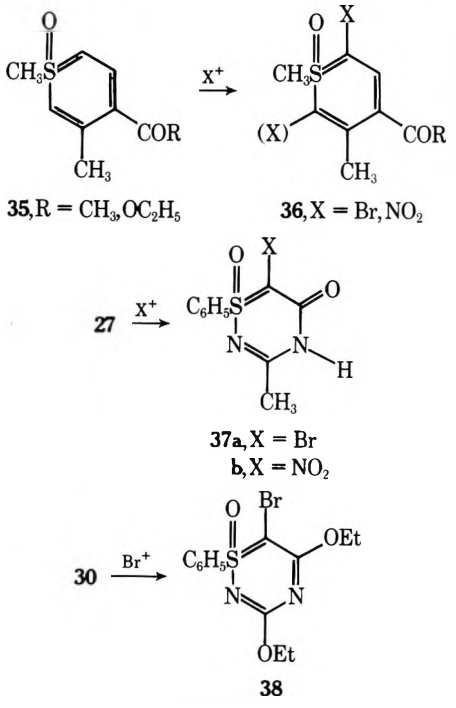


Chemical shift, ppm	Assignment
14.11, 14.29	14, 16
62.20, 63.02	13
67.13	15
126.89	6
129.25	9, 11
133.19	8, 12
142.89	10
161.59	7
168.58	5
	3

resonates at 67.13 ppm ($J_{^{13}C-H}$ = 184.4 Hz).[20] This is 7.7 ppm lower field than the same carbon in **27** (Chart II) and is presumably due to the distribution of electron density not only at C-6 but also to the nitrogens at positions 2 and 4. In **27** electron density is more localized at C-6. This is also reflected in the proton chemical shifts of **27** and **30** since the proton at C-6 appears at δ 4.90 with **30** vs. δ 4.33 with **27.** The mass spectrum shows, in addition to M^+ at *m/e* 280, a base peak at *m/e* 118 indicative of the phenyl migration discussed previously. The mass spectrum is best interpreted, however, as a loss of ethylene from the molecular ion to generate the M^+ of **27** followed by the fragmentation of that species.

The ylidic nature of thiabenzenes and thiabenzene 1-oxides is now well known, and ylidic electrophilic substitution in the 1-oxides has recently been reported[21] as shown by the conversion of **35** to **36.** In a similar manner, compound **27** was smoothly brominated by bromine in CH_2Cl_2 giving the 6-bromo derivative **37a** in 87% yield. Likewise, nitration was accomplished in 43% yield with acetyl nitrate producing the 6-nitro derivative **37b.** Attempts to reduce the nitro group of **37b** with hydrogen on Zn/HOAc failed. Bromination of **30** yielded as the only isolated product a substance best characterized as the dihydrobromide of **38.**[22] An attempt to hydrolyze **30** to **16,** as had been accomplished with **27,** produced a mixture from which neither **16** nor **27** could be clearly identified.

Scheme VI



In summary, physical properties such as ^{13}C NMR spectra and ^1H NMR spectra, and chemical properties such as electrophilic substitution and deuterium exchange at C-7, indicate **27** and **30** to be ylidic 1,2,4-thiadiazine 1-oxides.

Experimental Section

All melting and boiling points are uncorrected. NMR spectra were determined on Varian A-60D and CFT-20 spectrometers and are reported in δ units using tetramethylsilane as an internal reference. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Mass spectra were taken on an AEI-MS902 and are reported as *m/e* with relative intensity (percent of base peak) in parentheses. Extractions were usually worked up by washing, finally, with a saturated NaCl solution, drying over $MgSO_4$ followed by vacuum filtration, and evaporation of solvent under water pressure vacuum on a Rotavapor at 25–60 °C.

***S*-Methyl-*S*-phenyl-*N*-methoxycarbonylsulfoximine (10).** To a solution of 79.47 g (0.512 mol) of **7** in 400 ml of anhydrous dimethoxyethane was added under nitrogen at ambient temperature 30.86 g (0.768 mol) of 50% sodium hydride in portions. After complete addition the slurry was stirred for 2.5 h before the dropwise addition of 72.50 g (0.768 mol) of methyl chloroformate over 1 h. This slurry was stirred for 12–15 h. Suspended solid was removed by filtration, and the filtrate concentrated in vacuo to a yellow residue which was dissolved in 500 ml of $CHCl_3$. This solution was washed with 100 ml of water and with saturated NaCl (2 × 100 ml). The organic layer was dried, filtered, and concentrated in vacuo leaving a pale yellow solid which was washed with petroleum ether and recrystallized from ethyl acetate to give off-white crystals, 65.4 g (59.9%): mp 97–98 °C;[23] NMR (Me_2SO-d_6) δ 7.5–8.0 (m, 5 ArH), 3.38 and 3.41 (2 s, $-SCH_3$ and NCO_2CH_3); IR (Nujol) 1675 (s), 1260 (s), 1220 cm^{-1} (s); *m/e* (rel intensity) M^+ not observed, 198 (100), 182 (95).

***S*-Carboxymethyl-*S*-phenyl-*N*-methoxycarbonylsulfoximine (11).** A solution of 77.7 g of isopropylcyclohexylamine in 300 ml of dry THF was cooled to −10 °C and was treated with 324 ml of 2.25 M *n*-butyllithium in hexane. This solution was stirred for 1 h and to this was added at −70 °C 50.4 g of **10** in 400 ml of THF. This mixture was stirred for 2 h at −70 °C and transferred in portions (carefully to control foaming) to a second flask containing 1800 g of dry ice; the resulting slurry was stirred for 15 h and allowed to come to ambient temperature. To this was added 600 ml of water and, after vigorous mixing, the upper organic layer was separated. The aqueous layer was extracted several times with 50-ml portions of ether, then made acidic with acetic acid and extracted several times with $CHCl_3$. The $CHCl_3$

extracts were dried and concentrated in vacuo to give 55 g of amber oil which was taken up in 1–1.5 volumes of ether and allowed to stand overnight. There was obtained 42 g of the isopropylcyclohexylammonium salt of the acid **11**, mp 109 °C dec.

This substance was dissolved in water and passed through a Rexyn 101 (acid phase) column. As the eluent was collected from the column, the free acid crystallized. There was obtained a total of 20.56 g (33.9%) of acid **11**, mp 103–104 °C.

Anal. Calcd for $C_{10}H_{11}NO_5S$: C, 46.68; H, 4.31; N, 5.45. Found: C, 47.10; H, 4.47; N, 5.50. NMR (Me_2SO-d_6) δ 3.47 (s, OCH_3), 4.87 (s, CH_2), 7.4–8.0 (5 ArH), 12.9 (s, $-CO_2H$); IR (Nujol) 1735 (s), 1640 (s), 1260 and 1220 cm^{-1} (s); pK_a = 3.2.

***S*-(2-Dimethylaminovinyl)-*S*-phenyl-*N*-methoxycarbonylsulfoximine (12).** A mixture of 20.0 g (0.094 mol) of **10** and DMF diethyl acetal (23.34 g, 0.1 mol) was heated at reflux temperature for 4 h. The EtOH which formed was removed by a Dean-Stark trap. After standing overnight the crystalline solid which formed was collected and washed with EtOH giving 16.3 g (65%) of product, mp 130–145 °C. This material was essentially one spot on silica gel thin layer (1:9 MeOH/$CHCl_3$). One recrystallization from EtOH gave 12.7 g (50%) of **12**: mp 147–153 °C; NMR (Me_2SO-d_6) δ 7.4–7.9 (m, 5 ArH), 7.3 (1, d, J = 12 Hz), 3.4 (s, OCH_3), 2.85 [broad s, $-N(CH_3)_2$]; IR (Nujol) 1650 (sh, s), 1625 (s), 1220 (s), 965 cm^{-1} (s).

Anal. Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.71; H, 6.01; N, 10.44. Found: C, 53.71; H, 6.18; N, 10.20.

***S*-Methoxycarbonylmethyl-*S*-phenyl-*N*-methoxycarbonylsulfoximine (14).** To a solution of *N*-isopropylcyclohexylamine (54.1 ml, 41.9 g, 0.30 mol) in 225 ml of THF was added via syringe at −70 °C under nitrogen 147 ml (0.30 mol) of a 2.04 M solution of *n*-butyllithium in ether. To the stirred white suspension after 1 h was added a solution of 26.53 g (0.12 mol) of **10** in 280 ml of THF over 0.5 h. The temperature was maintained below −55 ° throughout the addition. The clear orange solution which resulted was stirred at −70 °C for 2 h and then added in portions to a solution of methyl chloroformate (30.8 g, 25.2 ml) in 95 ml of THF at −70 °C at such a rate that the temperature did not rise above −50 °C. After complete addition the clear, orange solution was stirred at −70 °C for 2 h and stored for ca. 18 h at −50 °C.

To the reaction mixture was added 250 ml of ice water and 300 ml of THF, and this mixture was stirred until room temperature was attained. The organic layer was separated, dried, and concentrated in vacuo to give a partially crystalline yellow-orange residue which was slurried, collected, and washed with a 2:1 ether–petroleum ether mixture. There was obtained after drying in vacuo for 3 h 21.9 g of **14**, mp 89–92 °C (67%). A second crop was obtained by washing the aqueous layer with ether and working up the residue as above to give 3.56 g, mp 88–91 °C; total yield 25.5 g (78%).

Anal. Calcd for $C_{11}H_{13}NO_5S$: C, 48.70; H, 4.83; N, 5.16; S, 11.82. Found: C, 48.89; N, 5.23; S, 11.68. NMR (Me_2SO-d_6) δ 7.50–8.00 (m, 5 ArH), 4.87 (s, $-CH_2-$), 3.48 (s, accidentally equivalent methoxyls); IR (Nujol) 1760 (ester C=O), 1660 cm^{-1} (=NC=O); *m/e* (rel intensity) M^+ not observed, 240 (30), 198 (100), 125 (15).

***S*-Aminocarbonylmethyl-*S*-phenyl-*N*-methoxycarbonylsulfoximide (15a).** To 360 ml of ammonia-saturated MeOH at 40 °C was added 32.2 g (0.12 mol) of **14** as the introduction of ammonia continued. Upon complete addition the yellow solution was maintained at 40 °C for 0.75 h. A thick white suspension formed; the reaction mixture was heated at reflux for 0.75 h while the passage of ammonia was continued. The suspension was cooled in an ice bath and the white product collected, washed with MeOH, and dried in vacuo to give 28.0 g (91%) of amide **15a**, mp 171–172 °C.

Anal. Calcd for $C_{10}H_{12}N_2O_4S$: C, 46.87; H, 4.72; N, 10.93; S, 12.52. Found: C, 46.92; H, 4.88; N, 10.85; S, 12.51. NMR (Me_2SO-d_6) δ 7.5–8.1 (5 ArH), 7.37 (s, NH_2), 4.64 (s, $-CH_2-$), 3.56 (s, OCH_3); IR (Nujol) 3300 (s), 3100 (s), 1640 (s), 1250 and 1210 cm^{-1} (s); *m/e* (rel intensity) 256 (M^+, 5), 225 (15), 198 (100), 125 (20), 58 (45).

***S*-Methylaminocarbonylmethyl-*S*-phenyl-*N*-methoxycarbonylsulfoximine (15b).** Methylamine was introduced into absolute MeOH (540 ml) for 1 h. While gassing was continued, 27.47 g (0.10 mol) of the diester **14** was added in one position. The resulting yellow solution was stirred at 30 °C (without external heating) for 3 h. The solution was concentrated in vacuo to give a white solid, 29 g, which on recrystallization from EtOH gave **15b**, 22.6 g (82.8%), as white crystals, mp 131.5–133.5 °C.

Anal. Calcd for $C_{11}H_{14}N_2O_4S$: C, 48.87; H, 5.22; N, 10.37. Found: C, 49.01; H, 5.32; N, 10.64. NMR (Me_2SO-d_6) δ 7.50–8.20 (m, 5 ArH and NH), 4.56 (s, $-CH_2-$), 3.50 ($-CO_2CH_3$), 2.50 (d, $-NCH_3$); IR 3450 (s), 1750 (s), 1600 (s), 1530–1500 (s), 1310 (s), 1260 cm^{-1} (s); UV max (EtOH, pH 2.0) 221 (ϵ 11 034), 961 (922), 267 (1209), 274 nm (984); (EtOH, pH 6.86) 221 (11 347), 260 (877), 266 (1174), 274 nm (954); (EtOH, pH 10.0) 221 (11 454), 260 (943), 266 (1209), 274 (989).

1-Phenyl-1,2,4-thiadiazine-3,5(4*H*,6*H*)-dione 1-Oxide (16). To a freshly prepared solution of sodium methoxide [from 3.61 g (0.157 mol) of sodium] in 750 ml of absolute MeOH was added under nitrogen at ambient temperature 19.57 g (0.076 mol) of amide **15a** in portions over 10 min. After complete addition the reaction mixture was heated at reflux temperature for 1.5 h. The near-solution was cooled and concentrated to a solid residue which was treated with 50 ml of 25% hydrochloric acid solution. This mixture was concentrated in vacuo, and the solid residue collected, washed with water, and dried at 60 °C (0.2 mmHg) for 4–5 h to give a white solid, 7.96 g (46.7%), mp 207–212 °C. The analytical sample was prepared by recrystallization from water, mp 223 °C.

Anal. Calcd for $C_9H_8N_2O_3S$: C, 48.20; H, 3.60; N, 12.49; S, 14.30. Found: C, 48.27; H, 3.72; N, 12.41; S, 14.41. NMR (Me_2SO-d_6) δ 11.30 (s, NH), 7.60–8.20 (m, 5 ArH), 4.90 (q, J = 17.0 Hz, $-CH_2-$); IR (Nujol) 3150 (m), 1705 (sh, s), 1675 (s), 1365 and 1350 (s), 1240 and 1225 cm^{-1} (s); *m/e* (rel intensity) 224 (M^+, 5), 181 (25), 125 (10), 91 (100), 77 (50); UV max (H_2O, pH 2.0) 219 (ϵ 15 614), 261 (1226), 267 (1510), 274 nm (1211); (H_2O, pH 6.86) 210 (15 205), 256 nm (5212); (H_2O, pH 10.0) 220 (14 991), 265 nm (5234).

The above filtrate from the isolation of **16** was concentrated in vacuo leaving a white residue which was suspended in 30 ml of hot water. This was slurried for 0.5 h and the suspended solid was collected to give 1.83 g, mp 164–166 °C, of a solid identified by spectral data as **17**: NMR (Me_2SO-d_6) δ 9.05 (s, NH_2), 7.50–8.30 (m, 5 ArH), 5.15 (s, $-CH_2$); IR (Nujol) 3200 (s), 3075 (s), 1680 (s), 1260 cm^{-1} (s); *m/e* (rel intensity) M^+ not observed, 155 (10), 92 (40), 77 (60), base peak at 36.

***S*-Methylaminocarbonylmethyl-*S*-phenylsulfoximine (18).** To a mixture of 3.40 g (0.013 mol) of **15b** in 100 ml of EtOH under nitrogen at ambient temperature was added 0.70 g (0.013 mol) of sodium methoxide in one portion. As the mixture was heated to reflux a clear solution was obtained; the solution was held at reflux for 1.5 h and allowed to stand overnight. The solution was then concentrated in vacuo to a white foam which was dissolved in 5 ml of water (pH of solution 10) and extracted with 2 × 25 ml of $CHCl_3$. The organic layers were dried and concentrated to give a white solid, 1.70 g (54.8%), mp 106–109 °C, which was suspended in ether and collected to give 1.23 g of **18**, mp 107–109 °C.

Anal. Calcd for $C_9H_{12}N_2O_2S$: C, 50.91; H, 5.70; N, 13.20. Found: C, 50.81; H, 5.75; N, 13.29. NMR ($CDCl_3$) δ 7.40–8.05 (5 ArH), 7.60 (1 H, –CONH), 5.02 (s, SCH_2CO), 3.72 (s, S=NH, exchanges with D_2O), 2.82 (s, NCH_3); mass spectrum *m/e* (rel intensity) M^+ not observed, 155 (45), 140 (20), 175 (30), 92 (80), 91 (70), 77 (100); IR (Nujol) 3700 (vs), 1620 (s), 1260 cm^{-1} (s).

4-Methyl-1-phenyl-1,2,4-thiadiazine-3,5(4*H*,6*H*)-dione 1-Oxide (19). To a suspension of 0.48 g (0.01 mol) of NaH (50% in mineral oil) in 40 ml of DMF under nitrogen at ambient temperature was added 2.80 g (0.01 mol) of **15b** in portions over 10 min. A clear solution resulted in about 0.5 h after addition. After stirring for 20 h TLC (silica gel, $CHCl_3$/MeOH, 8:2) showed incomplete reaction. The temperature was raised to 100 °C for 3 h at which time TLC indicated that the reaction was complete. The solution was cooled, treated with 50 ml of water, and concentrated to a clear, caramel-colored oil which was then triturated with petroleum ether twice to remove mineral oil. After decantation the residue was treated with 25 ml of 3 N HCl, and the solid, which formed immediately, was collected, washed with water, and air dried to give 1.78 g (74.8%) of **19**, mp 137–138 °C. TLC (8:2 $CHCl_3$–MeOH) was one spot.

Anal. Calcd for $C_{10}H_{10}N_2O_3S$: C, 50.41; H, 4.23; N, 11.76. Found: C, 50.18; H, 4.20; N, 11.52. NMR (Me_2SO-d_6) δ 7.6–8.2 (5 ArH), 5.13 (d, $-CH_2-$, J = 16 Hz), 3.25 (s, NCH_3); IR (Nujol) 1715 (s), 1675 (s), 1260 cm^{-1} (s); UV max (EtOH, pH 2.2) 222 (ϵ 16 854), 274 (1230), 2665 (1549), and 260 nm (1280); (EtOH, pH 6.86) 222 (14 188), 267 nm (4694); (EtOH, pH 10.0) 222 (13 481), 266 (4698) and 272 nm (4660); mass spectrum *m/e* (rel intensity) 238 (M^+, 40), 181 (50), 148 (20), 91 (100), 77 (40).

6,6-Dimethyl-1-phenyl-1,2,4-thiadiazine-3,5(4*H*,6*H*)-dione 1-Oxide (20). To a suspension of 2.59 g (0.054 mol) of 50% NaH in 150 ml of DMF under nitrogen was added at ambient temperature 6.00 g (0.027 mol) of **16**. The resulting mixture was stirred for 0.5 h, cooled to ca. 15 °C, and treated dropwise with a solution of 14.76 g (0.104 mol) of methyl iodide in 10 ml of DMF. This mixture was stirred for ca. 15 h. Addition of two volumes of ether to the reaction mixture caused a voluminous inorganic precipitate to form which was removed by filtration. The filtrate was concentrated in vacuo to a thick, dark amber oil which was heated at 50 °C (0.2 mmHg) to remove traces of DMF. Treatment of this oil with ethanol produced a solid which was collected, washed with EtOH, and pulled dry, yielding a white solid,

2.55 g (37.4%), mp 178–180 °C.

Anal. Calcd for $C_{11}H_{12}N_2O_3S$: C, 52.36; H, 4.80; N, 11.11. Found: C, 52.19; H, 5.07; N, 11.09. NMR (Me_2SO-d_6) δ 11.28 (s, NH), 7.65–8.20 (5 ArH), 1.30 and 1.54 (2 s, gem CH_3's); IR (Nujol) 3150 (m), 1700 (s), 1650 (broad, s), 1230 cm^{-1} (s); *m/e* (rel intensity) M^+ 252 (30), 209 (15), 125 (100), 77 (40), 69 (50); UV max (EtOH, pH 2.0) 223 (ε 16 480), 261 (1460), 268 (1648), 275 (1272); (EtOH, pH 6.86) 223 (16 318), 261 (1690), 268 (1889), 275 (1487); (EtOH, pH 10.0) 221 (12 418), 253 (1141), 260 (1259), 266 (1444), 274 (1109).

4,6,6-Trimethyl-1-phenyl-1,2,4-thiadiazine-3,5(4*H*,6*H*)-dione 1-Oxide (21). To a suspension of 0.08 g (0.0016 mol) of sodium hydride in 25 ml of DMF at ambient temperature was added dropwise a solution of 0.36 g (0.0016 mol) of **20** in 5 ml of DMF, and the resulting slurry stirred for 1 h. To this suspension was added dropwise 0.45 g (0.0032 mol) of methyl iodide in the same solvent, and this was stirred for 21 h. On dilution with ether an inorganic precipitate formed which was removed by filtration. The filtrate was concentrated in vacuo, and the residue treated with water and again concentrated in vacuo. The residue was successively slurried with EtOH and benzene and again evaporated to dryness in vacuo each time. Finally, the residue was triturated with petroleum ether–EtOH (1:1) and collected to yield 0.299 g (69.8%) of **21**, mp 135–137 °C.

NMR ($CDCl_3$) δ 7.6–8.2 (m, 5 ArH), 3.38 (s, NCH_3), 1.38 and 1.68 (singlets, CCH_3's); mass spectrum *m/e* (rel intensity) 266 (M^+, 25), 209 (50), 119 (100), 125 (70), 69 (25).

1,5-Diphenyl-1,2,4-thiadiazine-3,5(4*H*,6*H*)-dione 1-Oxide (24b). To a solution of *N*-isopropylcyclohexylamine (6.5 g, 0.046 mol) in 30 ml of THF at −20 °C under nitrogen was added 21 ml (0.046 mol) of a 2.2 M solution of *n*-BuLi in hexane via hypodermic syringe. After complete addition the clear solution was stirred at −60 to −70 °C for 1 h during which time a suspension formed. To this was added a solution of 5.0 g (0.023 mol) of **10** in 45 ml of THF dropwise. The clear yellow solution was stirred at −70 °C for 1.5 h prior to the addition of 2.74 g (0.023 mol) of phenyl isocyanate. During the dropwise addition an exotherm to −60 °C was noted. The mixture was stirred at −60 °C for 1.5 h and was then allowed to warm to room temperature during which time it changed to an orange suspension. The reaction mixture was diluted with water, the organic layer separated, and the aqueous layer washed with 50 ml of ether. The combined organic layers were dried and concentrated, leaving a partially crystalline residue. This was passed through a column of neutral alumina with $CHCl_3$. The crude crystalline product obtained was recrystallized from EtOH giving 520 mg (8%) of **24b**,[24] mp 184–186 °C.

Anal. Calcd for $C_{15}H_{12}N_2O_3S$: C, 59.98; H, 4.03; N, 9.33. Found: C, 59.79; H, 4.12; N, 9.32. NMR (Me_2SO-d_6) δ 7.1–8.2 (10 ArH in three multiplets), 4.82 (2 H, d, J = 16 Hz, exchanged by D_2O).

3-Ethyl-1-phenyl-1,2,4-thiadiazin-5(4*H*)-one 1-Oxide (27). To a suspension of 7.70 g (0.034 mol) of **16** in 150 ml of methylene chloride under nitrogen was added 68 ml (0.068 mol) of a 1.0 M solution of triethyloxonium tetrafluoroborate.[25] The suspension obtained was stirred at room temperature for 3.5 h at which time a clear solution had resulted. After an additional 2 h at room temperature the solution was washed with 2 × 25 ml of ice-cold 5% Na_2CO_3 solution and 1 × 25 ml of brine solution. The organic layer was dried, filtered, and concentrated in vacuo to give 10.4 g of a clear, colorless oil which on trituration with hot EtOH crystallized. The solid was collected and washed with EtOH to give 6.90 g (80.4%) of **27**, mp 174–176.5 °C. One recrystallization from EtOH gave mp 180–182 °C.

Anal. Calcd for $C_{11}H_{12}N_2O_3S$: C, 52.36; H, 4.80; N, 11.11. Found: C, 52.53; H, 4.95; N, 11.17. NMR (Me_2SO-d_6) δ 11.3 (NH, broad), 7.5–8.0 (5 ArH), 4.35 (s, S=CHCO, exchanges with NaOD or DCl), 4.28 (q, J = 7 Hz, $-OCH_2CH_3$), 1.24 (t, J = 7 Hz, $-CH_2CH_3$); IR (Nujol) 2700 (m), 1630–1580 (s), 1550 (s), 1520 (s), 1285 (s), 1245 (s), 1210 cm^{-1} (s); *m/e* (rel intensity) 252 (M^+, 80), 237 (10), 224 (10), 208 (10), 118 (100, C_8H_6O), 90 (25, C_7H_6); UV max (H_2O, pH 2.0) 217 (ε 13 807), 260 (2052), 266 (2166), 274 (1818); (H_2O, pH 6.86) 220 (16 650), 260 (3978), 266 (4010), 273 (3544); (H_2O, pH 10) 229 (12 997), 265 (3736), 273 (3672).

3-Ethoxy-4-methyl-1-phenyl-1,2,4-thiadiazin-5(4*H*)-one 1-Oxide (28). A. By Action of Meerwein Reagent on 19. To a mixture of 1.51 g (0.006 mol) of **19** in 15 ml of CH_2Cl_2 at room temperature was added 6.0 ml (0.006 mol) of a 1 M solution of triethyloxonium tetrafluoroborate in CH_2Cl_2. The cloudy suspension was stirred for 2 h [TLC (silica gel, 9:1 $CHCl_3$–MeOH) showed no change after 1 h] and washed with 5% Na_2CO_3 solution (2 × 5 ml) followed by a brine wash (1 × 5 ml). The organic layer was dried, filtered, and concentrated in vacuo to give 1.61 g of a clear, amber oil which on standing partially crystallized. The solid which formed was collected and washed with EtOH to give a white solid, 0.63 g (39.4%) of **28**, mp 117–119 °C. One recrystallization (EtOH) raised the melting point to 118–120 °C.

B. By Methylation of 27. To a suspension of 100 mg (0.002 mol) of NaH in 20 ml of DMF at room temperature under nitrogen was added 500 mg (0.002 mol) of **27** in one portion. A slight exotherm was seen and the mixture was allowed to stir for 20 min while cooling to room temperature. A solution of 0.85 g (0.006 mol) of methyl iodide in 5 ml of DMF was added dropwise and the resulting solution was stirred overnight at ambient temperature. It was then diluted with ether and a solid formed which was removed by filtration. The filtrate was then concentrated, first on a rotary evaporator, then at 50 °C (20 mmHg) to remove DMF. The resulting brown oil partially crystallized on standing. TLC (silica gel, 9:1 $CHCl_3$–MeOH) suggested the same product as in A which was confirmed by NMR and mass spectra.

Anal. Calcd for $C_{12}H_{14}N_2O_3S$: C, 54.12; H, 5.30; N, 10.52. Found: C, 54.19; H, 5.24; N, 10.26. NMR (Me_2SO-d_6) δ 7.5–8.2 (5 ArH), 4.40 (q, J = 7 Hz, $-CH_2CH_3$), 4.38 (s, S=CCO, exchange with D_2O), 3.35 (s, NCH_3), 1.35 (t, J = 7 Hz, $-CCH_3$); IR (Nujol) 1635 (s), 1550 (s), 1220 cm^{-1} (s); *m/e* (rel intensity) 266 (M^+, 60) 208 (10), 118 (100), 77 (50).

3,5-Diethoxy-1-phenyl-1,2,4-thiadiazine 1-Oxide (30). To a suspension of 1.0 g (0.004 mol) of **27** in 25 ml of water at room temperature was added 1.6 ml of a solution of 10 g of NaOH in 100 ml of water. To the resulting clear solution was added dropwise a solution of 0.68 g (0.004 mol) of silver nitrate in 7 ml of water. A white precipitate formed immediately. After complete addition the suspension was stirred for ca. 1 h and the solid was collected by filtration, washed with water and EtOH, and dried in vacuo, giving 1.29 g, mp 196–199 °C dec, of the crude silver salt of **27**: infrared (Nujol) 1560 (sh, s), 1525 (vs), 1350 (s), and 1210 cm^{-1} (s).

To a suspension of this material (1.29 g, 3.6 mmol) in 50 ml of ether was added 0.56 g (3.6 mmol) of ethyl iodide all at once. The resulting suspension was stirred in the dark for 23 h and in the light for 1 h. The slurry was filtered and the filtrate concentrated to a clear, colorless oil, 260 mg (26%) of **30**. TLC (silica gel, $CHCl_3$–MeOH, 9:1) indicated one clean component: NMR (Me_2SO-d_6) δ 7.4–7.9 (m, 5 ArH), 4.33 (center of two overlapping $-CH_2-$ groups, J = 6.5 Hz for each), 1.35 (two CH_3's, J = 6.5 Hz); *m/e* (rel intensity) 280 (M^+, 35), 265 (50), 252 (25), 237 (25), 125 (90), 118 (100), 77 (80); IR (Nujol) 1610 (m), 1575 (sh, m), 1545 (s), 1320 (s), and 1240 cm^{-1} (s).

Electrophilic Substitution of 27. A. Bromination. To a clear, colorless solution of 100 mg of **27** in 5 ml of $CHCl_3$ at room temperature was added dropwise a dilute solution of bromine in $CHCl_3$ until the color of bromine just failed to be discharged. The yellow solution became cloudy in ca. 15 min as a solid formed. After 0.5 h this solid was collected and washed with $CHCl_3$ leaving 116 mg (87%) of **37a**: mp 97 °C dec; NMR (Me_2SO-d_6) δ 7.6–8.0 (5 ArH), 4.33 (q, J = 7 Hz, $-OCH_2CH_3$), 1.23 (t, J = 7 Hz, $-CH_2CH_3$); IR (Nujol) 3400 (w), 2700 (m), 1740 (m), 1650 (m), 1550 (s), 1250 (s), 1260 cm^{-1} (s); high resolution *m/e* (rel intensity) 330 (M^+, 10), 302 (5), 259 (5), 184 (80, $C_7H_6NO_3S$), 141 (30), 125 (100), 77 (80).

B. Nitration. A solution of 630 mg of **27** in 10 ml of Ac_2O and 4 ml of HOAc was added dropwise to a cold solution (−5 °C) of acetyl nitrate which had been prepared by addition of 1.8 ml of 70% HNO_3 to 12 ml of Ac_2O at −5 °C. After addition was complete the resulting orange solution was stirred for 10 min at −5 °C, allowed to warm to room temperature (ca. 1 h), poured into ice and water, and stirred for 1 h. The orange solid which separated was collected by filtration and washed with water, leaving 0.32 g (43%) of **37b**, mp 204 °C dec.

Anal. Calcd for $C_{11}H_{11}N_3O_5S$: C, 44.44; H, 3.73; N, 14.13; Found: C, 44.54; H, 4.00; N, 13.90. NMR (Me_2SO-d_6) δ 12.45 (s, broad, NH), 7.48–8.25 (5 ArH), 4.36 (q, J = 7 Hz, $-CH_2CH_3$), 1.25 (t, J = 7 Hz, $-CH_2CH_3$); IR (Nujol) 3350 (w), 1675 (s), 1580 (s), 1540 (s), 1300 (s), 1250 (s), 915 cm^{-1} (s); *m/e* (rel intensity) 297 (M^+, 15), 125 (100), 77 (95).

Bromination of 30. To a solution of 19 mg of **30** in 4 ml of $CHCl_3$ was added dropwise at room temperature approximately 1 ml of a solution prepared from 1 ml of bromine and 9 ml of $CHCl_3$. Addition was carried out until the bromine color was no longer discharged.[22] The solution was stirred for 1 h at which time a precipitate had formed. The mixture was concentrated in vacuo, yielding a yellow solid which was suspended in $CHCl_3$ and collected by vacuum filtration to give 65 mg of yellow solid, mp 117 °C dec. The analysis best fits a dihydrobromide.

Anal. Calcd for $C_{13}H_{15}BrN_2O_3S \cdot 2HBr$: C, 29.96; H, 3.29; N, 5.38. Found: C, 28.36; H, 2.91; N, 5.05. NMR (Me_2SO-d_6) δ 7.5–7.75 (5 ArH + 2 HBr, exchanges), 4.25 (center of two overlapping CH_2's), 1.23 (two $-CH_2CH_3$, s); IR (Nujol) 1620 (vs), 1260 cm^{-1} (vs); *m/e* (rel intensity) 358 (M^+, 15), 343 (5), 330 (5), 315 (5), 302 (5), 125 (100), 80 (45, HBr).

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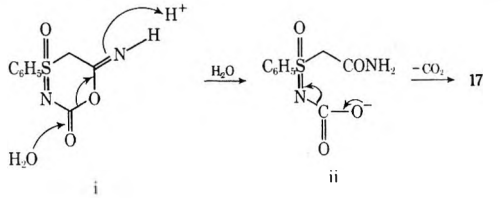
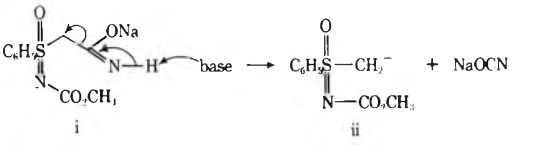
Registry No.—**7,** 4381-25-3; **10,** 61177-70-6; **11,** 61177-71-7; **11** isopropylcyclohexylammonia salt, 61218-49-3; **12,** 61177-72-8; **14,** 61177-73-9; **15a,** 61177-74-0; **15b,** 61177-75-1; **16,** 61177-76-2; **17,** 61202-86-6; **18,** 61177-77-3; **19,** 61177-78-4; **20,** 61177-79-5; **21,** 61177-80-8; **24b,** 61177-81-9; **27,** 61177-82-0; **27** Ag salt, 61177-83-1; **28,** 61177-84-2; **30,** 61177-85-3; **37a,** 61177-86-4; **37b,** 61177-87-5; **38** 2HBr, 61177-88-6; methyl chloroformate, 79-22-1; *N*-isopropylcyclohexylamine, 1195-42-2; DMF diethyl acetal, 1188-33-6; phenyl isocyanate, 103-71-9; acetyl nitrate, 591-09-3; methyl iodide, 74-88-4; ethyl iodide, 75-03-6; bromine, 7726-95-6.

References and Notes

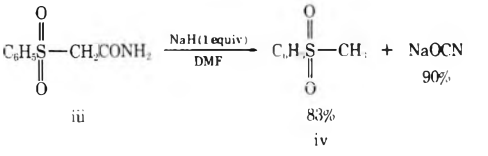
(1) A portion of this work was presented at the Fifth International Congress of Heterocyclic Chemistry, Ljubljana, Yugoslavia, July 8–13, 1975, Abstracts, p 305.
(2) Exchange Scientist, 1973, from the Research Department, Pharmaceutical Division, CIBA-GEIGY A.G., 4002 Basel, Switzerland.
(3) S. L. Huang and D. Swern, *Int. J. Sulfur Chem.*, **9,** 210 (1974); P. D. Kennewell and J. B. Taylor, *Chem. Soc. Rev.*, **4,** 189 (1975).
(4) See P. Stoss and G. Satzinger, *Chem. Ber.*, **108,** 3855 (1975), and references cited therein.
(5) T. R. Williams and D. J. Cram, *J. Org. Chem.*, **38,** 20 (1973).
(6) A. C. Barnes, P. D. Kennewell, and J. B. Taylor, *J. Chem. Soc., Chem. Commun.*, 776 (1973).
(7) Prepared by conversion of the commercially available acid via the acid chloride to the amide followed by oxidation with $NaIO_4$, mp 136–137 °C.
(8) (a) F. Misani, T. W. Fair, and J. Reiner, *J. Am. Chem. Soc.*, **73,** 459 (1951); (b) G. Satzinger and P. Stoss, *Arzneim.-Forsch.*, **20,** 1214 (1970).
(9) (a) Y. Tamura, K. Sumato, J. Minamikawa, and M. Ikeda, *Tetrahedron Lett.*, 4137 (1972); (b) C. R. Johnson, R. A. Kirchhoff, and H. G. Corkins, *J. Org. Chem.*, **39,** 2458 (1974).
(10) C. R. Johnson, M. Haake, and C. W. Schroeck, *J. Am. Chem. Soc.*, **92,** 6594 (1970).
(11) (a) A. T. Fuller, I. M. Tonkin, and J. Walker, *J. Chem. Soc.*, 636 (1945); (b) R. L. Heath and A. Lambert, *ibid.*, 1477 (1947).
(12) H. Bredereck, F. Effenberger, and H. Botsch, *Chem. Ber.*, **97,** 3397 (1964).
(13) The amide **17** might arise from simple attack of methoxide on the *N*-methoxycarbonyl of **15a** or by internal attack of the amide oxygen of **15a** giving rise to i which on hydrolysis and decarboxylation would give **17.**



i ii
(14) One possible explanation of this cleavage reaction which occurs with **15a** but *not* with **15b** would be the generation, even with 1 equiv of NaH, of the dianion of i which cleaves, as shown, to give ii and NaOCN. Proton abstraction by ii, now fulfilling the role of base would form **10.** Such a cleavage



would be unavailable to the *sec*-amide. Deprotonation of i could be accomplished by NaH but not by $NaOCH_3$. Treatment of the model sulfone iii with 1 equiv of NaH under these same conditions gave complete cleavage in 3 h at 100 °C with products isolated and identified as shown. No sulfone iv is formed in refluxing methanol–$NaOCH_3$. We intend to examine this



cleavage process more closely. The formation of LiOCN via a cleavage process has been reported by U. Schollkopf and F. Gerhart, *Angew. Chem.*, **80,** 842 (1968).
(15) S. Oae, K. Harada, K. Isiyikara, and N. Furukawa, *Int. J. Sulfur Chem., Part A,* 49 (1972).
(16) The β carbon of vinyl ethers is somewhat shielded and appears in the 85–90-ppm (relative to Me_4Si) range, far below the 59.3-ppm value for **27.** See J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, Table 5.47, p 184.
(17) (a) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, **77,** 6269 (1955); (b) H. vonPechmann and O. Baltzer, *Chem. Ber.*, **24,** 3148 (1891).
(18) G. H. Senkler, Jr., J. Stackhouse, B. E. Maryanoff, and K. Mislow, *J. Am. Chem. Soc.*, **96,** 5648, 5650, 5651 (1974).
(19) A. Hortmann and R. L. Harris, *J. Am. Chem. Soc.*, **93,** 2471 (1971); A. Hortmann, R. L. Harris, and J. A. Miles, *ibid.*, **96,** 6119 (1974).
(20) For comparison, the comparable carbon in **2** resonates at 78.9 ppm, in 1,3,5-trimethylthiabenzene 1-oxide at 83.7 ppm, and in **35** (R = CH_3) at 92.1 ppm relative to Me_4Si.
(21) Y. Tamura, H. Taniguchi, T. Miyamoto, M. Isumekawa, and M. Ikeda, *J. Org. Chem.*, **39,** 3519 (1974).
(22) Unfortunately an excess of bromine was mistakenly employed in this final experiment which exhausted our supply of **30.**
(23) The ethoxycarbonyl derivative of **7** is reported as an oil in ref 5.
(24) Compound **24b,** mp 148–151 °C, was obtained in a similar manner in 4% yield.
(25) H. Meerwein, *Org. Synth.*, **46,** 113 (1966).

Reactions of Alkyl or Aryl Chlorosulfites with Thiocarboxylic Acids

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Alkyl or aryl chlorosulfites (**7**) reacted with *p*-nitrothiobenzoic acid to give *S*-acylalkyl or *S*-acylaryl thiosulfites (**6**). However, treatment of alkyl chlorosulfites with aliphatic thiocarboxylic acids afforded acylalkyl sulfites (**5**) and acylalkoxy trisulfides (**8**) as a result of disproportionation of **6.** These trisulfides were also obtained by the reaction of dialkoxy disulfides with thiocarboxylic acids. Thermal decomposition of **6** gave **8** and carboxylic esters.

In contrast to ordinary sulfites and monothiosulfites,[1] RSS(O)OR′ (**1**), dithiosulfites,[2] RSS(O)SR (**2**) (R = Ar or *tert*-alkyl), prepared from thionyl chloride and mercaptans are relatively unstable compound and readily decompose to give di- and trisulfides. Previously, we have reported the preparation of diacyl dithiosulfites,[3] RCOSS(O)SCOR′ (**3**), and acylaryl dithiosulfites,[4] RCOSS(O)SR′ (**4**), by the reaction of acyl thiochlorosulfites with thiocarboxylic acids or thiophenols. These acyl derivatives of dithiosulfites were found to be reasonably stable on standing but decomposed to afford carboxylic anhydrides (from **3**) or disulfides and carboxylic anhydrides (from **4**) on heating. Acyl derivative of ordinary sulfites,[5] RCOOS(O)OR′ (**5**), are stable at room temperature but decompose on heating into carboxylic esters or carboxylic

Table I
p-$O_2NC_6H_4CSSOR'$
‖ ↓
O O
6

Registry no.	Compd	R′	Mp, °C	Yield, %	IR (KBr), cm^{-1} $\nu_{C=O}$	IR (KBr), cm^{-1} $\nu_{S\rightarrow O}$	Anal. Calcd (found), % C	H	S
61268-11-9	6a	CH_3	76–78	73	1670	1165	36.78 (37.09)	2.70 (2.77)	24.54 (24.32)
61268-12-0	6b	C_2H_5	84–85	52	1670	1170	39.27 (39.44)	3.30 (3.28)	23.29 (23.04)
61268-13-1	6c	n-C_3H_7	72–73	62	1665	1165	41.51 (41.82)	3.84 (3.63)	22.15 (21.98)
61268-14-2	6d	i-C_3H_7	96–98	58	1640	1135	41.51 (41.28)	3.84 (3.53)	22.15 (21.82)
61268-15-3	6e	C_6H_5	78–79	46	1630	1140	48.29 (48.30)	2.81 (2.66)	19.83 (19.80)
61268-16-4	6f	p-$CH_3C_6H_4$	74–76	64	1670	1140	49.86 (50.22)	3.29 (3.28)	19.01 (18.83)
61268-17-5	6g	p-$C_2H_5C_6H_4$	72–73	79	1650	1140	51.29 (51.60)	3.73 (3.73)	18.26 (18.31)
61268-18-6	6h	2,4-$(CH_3)_2C_6H_3$	87–88	74	1660	1150	51.29 (51.50)	3.73 (3.67)	18.26 (18.21)

Table II. NMR Spectral Data for *S*-Acyl Thiosulfites (6)

Compd	δ ($CDCl_3$)[a]
6a	8.14 (q, 4 H) 4.00 (s, 3 H)
6b	8.15 (q, 4 H) 4.42 (m, 2 H)[b] 1.49 (t, 3 H)
6c	8.17 (q, 4 H) 4.35 (m, 2 H)[b] 1.86 (m, 2 H) 1.02 (t, 3 H)
6d	8.17 (q, 4 H) 5.18 (m, 1 H) 1.47 (d, 6 H)
6f	8.09 (q, 4 H) 7.13 (s, 4 H) 2.33 (s, 3 H)
6g	8.11 (q, 4 H) 7.17 (s, 4 H) 2.67 (q, 2 H) 1.24 (t, 3 H)
6h	8.14 (q, 4 H) 7.11 (m, 3 H) 2.33 (s, 3 H) 2.29 (s, 3 H)

[a] Chemical shifts are in parts per million from internal Me_4Si. [b] $-OCH_2-$ protons showed ABX_3 or ABX_2 type coupling. Coupling constant and chemical shift: **6b**, J_{AB} = 9.35, $\nu_A - \nu_B$ = 19.6 Hz; **6c**, J_{AB} = 9.75, $\nu_A - \nu_B$ = 21.5 Hz, 20% $CDCl_3$, 60 MHz. Measurement of spectrum of **6e** was omitted, as it has no aliphatic protons.

anhydrides depending on the condition. Accordingly, we are interested in studying acyl derivative of monothiosulfites, RCOSS(O)OR′ (**6**), in the present investigation.

Results and Discussion

Alkyl or aryl chlorosulfites (**7**) prepared from thionyl chloride and alcohols or phenols were allowed to react with p-nitrothiobenzoic acid. Crystalline *S*-acyl thiosulfites (**6a–h**)

$$R'OH \xrightarrow{SOCl_2} \underset{\underset{O}{\downarrow}}{R'OSCl} \xrightarrow{\overset{RCSH}{\overset{\|}{O}}} \underset{\underset{O\ O}{\|\ \downarrow}}{RCSSOR'} \qquad (1)$$

7 6

were obtained in fairly good yields. The IR spectra of **6** showed the carbonyl and sulfinyl absorptions in the region of 1630–1670 and 1135–1170 cm^{-1}. The results are shown in Table I. The NMR spectrum of **6b** or **6c** showed ABX_3 or ABX_2 type coupling in its protons of methylene adjacent to the oxygen atom. This magnetic nonequivalence may arise by the asymmetric center of sulfinyl group as in the case of ordinary sulfites.[6] The pertinent NMR data are given in Table II.

On the other hand, the reaction of thioacetic acid with ethyl chlorosulfite gave an unexpected result. Two products, A and B, were obtained in nearly equal amount. The former low-boiling product A was found to be the already known acetylethyl sulfite (**5b**)[5] and the latter high-boiling product B was

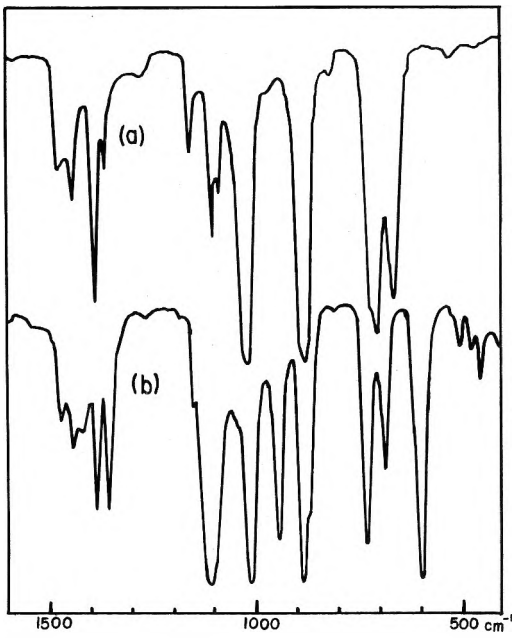


Figure 1. IR spectra of diethoxy disulfide (a) and acetylethoxy trisulfide (b) (neat).

proved to have a formula $C_4H_8O_2S_3$ by elemental analysis. The IR spectrum of B showed a carbonyl band at 1735 cm^{-1} but no sulfinyl band in the region of 1100–1200 cm^{-1}. In order to determine the structure of B we have carried out the following experiment. When diethoxy disulfide (**9**) was treated with equimolar thioacetic acid, one ethoxy group was readily displaced with CH_3COS group and acetylethoxy trisulfide and ethanol were obtained in good yield (eq 2). The IR spectrum

$$\underset{9}{R'OSSOR'} + RCSH \longrightarrow \underset{\underset{O}{\|}\qquad\underset{O}{\|}}{RCSSSOR'} + R'OH \qquad (2)$$

8

of this sulfide was completely identical with that of B. The sulfur linkage of dialkoxy disulfides is unbranched[7] and the IR spectra of B and diethoxy disulfide showed similar absorptions in –S–O– (660–730 cm^{-1}) and >C–O– (1010 and 880 cm^{-1}) stretching bands as shown in Figure 1. Accordingly, it has been elucidated that B is unbranched trisulfide

Table III. Reaction Products of Alkyl Chlorosulfites with Aliphatic Thiocarboxylic Acids

		RCOSOR′ (5)				RCSSSOR′ (8)					
								Anal. Calcd (found), %			
R	R′		Yield, %[a]	Bp, °C (mm)	Registry no.		Yield, %[a]	Bp, °C (mm)	C	H	S	Registry no.
CH_3	CH_3	5a	36	43–44 (3)	5308-06-5	8a	29	51 (0.4)	21.16 (21.44)	3.55 (3.43)	56.49 (56.33)	61268-22-2
CH_3	C_2H_5	5b	49	51 (2)	5308-11-2	8b	41	62 (0.4)	26.07 (26.31)	4.37 (4.20)	52.20 (52.06)	61268-23-3
CH_3	n-C_3H_7	5c	78	66–66.5 (2.5)	1666-21-3	8c	35	72 (0.5)	30.27 (30.64)	5.10 (5.30)	48.50 (48.26)	61268-24-4
CH_3	i-C_3H_7	5d	75	56–57 (1.5)	61268-19-7	8d	58	73.5 (0.6)	30.27 (30.54)	5.10 (5.11)	48.50 (48.37)	61268-25-5
C_2H_5	C_2H_5	5e	56	64–65 (2)	61268-20-0	8e	30	71 (0.35)	30.27 (30.31)	5.10 (5.20)	48.50 (48.47)	61268-26-6
n-C_3H_7	C_2H_5	5f	48	67–68 (1)	61268-21-1	8f	39	82–83 (0.5)	33.94 (34.02)	5.70 (5.78)	45.30 (45.18)	61268-27-7

[a] Yields of 5 and 8 are calculated on the basis of eq 3.

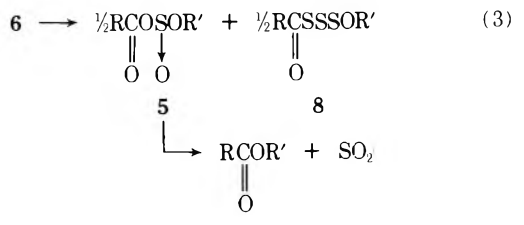
Table IV. Spectral Data for Acylalkoxy Trisulfides (8)

Compd	NMR, δ (CCl_4)[a]			IR (neat), $\nu_{C=O}$, cm^{-1}
8a	3.73 (s, 3 H)	2.46 (s, 3 H)		1735
8b	3.93 (q, 2 H)	2.45 (s, 3 H)	1.23 (t, 3 H)	1735
8c	3.83 (t, 2 H)	2.45 (s, 3 H)	1.67 (m, 2 H)	1735
	0.93 (t, 3 H)			
8d	4.14 (m, 1 H)	2.47 (s, 3 H)	1.28 (d, 6 H)	1735
8e	3.94 (q, 2 H)	2.71 (q, 2 H)	1.29 (t, 3 H)	1725
	1.23 (t, 3 H)			
8f	3.94 (q, 2 H)	2.70 (t, 2 H)	1.71 (m, 2 H)	1730
	1.25 (t, 3 H)	0.95 (t, 3 H)		

[a] Chemical shifts are in parts per million from internal Me_4Si.

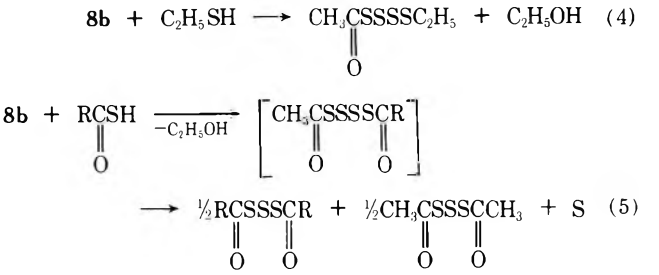
$CH_3C(O)SSSOC_2H_5$ (**8b**). Similarly, the other acylalkoxy trisulfides (**8**) were obtained by the reaction of alkyl chlorosulfites (**7**) with aliphatic thiocarboxylic acids or by the reaction of dialkoxy disulfides (**9**) with thiocarboxylic acids. The results are shown in Tables III and IV.

Thermal decomposition of *S*-*p*-nitrobenzoylisopropyl thiosulfite (**6d**) gave bis(*p*-nitrobenzoyl) disulfides, isopropyl *p*-nitrobenzoate, and *p*-nitrobenzoylisopropoxy trisulfide. As it has been considered that isopropyl *p*-nitrobenzoate would formed from *p*-nitrobenzoylisopropyl sulfite with loss of sulfur dioxide, this result indicates that **5** and **8** would be formed by disproportionation of initially formed **6** (eq 3). This decomposition of **6** is characteristic as compared with those of the related compounds **2–5.**



(3)

The alkoxy group of **8** could be further displaced by –SR′ or –SC(O)R′ group. Reaction of **8b** with ethyl mercaptan was carried out at room temperature to give acetylethyl tetrasulfide and ethanol (eq 4). Reaction of **8b** with thiobenzoic acid or *p*-chlorothiobenzoic acid proceeded in refluxing CCl_4 and symmetrical trisulfides, sulfur, and ethanol were obtained. These products are assumed to be formed by disproportionation of initially formed acetylbenzoyl tetrasulfide to dibenzoyl tetrasulfide and diacetyl tetrasulfide followed by desulfurization.



(4)

(5)

Experimental Section

Infrared spectra were measured with a Hitachi EPI-G2 spectrometer. The NMR spectra were determined on $CDCl_3$ or CCl_4 solution with a Varian A-60 spectrometer. *p*-Nitrothiobenzoic acid was prepared as previously described.[3] Alkyl chlorosulfites,[8] phenyl chlorosulfite,[9] and dialkoxy disulfides[7,10] were prepared by the method of the literature. *p*-Tolyl chlorosulfite, bp 81 °C (1.5 mm), *p*-ethylphenyl chlorosulfite, bp 83 °C (1.5 mm), and 2,4-dimethylphenyl chlorosulfite, bp 94 °C (1.5 mm), were prepared in a similar way to the preparation of alkyl chlorosulfites. All other reagents were obtained commercially.

***S*-Acylalkyl and *S*-Acylaryl Thiosulfites (6a–h).** To a solution of 3.4 g (0.03 mol) of methyl chlorosulfite in 10 ml of ether, a solution 5.5 g (0.03 mol) of *p*-nitrothiobenzoic acid in 40 ml of ether was added dropwise over 0.5 h at −30 °C. The stirring was continued for an additional 3 h and then the temperature of the mixture was allowed to rise to −10 °C. The reaction mixture was evaporated under reduced pressure and the residual solid was recrystallized from chloroform–petroleum ether to give 5.7 g (73%) of **6a** as light yellow needles, mp 76–78 °C. The other compounds (**6b–h**) were prepared in a similar way.

Reaction of Alkyl Chlorosulfites with Aliphatic Thiocarboxylic Acids. A solution of 22.8 g (0.3 mol) of thioacetic acid in 20 ml of ether was added to a stirred solution of 38.5 g (0.3 mol) of ethyl chlorosulfite in 80 ml of ether at −30 °C during 1 h. The stirring was continued for an additional 2 h and then the temperature of the mixture was allowed to rise to room temperature. The reaction mixture was evaporated under reduced pressure and fractional distillation of the residue gave two fractions. Rectification of these fractions gave 8.9 g of acetylethyl sulfite (**5b**), bp 51 °C (2 mm) [lit.[5] bp 44 °C (1 mm)], identified by elemental analysis and IR spectrum, $\nu_{C=O}$ 1750, $\nu_{S\rightarrow O}$ 1190 cm^{-1}, and 10.5 g of acetylethoxy trisulfide (**8b**), bp 62 °C (0.4 mm). The other compounds (**5** and **8**) were obtained in a similar way.

Decomposition of 6d. *S*-*p*-Nitrobenzoylisopropyl thiosulfite (**6d,** 1.3 g) was heated at 110–120 °C for 1 h under nitrogen atmosphere. After standing at room temperature, the mass turned to a reddish-yellow solid. Recrystallization of the solid from chloroform–petroleum ether gave 0.4 g of bis(*p*-nitrobenzoyl) disulfide, mp 183–184 °C (lit.[11] mp 183 °C). The filtrate was evaporated and the residue was chro-

matographed on silica gel using benzene as eluent to give 0.1 g of isopropyl *p*-nitrobenzoate, mp 107–110 °C (lit. mp 108–110 °C), and 0.1 g of *p*-nitrobenzoylisopropoxy trisulfide: mp 77–79 °C; IR $\nu_{C=O}$ 1685 cm^{-1}; NMR ($CDCl_3$) δ 8.22 (q, 4 H), 4.23 (m, 1 H), 1.33 (d, 6 H). Anal. Calcd for $C_{10}H_{11}NO_4S_3$: C, 39.33; H, 3.63; S, 31.50. Found: C, 39.41; H, 3.65; S, 31.52.

Reaction of Dialkoxy Disulfides with Thiocarboxylic Acids. A solution of 3.8 g (0.05 mol) of thioacetic acid in 20 ml of CCl_4 was added to a stirred solution of 7.7 g (0.05 mol) of diethoxy disulfide in 30 ml of CCl_4 at room temperature, and then the temperature of the mixture was gradually raised to 60 °C during 1 h. Finally, the reaction mixture was refluxed for 1 h and EtOH was removed as its CCl_4 azeotrope by evaporation. The residual liquid was distilled to give 5.8 g of acetylethoxy trisulfide (**8b**), bp 60–61 °C (0.35 mm), yield 63%. Similarly, **8a, 8d,** and **8e** were obtained: yield of **8a,** 65%; **8d,** 69%; **8e,** 77%. *p*-Nitrobenzoylisopropoxy trisulfide was purified by recrystallization from *n*-hexane, mp 79 °C, yield 74%.

Reaction of 8b with Ethyl Mercaptan. A solution of 2.4 g (0.038 mol) of ethyl mercaptan in 20 ml of CCl_4 was added to a stirred solution of 7.0 g (0.038 mol) of **8b** in 30 ml of CCl_4 at room temperature for 1 h and then stirring was continued for an additional 3 h. The CCl_4 solution was then concentrated under reduced pressure and the residual liquid was distilled to give 3.0 g (47%) of acetylethyl tetrasulfide: bp 67–71 °C (0.3 mm); NMR δ 2.50 (s, 3 H), 2.93 (q, 2 H), 1.42 (t, 3 H). Anal. Calcd for $C_4H_8OS_4$: C, 23.98; H, 4.03; S, 64.01. Found: C, 24.06; H, 4.08; S, 63.98. IR $\nu_{C=O}$ 1730 cm^{-1}.

Reaction of 8b with Thiobenzoic Acid. A solution of 2.7 g (0.015 mol) of **8b** and 2.0 g (0.015 mol) of thiobenzoic acid in 50 ml of CCl_4 was stirred at 70 °C for 10 h and the solution became light yellow. The reaction mixture was cooled and the precipitate was collected and recrystallized from benzene to give 0.79 g (34%) of dibenzoyl trisulfide, mp 114–115 °C, IR $\nu_{C=O}$ 1690 cm^{-1}. Anal. Calcd for $C_{14}H_{10}O_2S_3$: C, 54.86; H, 3.29; S, 31.39. Found: C, 54.92; H, 3.30; S, 31.24. The filtrate was chromatographed on silica gel using CCl_4–chloroform (1:1) as eluent to give 0.45 g (11%) of dibenzoyl disulfide, mp 127–129 °C (lit.[12] mp 130 °C), and a small amount of diacetyl disulfide and trisulfide. Similarly, *p*-chlorothiobenzoic acid reacted with **8b** to give bis(*p*-chlorobenzoyl) trisulfide, mp 124–125 °C (lit.[4] 125–126 °C), and a small amount of diacetyl disulfide and trisulfide. Disulfide was formed during the operation of chromatography.

Registry No.—**7** (R′ = CH_3), 13165-72-5; **7** (R′ = Et), 6378-11-6; **7** (R′ = Pr), 22598-38-5; **7** (R′ = Pr-*i*), 22598-56-7; **7** (R′ = Ph), 13165-73-6; **7** (R′ = *p*-$CH_3C_6H_4$), 61268-28-8; **7** (R′ = *p*-$C_2H_5C_6H_4$), 61268-29-9; **7** (R′ = 2,4-$(CH_3)_2C_6H_3$), 61268-30-2; **9** (R′ = CH_3), 28752-21-8; **9** (R′ = Pr), 3359-05-5; **9** (R′ = Pr-*i*), 3359-04-4; **9** (R′ = Et), 28752-22-9; RCOSH (R = O_2N-*p*-C_6H_4), 39923-99-4; RCOSH (R = CH_3), 507-09-5; RCOSH (R = C_2H_5), 1892-31-5; RCOSH (R = C_3H_7), 3931-64-4; RCOSH (R = Ph), 98-91-9; *p*-nitrobenzoylisopropoxy trisulfide, 61268-31-3; ethyl mercaptan, 75-08-1; acetylethyl tetrasulfide, 61268-32-4; dibenzoyl trisulfide, 61268-33-5.

References and Notes

(1) G. Zinner, *Angew. Chem.*, **69,** 508 (1957).
(2) L. Field and W. B. Lacefield, *J. Org. Chem.*, **31,** 3555 (1966).
(3) S. Motoki and H. Satsumabayashi, *J. Org. Chem.*, **38,** 3654 (1973); **39,** 3617 (1974).
(4) S. Motoki and H. Kagami, *J. Org. Chem.*, **41,** 2759 (1976).
(5) M. Kobayashi and A. Yamamoto, *Chem. Ind. (London)*, 1930 (1965); M. Kobayashi and A. Yamamoto, *Bull. Chem. Soc. Jpn.*, **39,** 961 (1966); M. Kobayashi, *Ibid.*, **43,** 905 (1970).
(6) F. Kaplan and J. D. Roberts, *J. Am. Chem. Soc.*, **83,** 4666 (1961).
(7) Q. E. Thompson, M. M. Crutchfield, M. W. Dietrich, and E. Pierron, *J. Org. Chem.*, **30,** 2692 (1965).
(8) M. S. Newmann and W. S. Fones, *J. Am. Chem Soc.*, **69,** 1046 (1947).
(9) W. E. Bissinger and F. E. Kung, *J. Am. Chem. Soc.*, **70,** 2664 (1948).
(10) A. Meuwsen, *Ber.*, **B68,** 121 (1935).
(11) A. M. Khaletskii and A. M. Yanovitskaya, *J. Gen. Chem. USSR (Engl. Transl.)*, **19,** 1187, 1193 (1949).
(12) H. Adkins and Q. E. Thompson, *J. Am. Chem. Soc.*, **71,** 2242 (1949).

An X-Ray Crystallographic Structural Study of Sulfoxides Derived from 2-Phenyl-1,3-dithiane

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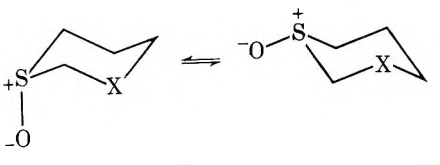
Single-crystal x-ray structure analyses have been carried out for *trans*-2-phenyl-1,3-dithiane 1-oxide (**5**), *cis*-2-phenyl-1,3-dithiane 1-oxide (**6**), and 2-phenyl-1,3-dithiane *trans*-1,*trans*-3-dioxide (**7**) to examine the effects of oxygen substitution on the geometry of the 1,3-dithiane ring. For **5**, a = 12.206 (2), b = 5.749 (1), c = 14.809 (2) Å, β = 97.11 (1)°; for **6**, a = 5.007 (1), b = 20.134 (4), c = 10.095 (3) Å, β = 98.76 (3)°; and for **7**, a = 12.315 (3), b = 5.851 (1), c = 14.829 (3) Å, β = 98.44 (2)°. The space group is $P2_1/c$ in each case with Z = 4. The dithiane rings have a chair conformation somewhat more puckered than that of cyclohexane with endocyclic torsion angles in the range 58–73°. The endocyclic C(2) valence angle shows a marked variation from compound to compound, being 109.6° in **5,** 112.9° in **6,** 114.2° in **7,** as compared to 114.9° in 2-phenyl-1,3-dithiane (**4**) itself. An argument accounting for the steric dependence of this angular variation is offered in terms of transannular dipolar interactions between the two sulfur atoms and oxygen and is discussed in relation to conformational equilibria in solution. Short C–H···O contacts indicative of significant dipolar interactions are found in all three crystal structures.

The conformational preferences exhibited by six-membered cyclic sulfoxides are strongly dependent upon the nature of the other ring atoms, especially those which bear a 1,3 relationship to the sulfoxide group (eq 1).[1] The more stable chair



(1)

1, X = CH_2 $\Delta G°$ = +0.17 to 1.3 kcal/mol
2, X = O $\Delta G°$ = +0.6 kcal/mol
3, X = S $\Delta G°$ = −0.6 kcal/mol

conformation of thiane 1-oxide (**1**) has the oxygen axial.[2] This conformation appears to be the more stable for 1,3-oxathiane 3-oxide (**2**) as well.[3] In 1,3-dithiane 1-oxide (**3**), however, it is the conformation with the sulfoxide oxygen equatorial which is the more stable.[3a,4] The reasons for these differences in conformational preference are not completely understood. It has been suggested that the axial conformation of **1** is stabilized by an attractive van der Waals interaction between the sulfoxide oxygen and the syn-axial C–H bonds.[2a,b] Electrostatic interactions between the polar sulfoxide group and the cross-ring heteroatom are expected to make important contributions to the conformational energies of **2** and **3.** Indeed, molecular mechanics calculations indicate that most of the

Table I. Atomic Parameters Defining the Crystal Structures of 2-Phenyl-1,3-dithiane 1-Oxides[a]

Atom	x/a	y/b	z/c	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
			A. *trans*-2-Phenyl-1,3-dithiane 1-Oxide (5)						
S(1)	8809.5 (4)	3325.4 (9)	2084.5 (3)	48.3 (4)	175 (1)	21.0 (2)	−10.4 (6)	1.4 (2)	−0.6 (5)
S(3)	7064.3 (5)	1099.8 (13)	785.8 (4)	50.1 (4)	471 (3)	22.6 (3)	−30.8 (9)	−1.2 (3)	−14.5 (7)
C(2)	7864 (2)	854 (4)	1899 (2)	48 (2)	202 (7)	25 (1)	−10 (3)	3 (1)	−2 (2)
C(4)	8151 (2)	905 (5)	63 (2)	64 (2)	388 (10)	23 (1)	−21 (3)	6 (1)	−23 (3)
C(5)	8993 (2)	2821 (4)	234 (2)	60 (2)	308 (9)	24 (1)	−2 (3)	10 (1)	10 (2)
C(6)	9636 (2)	2738 (4)	1180 (2)	47 (2)	252 (8)	25 (1)	−13 (3)	4 (1)	11 (2)
C(11)	7086 (2)	920 (4)	2610 (1)	43 (2)	224 (7)	24 (1)	−17 (3)	−1 (1)	−1 (2)
C(12)	7063 (2)	−883 (4)	3231 (2)	62 (2)	248 (8)	32 (1)	−7 (3)	4 (1)	16 (2)
C(13)	6326 (2)	−808 (5)	3875 (2)	82 (2)	369 (10)	32 (1)	−31 (4)	11 (1)	31 (3)
C(14)	5613 (2)	1039 (5)	3898 (2)	63 (2)	435 (11)	33 (1)	−28 (4)	13 (1)	−4 (3)
C(15)	5637 (2)	2829 (5)	3289 (2)	51 (2)	370 (10)	42 (1)	15 (3)	8 (1)	−12 (3)
C(16)	6370 (2)	2774 (4)	2652 (2)	54 (2)	287 (8)	31 (1)	4 (3)	4 (1)	13 (2)
O	9539 (1)	2774 (3)	2946 (1)	70 (1)	314 (6)	25 (1)	−22 (2)	−7 (1)	4 (2)
H(2a)	830 (2)	−58 (4)	194 (2)	3.2 (5)					
H(4a)	856 (2)	−65 (4)	18 (2)	4.0 (6)					
H(4e)	779 (2)	96 (5)	−54 (2)	3.8 (6)					
H(5a)	859 (2)	429 (4)	16 (2)	3.4 (5)					
H(5e)	953 (2)	274 (5)	−17 (2)	3.8 (6)					
H(6a)	997 (2)	115 (4)	131 (2)	3.4 (5)					
H(6e)	1021 (2)	389 (4)	127 (2)	3.6 (5)					
H(12)	755 (2)	−244 (4)	320 (2)	3.6 (5)					
H(13)	633 (2)	−211 (5)	430 (2)	4.7 (6)					
H(14)	509 (2)	109 (5)	436 (2)	4.2 (6)					
H(15)	517 (2)	401 (5)	328 (2)	4.5 (6)					
H(16)	639 (2)	406 (4)	224 (2)	3.6 (5)					
			B. *cis*-2-Phenyl-1,3-dithiane 1-Oxide (6)						
S(1)	3430 (2)	623.3 (4)	6336 (1)	299 (3)	17.0 (2)	94 (1)	0 (1)	14 (1)	−5.9 (4)
S(3)	2917 (2)	2109.8 (4)	6727 (1)	704 (5)	16.2 (2)	106 (1)	−1 (1)	−9 (2)	−3.9 (4)
O	6278 (4)	746 (1)	6246 (2)	275 (8)	38 (1)	165 (3)	8 (2)	42 (4)	−19 (1)
C(2)	2234 (5)	1297 (1)	7327 (3)	269 (11)	20 (1)	90 (4)	3 (3)	25 (5)	−4 (1)
C(4)	1036 (7)	2057 (2)	5054 (3)	609 (19)	22 (1)	105 (4)	8 (4)	−6 (7)	10 (2)
C(5)	2043 (6)	1518 (2)	4224 (3)	455 (17)	30 (1)	94 (4)	−7 (3)	14 (7)	1 (2)
C(6)	1552 (6)	827 (2)	4719 (3)	365 (14)	26 (1)	85 (4)	−6 (3)	20 (6)	−6 (2)
C(11)	3439 (6)	1200 (2)	8773 (3)	284 (12)	22 (1)	84 (4)	6 (3)	26 (5)	−5 (1)
C(12)	5686 (7)	1532 (2)	9358 (4)	486 (19)	35 (1)	123 (5)	−40 (4)	−48 (7)	11 (2)
C(13)	6711 (7)	1437 (2)	10676 (4)	569 (20)	42 (2)	118 (5)	−34 (5)	−97 (8)	2 (2)
C(14)	5596 (7)	997 (2)	11441 (3)	542 (19)	39 (1)	89 (4)	27 (4)	−3 (7)	−3 (2)
C(15)	3409 (8)	660 (2)	10877 (4)	741 (22)	53 (2)	116 (5)	−63 (6)	24 (8)	19 (2)
C(16)	2305 (7)	765 (2)	9551 (4)	553 (18)	47 (2)	96 (4)	−75 (4)	−3 (7)	5 (2)
H(2a)	36 (5)	120 (1)	721 (3)	3.0 (6)					
H(4a)	−82 (6)	198 (2)	521 (3)	5.6 (8)					
H(4e)	121 (6)	248 (2)	462 (3)	5.7 (8)					
H(5a)	399 (5)	157 (1)	422 (3)	4.7 (3)					
H(5e)	110 (6)	157 (1)	335 (3)	4.9 (7)					
H(6a)	−35 (5)	75 (1)	480 (3)	3.5 (6)					
H(6e)	208 (5)	48 (1)	405 (3)	4.7 (7)					
H(12)	659 (7)	181 (2)	881 (4)	7.7 (10)					
H(13)	836 (4)	162 (2)	1109 (3)	7.1 (9)					
H(14)	636 (6)	89 (2)	1236 (3)	5.8 (8)					
H(15)	244 (7)	43 (2)	1133 (4)	10.2 (12)					
H(16)	76 (6)	55 (2)	906 (3)	6.8 (9)					
			C. 2-Phenyl-1,3-dithiane *trans*-1,*trans*-3-Dioxide (7)						
S(1)	8833 (1)	3588 (3)	2098 (1)	54 (1)	172 (4)	30.3 (6)	−21 (2)	1.3 (6)	7 (2)
S(3)	7097 (1)	976 (3)	785 (1)	52 (1)	563 (8)	28.6 (7)	−57 (3)	2.5 (7)	−28 (2)
O(1)	9556 (3)	3090 (7)	2979 (2)	71 (3)	283 (17)	36 (2)	−30 (6)	−6 (2)	1 (4)
O(3)	6608 (3)	−1311 (10)	734 (2)	135 (3)	825 (28)	50 (2)	−238 (11)	33 (3)	−104 (8)
C(2)	7930 (4)	1088 (9)	1915 (3)	41 (3)	182 (18)	32 (2)	−4 (8)	4 (2)	−7 (7)
C(4)	8210 (4)	904 (13)	135 (3)	80 (5)	541 (33)	26 (3)	−30 (12)	8 (3)	2 (9)
C(5)	8938 (4)	2996 (10)	270 (3)	72 (5)	330 (26)	34 (3)	−39 (9)	9 (3)	32 (7)
C(6)	9633 (4)	2984 (9)	1200 (3)	60 (4)	211 (22)	37 (2)	−44 (7)	12 (3)	26 (6)
C(11)	7149 (3)	1164 (10)	2616 (3)	33 (3)	188 (18)	30 (2)	17 (8)	−7 (2)	−5 (7)
C(12)	7099 (4)	−642 (10)	3216 (3)	59 (4)	239 (22)	32 (3)	7 (8)	7 (3)	16 (7)
C(13)	6354 (4)	−578 (11)	3822 (3)	66 (5)	365 (27)	34 (2)	−16 (9)	2 (3)	28 (8)
C(14)	5671 (4)	1235 (13)	3849 (3)	55 (5)	453 (27)	36 (3)	−5 (11)	16 (3)	−9 (9)
C(15)	5696 (4)	2993 (11)	3259 (4)	46 (4)	378 (27)	47 (3)	21 (9)	−4 (3)	−14 (7)
C(16)	6450 (4)	2979 (10)	2637 (3)	61 (4)	242 (23)	38 (3)	−2 (8)	0 (3)	29 (6)
H(2a)	841 (3)	−15 (7)	196 (2)	1.1 (8)					

Table I (*Continued*)

Atom	x/a	y/b	z/c	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
H(4a)	862 (3)	−53 (8)	36 (3)	3.1 (11)					
H(4e)	793 (3)	105 (8)	−38 (2)	3.9 (10)					
H(5a)	943 (3)	304 (9)	−20 (3)	4.3 (12)					
H(5e)	845 (3)	458 (8)	13 (3)	3.3 (11)					
H(6a)	1004 (4)	137 (10)	144 (3)	6.4 (14)					
H(6e)	1009 (3)	419 (6)	122 (2)	1.0 (8)					
H(12)	755 (3)	−213 (8)	313 (3)	2.9 (11)					
H(13)	645 (3)	−162 (8)	429 (2)	2.6 (10)					
H(14)	517 (3)	134 (8)	424 (3)	2.9 (10)					
H(15)	530 (4)	429 (10)	319 (3)	6.7 (15)					
H(16)	647 (3)	423 (8)	228 (2)	2.1 (9)					

[a] Positional parameters are given as fractions of the unit cell edges (C, O, and S × 10^4, H × 10^3) and anisotropic thermal parameters as coefficients to conform to the exponent $-[\beta_{ii}h_i^2 + \cdots 2\beta_{ij}h_ih_j + \cdots]$. Isotropic thermal parameters for hydrogen are given as B (Å^2). Estimated standard deviations are given, on the same scale, in parentheses.

Table II. Torsion Angles of Dithiane Ring Portion of 2-Phenyl-1,3-dithiane and Related Sulfoxides

	Endocyclic torsion angles, deg			
Central bond	4[a]	5	6	7
S(1)–C(2)	−57	−63	−59	−61
C(2)–S(3)	57	63	61	60
S(3)–C(4)	−56	−61	−62	−61
C(4)–C(5)	63	64	68	72
C(5)–C(6)	−61	−67	−67	−73
C(6)–S(1)	54	63	58	62

[a] Values of Kalff and Romers (ref 6).

Table III. Bond Angles of Dithiane Ring Portion of 2-Phenyl-1,3-dithiane and Related Sulfoxides[a]

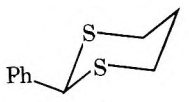
	Valence angle, deg			
	4[b]	5	6	7
S(1)–C(2)–S(3)	115.2	109.6 (2)	112.9 (2)	114.2 (3)
C(2)–S(3)–C(4)	99.2	100.5 (2)	99.2 (2)	97.0 (2)
S(3)–C(4)–C(5)	116.1	113.0 (2)	112.6 (2)	113.4 (4)
C(4)–C(5)–C(6)	116.5	113.3 (2)	113.0 (3)	111.2 (4)
C(5)–C(6)–S(1)	114.9	114.0 (2)	114.6 (2)	112.0 (3)
C(6)–S(1)–C(2)	100.9	98.2 (2)	98.7 (2)	96.9 (2)
C(6)–S(1)–O		105.4 (1)	106.9 (2)	106.7 (2)
C(2)–S(1)–O		105.2 (1)	108.4 (2)	104.1 (2)
C(2)–S(3)–O				104.5 (3)
C(4)–S(3)–O				107.0 (3)

[a] Standard deviations indicated in parentheses. [b] Values of Kalff and Romers (ref 6). Esd's ~1.5°.

Table IV. Bond Distances of Dithiane Ring Portion of 2-Phenyl-1,3-dithiane and Related Sulfoxides[a]

	Bond distance, Å			
Bond	4[b]	5	6	7
S(1)–C(2)	1.79	1.830 (2)	1.843 (2)	1.834 (5)
C(2)–S(3)	1.80	1.814 (2)	1.797 (3)	1.833 (4)
S(3)–C(4)	1.83	1.808 (2)	1.812 (3)	1.787 (5)
C(4)–C(5)	1.46	1.506 (3)	1.508 (4)	1.513 (8)
C(5)–C(6)	1.51	1.519 (2)	1.512 (4)	1.513 (6)
C(6)–S(1)	1.81	1.806 (2)	1.808 (3)	1.803 (5)
S(1)–O		1.497 (1)	1.484 (2)	1.498 (3)
S(3)–O				1.465 (3)
C(2)–Ph	1.52	1.503 (2)	1.506 (3)	1.518 (6)

[a] Standard deviations indicated in parentheses. [b] Values of Kalff and Romers (ref 6). Esd's ~0.03 Å.



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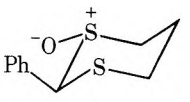

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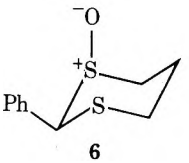

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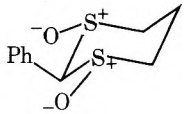

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energy difference between the equatorial and axial conformations of **3** arises from dipole–dipole interactions.[5] The conformation of **3** which has the oxygen axial is less stable than the conformation with the oxygen equatorial largely because of the closer proximity of the two sites of high electron density, the sulfoxide oxygen and the cross-ring sulfur. Dipolar interactions are presumed to be significant in **2** as well, but variations in other nonbonded interactions brought about by the reduced C–O bond length (relative to C–C and C–S) make the net effect difficult to assess.

In order to understand the dynamic processes represented by eq 1, reliable structural information is required. This paper describes a detailed investigation, using single-crystal x-ray diffraction techniques, of a series of oxides of 2-phenyl-1,3-dithiane (**4**). A structure determination had been reported for **4** earlier by Kalff and Romers.[6] We have prepared *trans*-2-phenyl-1,3-dithiane 1-oxide (**5**) and *cis*-2-phenyl-1,3-dithiane 1-oxide (**6**) in connection with another aspect of this work, and have assigned configurations on chemical and spectroscopic grounds.[7] These compounds seemed appropriate models for an equatorial oxide of 1,3-dithiane and an axial oxide, respectively, so their structures were determined crystallographically. The postulated importance of dipole–dipole interactions in **3** suggested that a structure determination of 2-phenyl-1,3-dithiane *trans*-1,*trans*-3-dioxide (**7**) would also be useful.[8]

Results and Discussion

The atomic parameters which define the crystal structures of **5, 6,** and **7** are recorded in Table I, and torsion angle, bond angle, and bond distance data for the dithiane ring portions of **4–7** are collected in Tables II–IV. The structures of **5, 6** and **7** are depicted by the ORTEP[9] drawings shown in Figures 1–3, respectively. The stereochemical assignments of **5** and **6** are confirmed by the x-ray structure determinations. The dithiane

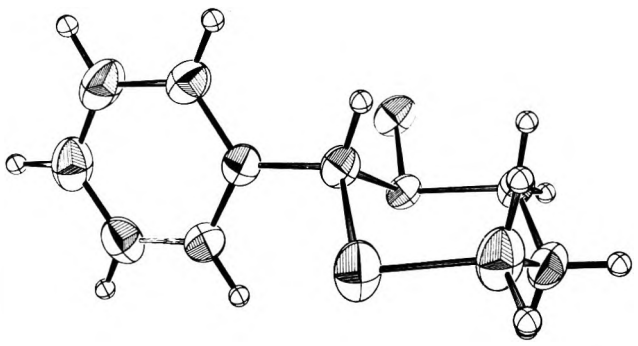


Figure 1. ORTEP drawing of the structure of **5**. Thermal ellipsoids for S, O, and C are drawn with the 50% probability level as boundary surface. Hydrogen atoms are represented by spheres of arbitrary radius.

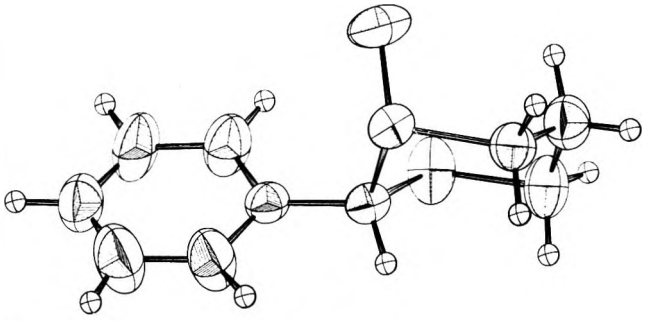


Figure 2. ORTEP drawing of the structure of **6**.

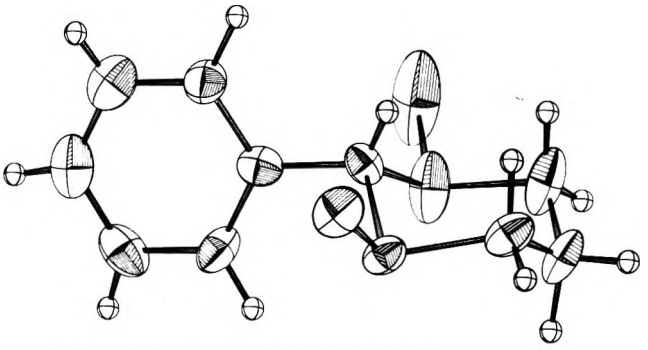


Figure 3. ORTEP drawing of the structure of **7**.

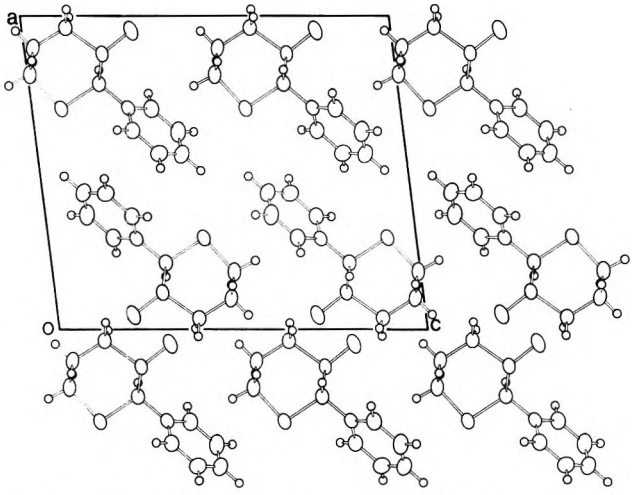
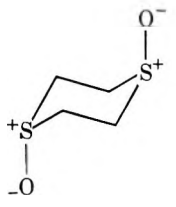


Figure 4. View in *b*-axis projection of the molecular packing in **5**.

ring portions of all of the compounds adopt chair conformations in the crystal with the phenyl group occupying an equatorial site. A chair conformation in solution has been inferred for **4** from NMR and dipole moment measurements.[10] The 1,3-dithiane rings are all more highly puckered than cyclohexane (for which the torsion angles are 56°), with the puckering most pronounced in the C(4)–C(5)–C(6) region. This puckering is quite apparent in the disulfoxide **7** where the ring torsion angles involving C(5) average 72.5°.

The most significant structural difference observed among the compounds is the large variation in the S(1)–C(2)–S(3) valence angle (Table III). This angle is larger in **4** (114.9°) than in either of the corresponding monosulfoxides **5** and **6**, but almost identical with that of the disulfoxide **7** (114.2°). The amount of bond angle contraction between **4** and the monosulfoxides is stereochemically dependent, being more pronounced in the equatorial oxide **5** (109.6°) than in the axial oxide **6** (112.9°). These observations support the view that transannular dipolar interactions are important determinants of structure in the 1,3-dithiane 1-oxide system. The smaller S(1)–C(2)–S(3) angles in **5** and **6** are reasonably attributed to a more favorable electrostatic interaction between the sulfur atoms. The sulfur of the sulfoxide group is positively polarized and an attractive interaction with S(3) compresses the C(2) valence angle in **5** and **6**. The effect is smaller in **6** than in **5** because it is opposed by repulsion between the negatively polarized axial oxygen and S(3). In the disulfoxide **7**, the attractive interaction is replaced by a dipolar repulsion between two positively polarized sulfur atoms and the bond angle is increased.[11]

The endocyclic bond angles around C(4), C(5), and C(6) are all smaller in the oxides **5**–**7** than in **4**. These angles average 115.8° in **4**, but only 113.4° in **5** and **6** and 112.2° in **7**. These differences are related to the increased puckering in this region mentioned earlier, and may indicate additional attractive interactions in which the sulfoxide sulfur is involved. Interaction of the sulfoxide sulfur with the electrons in the γ-C–C bond would be capable of producing such a distortion, and is consistent with the effect being most pronounced in the disulfoxide **7**. The C–S–C angles are similar to those reported for *trans*-1,4-dithiane 1,4-dioxide (**8**, 97.9°)[12] and *cis*-1,4-dithiane 1,4-dioxide (**9**, 96.6 and 97.6°).[13] The C–S–O angles



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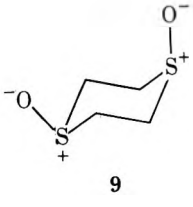

9

in the equatorial sulfoxides **5** and **7** are slightly smaller than those in the axial sulfoxide **6**. These angles average 105.3° in **5**, 105.6° in **7**, and 107.6° in **6**. A similar effect has been observed in **9** where the C–S–O angles around the equatorial sulfoxide are 109.4° while those around the axial sulfoxide are 111.4°.

There are no systematic trends evident in bond distances among the various molecules though the C–C bond distances in all are significantly shorter than the standard C_{sp^3}–C_{sp^3} bond length of 1.54 Å, an effect consistent with the opened valence angles at the carbon atoms involved. The wide variation in S–O bond distances is more apparent than real with all the distances subject to error owing to the pronounced thermal anisotropy of the oxygen atoms. The pattern of motion observed and the mass difference between sulfur and oxygen suggest that the oxygen rides on sulfur and when a correction for this motion is applied a good consistency of values results: 1.512 Å in **5**; 1.509 Å in **6**; and 1.507 and 1.510 Å in **7**. Thermally uncorrected S–O bond distances reported

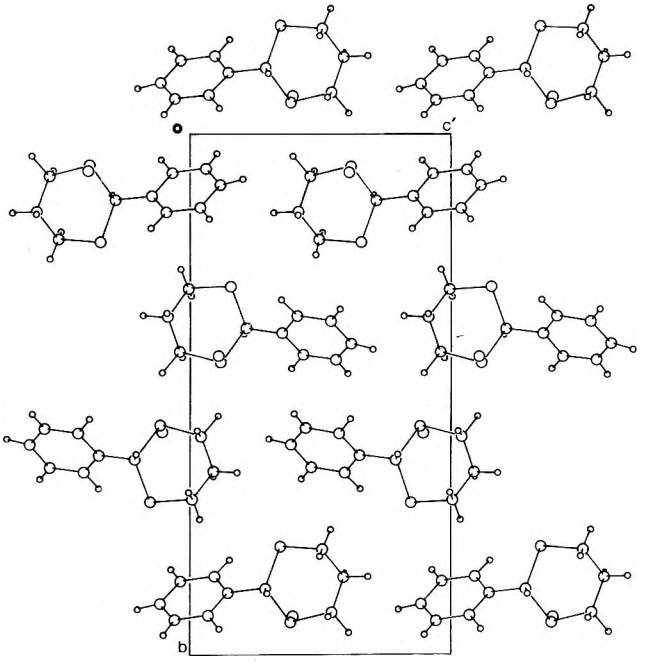

Figure 5. View in *a*-axis projection of the molecular packing in **6**.

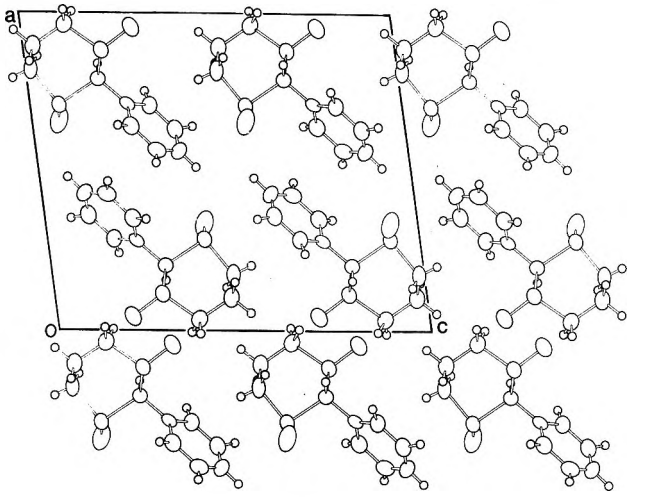

Figure 6. View in *b*-axis projection of the molecular packing in **7**. Note the similarity to Figure 4.

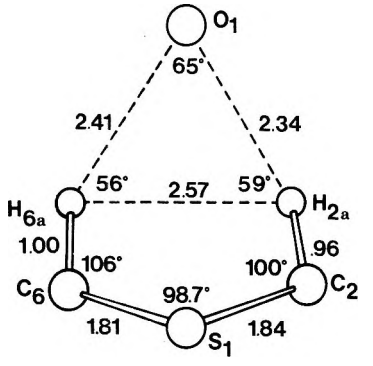

Figure 7. C–H···O approaches in the axial oxide **6**. Distances are given in Å.

in the literature show wide variations. The 1,4-diaxial oxide **8** has S–O 1.48 Å, and that determined for dimethyl sulfoxide by electron diffraction[14a] is 1.47 Å, by x-ray diffraction[14b] 1.499 Å. Smaller S–O distances have been reported for both the axial (1.43 Å) and equatorial (1.40 Å) sulfoxide groups in **9**.

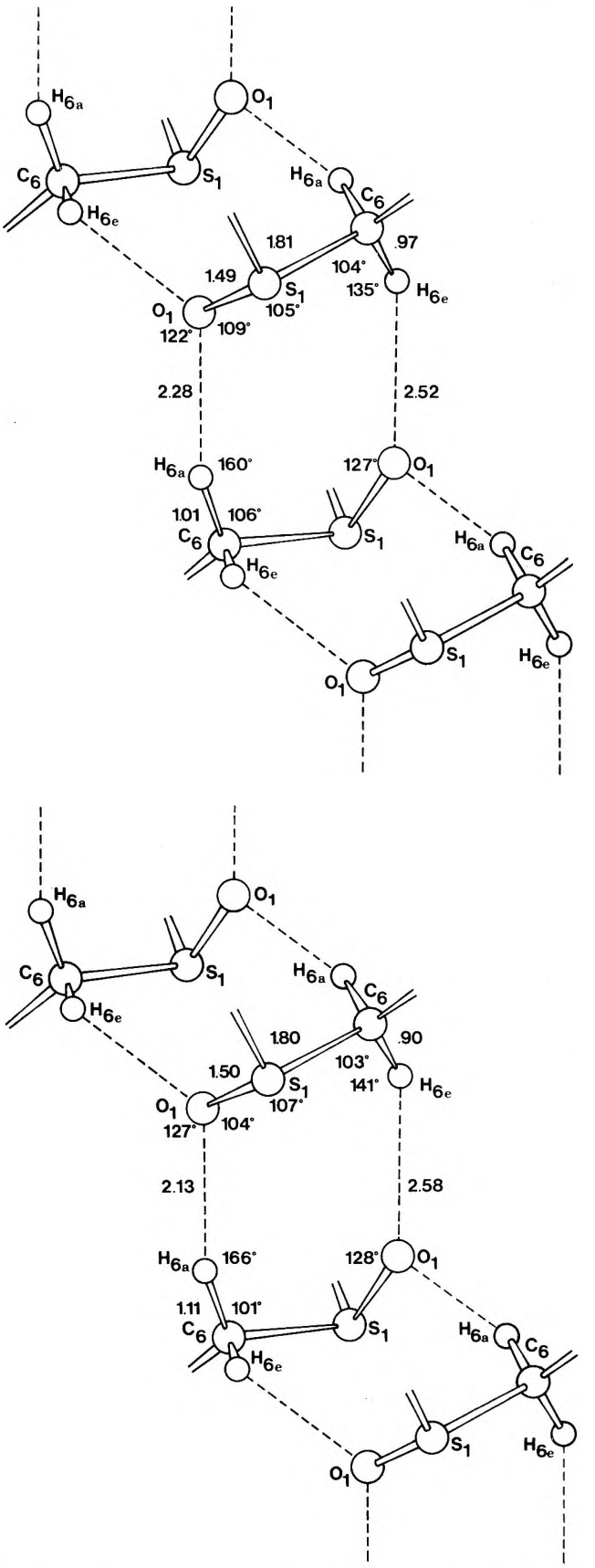

Figure 8. C–H···O approaches in (a) the equatorial oxide **5** and (b) dioxide **7**. Distances are given in Å.

The structural features associated with the 2-phenyl substituents appear normal and do not require comment.[15]

Some striking intermolecular interactions are found in the crystal structures of the oxides which may be of significance

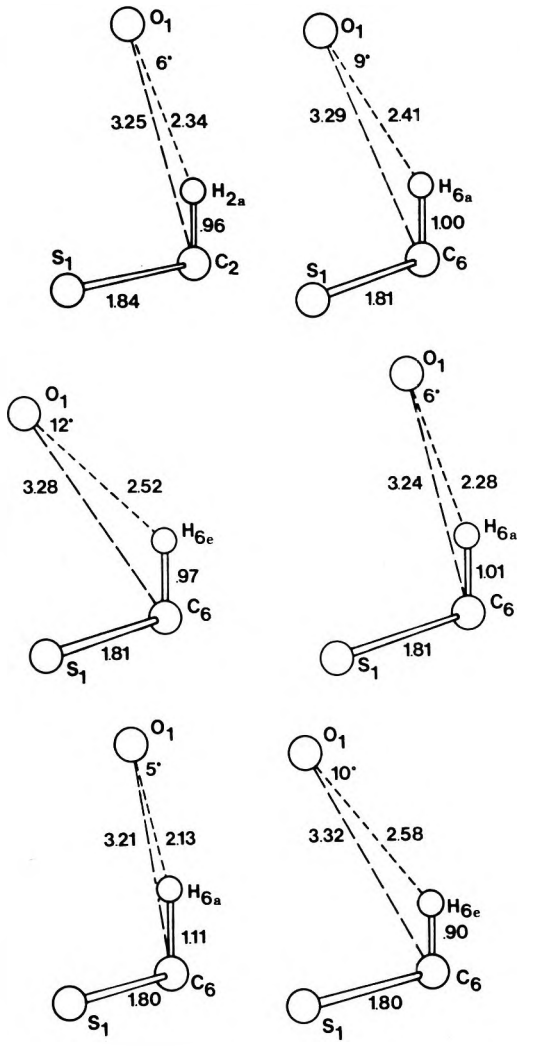

Figure 9. View of C–H···O contacts projected onto the C–H···O plane, (a) in the axial oxide **6**, (b) in the equatorial oxide **5**, (c) in the dioxide **7**.Note that the shorter O···H separations are associated with smaller C···O···H angles. Distances are given in Å.

in relation to intramolecular and intermolecular interactions in solution. Packing diagrams for **5**, **6** and **7** are presented in Figures 4–6. Interactions involving the sulfoxide oxygen and certain axial C–H bonds are suggested by the occurrence of several C–H···O contacts markedly less than the sum of the normal van der Waals radii of oxygen and hydrogen (2.48 Å), and detailed views of these contacts are shown in Figures 7 and 8. The equatorial oxide **5** and dioxide **7** are isostructural and a similar pattern of contacts involving O(1) is found in each with the axial hydrogen of C(6) of a neighboring molecule 2.28 Å distant from O(1) in **5** and 2.13 Å distant in **7**. By contrast, the contact between the equatorial hydrogen of C(6) and O(1) of a neighbor is of normal length in both **5** and **7**, 2.52 and 2.58 Å, respectively. In the axial sulfoxide **6**, the closest intermolecular contacts of the sulfoxide group involve the oxygen atom and the axial hydrogens at C(2) and C(6) of a neighbor with O···H separations of 2.34 and 2.41 Å. The structural similarity of all these close C–H···O contacts is shown by Figure 9 in which the near linearity of the C–H···O system is clearly seen in each case.

Although these contacts involve hydrogen atoms in observed positions and are hence subject to the fairly large esd's associated with such quantities (ca. 0.05 Å), the same pattern of short contact distances persists if hydrogen atoms are assumed in plausible calculated positions. Indeed the effects are even more pronounced if, in these calculations, the C–H bond distance is taken at its internuclear value, 1.08 Å, rather than at the shorter x-ray values found.

Table V

Compd	5	6	7
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
a, Å	12.206 (2)	5.007 (1)	12.315 (3)
b	5.749 (1)	20.134 (4)	5.851 (1)
c	14.809 (2)	10.095 (3)	14.829 (3)
β, deg	97.11 (1)	98.76 (3)	98.44 (2)
ρ_{obsd}, g cm^{-3}	1.37	1.37	1.42
ρ_{calcd}	1.37	1.38	1.43
U, Å^3	1031	1020	1057
Z	4	4	4
F(000)	448	448	480
μ(Mo Kα), cm^{-1}	4.6	4.6	4.6
Crystal size, mm^3	0.6 × 0.4 × 0.1	0.25 × 0.25 × 0.25	0.25 × 0.05 × 0.1
Significant reflns ($2\theta_{max}$ 60°)	1589	1446	953

Contacts between sulfur and oxygen of sulfoxide groups of neighboring molecules in the crystal appear normal. The normal S···O van der Waals separation of 3.22 Å[16] is similar to that observed in **5** (3.26 Å) and **7** (3.31 Å). The separation is somewhat larger in the axial oxide **6**, where it is 3.63 Å. Thus, orientation of the S–O dipoles in an antiparallel fashion with respect to each other does not play as significant a role in crystal packing as do S–O···H–C interactions. Inasmuch as these interactions involve hydrogen atoms on carbon bonded to sulfinyl groups, it is tempting to interpret them as electrostatic effects. A sulfinyl group will strongly polarize an adjacent C–H bond so that the hydrogen is more positive than a C–H bond in, for example, a hydrocarbon allowing for effective electrostatic interactions with the sulfoxide oxygen of a neighboring molecule.

Experimental Section

The preparations of 2-phenyl-1,3-dithiane (**4**),[17] *trans*-2-phenyl-1,3-dithiane 1-oxide (**5**),[7a] and *cis*-2-phenyl-1,3-dithiane 1-oxide (**6**)[7a] have been previously described. Stereochemical assignments to **5**, mp 145–147 °C, and **6**, mp 163.5–165.5 °C, made on the basis of chemical behavior, synthesis, and NMR spectra were confirmed by the x-ray crystallographic determinations. Treatment of **4** with 2 equiv of *m*-chloroperoxybenzoic acid in dichloromethane (−18 to −30 °C) gives 2-phenyl-1,3-dithiane *trans*-1,*trans*-3-dioxide (**7**, mp 187–188 °C) as the major product in 71% yield.[18] The NMR spectrum was suggestive of the stereochemistry shown, but rigorous structure proof required the x-ray determination described here.

X-Ray Crystallographic Measurements. Crystal Data. Unit cell symmetry and preliminary cell dimensions were derived from observations of systematic absences and measurements made on 25° precession photographs taken with Mo Kα radiation. Accurate cell dimensions were obtained by a least-squares fit to carefully measured diffractometer values of $\pm 2\theta$ for 17–25 strong general reflections (λ = 0.71069 Å). Relevant data for compounds **5**–**7** are summarized in Table V.

Intensity Data. Measurements of intensity for the three compounds were made using a Picker four-circle diffractometer controlled by an XDS Sigma 2 computer. Mo Kα radiation, made monochromatic by Bragg reflection from a highly oriented graphite crystal, was used with scintillation counting and pulse-height analysis with θ–2θ scans at a scan rate of 2°/min. Background intensity was determined either by direct measurement with both crystal and counter stationary at either end of the scan ranges or by interpolation from a carefully predetermined curve of scattered background intensity vs. diffractometer angle. Measurements were made for the appropriate nonredundant section of reciprocal space, but an additional symmetry-related zone of reflections was included in each case to check crystal alignment. The deviation from the mean in these averaged reflections was typically <3%. Stability of the experimental conditions during the course of the data collection was monitored by measurement of two or three reference reflections after every 50 scans. A similar

variation in intensity was noted in these standards but no systematic trends were evident. Scattered intensity in a scan was assumed significant at the 3σ level. No absorption corrections were applied and the data were converted to structure amplitudes in the usual way.

Structure Determination and Refinement. For **5**, the positions of the two sulfur atoms were found from a sharpened three-dimensional Patterson function and the structure solved by the heavy atom method. Compound **7** is isostructural with **5** and parameters for the atoms of **5** were used to phase the reflections of **7**. The additional oxygen atom was found from a difference map. The program MULTAN[19] was used to solve the structure of **6** in a routine way.

Hydrogen atoms were located in all cases from difference electron-density maps and included in the block-diagonal least-squares refinement. A conventional weighting scheme was used,[20] and anisotropic thermal parameters were assigned to S, O, and C atoms, isotropic B values to H. Damping factors were applied to assure smooth convergence and refinement continued until no calculated shift in any parameter exceeded one-tenth of the corresponding esd. The final conventional unweighted and weighted residuals were 0.044 and 0.040 for **5**, 0.045 and 0.032 for **6**, and 0.047 and 0.036 for **7**. The scattering curves used for S, O, and C were taken from Hanson et al.[21] and for hydrogen from Stewart et al.[22] Programs used, other than MULTAN and ORTEP, were written in this laboratory for the XDS Sigma 2 computer.

Registry No.—**4**, 5425-44-5; **5**, 60349-76-0; **6**, 60349-79-3; **7**, 61158-78-9.

Supplementary Material Available. Listings of observed and calculated structure amplitudes, complete bond length and angle calculations, and information on least-squares mean planes of interest and on intermolecular contacts (35 pages). Ordering information is given on any current masthead page.

References and Notes

(1) For reviews of conformational properties of sulfur heterocycles, see (a) C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Top. Stereochem.*, **4**, 29 (1969); (b) E. L. Eliel, *Acc. Chem. Res.*, **3**, 1 (1970); (c) J. B. Lambert and S. I. Featherman, *Chem. Rev.*, **75**, 611 (1975).
(2) (a) C. R. Johnson and D. McCants, Jr., *J. Am. Chem. Soc.*, **87**, 1109 (1965); (b) *ibid.*, **86**, 2935 (1964); (c) J. C. Martin and J. J. Uebel, *ibid.*, **86**, 2936 (1964); (d) J. B. Lambert and R. G. Keske, *J. Org. Chem.*, **31**, 3429 (1966).
(3) (a) L. Van Acker and M. Anteunis, *Tetrahedron Lett.*, 225 (1974); (b) K. Bergesen, M. J. Cook, and A. P. Tonge, *Org. Magn. Reson.*, **6**, 127 (1974).
(4) (a) M. J. Cook and A. P. Tonge, *Tetrahedron Lett.*, 849 (1973); (b) M. J. Cook and A. P. Tonge, *J. Chem. Soc., Perkin Trans. 2*, 767(1974); c) S. A. Khan, J. B. Lambert, O. Hernandez, and F. A. Carey, *J. Am. Chem. Soc.*, **97**, 1468 (1975).
(5) N. L. Allinger and J. Kao, *Tetrahedron*, **32**, 529 (1976).
(6) H. T. Kalff and C. Romers, *Acta Crystallogr.*, **20**, 490 (1966).
(7) (a) F. A. Carey, O. D. Dailey, Jr., O. Hernandez, and J. R. Tucker, *J. Org. Chem.*, **41**, 3975 (1976); (b) F. A. Carey, O. D. Dailey, Jr., and O. Hernandez, *ibid.*, **41**, 3979 (1976).
(8) After this work was completed a crystallographic study of 4,6-dimethyl-1,3-dithiane, its equatorial oxide, and diequatorial dioxide was reported: A. T. McPhail, K. D. Onan, and J. Koskimies, *J. Chem. Soc., Perkin Trans. 2*, 1004 (1976).
(9) C. K. Johnson, "ORTEP-II. A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustration", ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn.
(10) H. T. Kalff and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **85**, 467 (1966).
(11) A stabilization of 2.3 kcal/mol for a C(5)-axial methylsulfinyl substituent in 1,3-dioxanes has been attributed to an electrostatic interaction between unlike dipoles: see E. L. Eliel and S. A. Evans, *J. Am. Chem. Soc.*, **94**, 8587 (1972); E. L. Eliel and F. Alcudia, *ibid.*, **96**, 1940 (1974).
(12) H. M. M. Shearer, *J. Chem. Soc.*, 1394 (1959).
(13) H. Montgomery, *Acta Crystallogr.*, **13**, 381 (1960).
(14) (a) O. Bastiansen and H. Viervoll, *Acta Chem. Scand.*, **2**, 702 (1948); (b) R. J. Sundberg, R. F. Bryan, I. F. Taylor, Jr., and H. Taube, *J. Am. Chem. Soc.*, **96**, 381 (1974).
(15) See paragraph at end of paper regarding supplementary material.
(16) A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964).
(17) D. Seebach, B. W. Erickson, and G. Singh, *J. Org. Chem.*, **31**, 4303 (1966).
(18) Unpublished work of J. Richard Toler.
(19) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
(20) D. F. Grant, R. C. G. Killean, and J. L. Lawrence, *Acta Crystallogr., Sect. B*, **25**, 374 (1969).
(21) H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Crystallogr.*, **17**, 1040 (1964).
(22) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **53**, 1891 (1970).

Chemistry of the Sulfur–Nitrogen Bond. 12.[1] Metal-Assisted Synthesis of Sulfenamide Derivatives from Aliphatic and Aromatic Disulfides

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The metal-assisted synthesis of sulfenamide derivatives 1 and 2 from aliphatic and aromatic disulfides and amines was explored. This method is more convenient and results in higher yields and a less reactive product than sulfenamides prepared from sulfenyl chlorides. Sulfenamides containing reactive functional groups, not accessible from sulfenyl chlorides, can be prepared using this procedure. With ammonia and aromatic disulfides this method yields bis(arenesulfen)imides 4 when the groups attached to sulfur are more electron donating than a 3,4-dichlorophenyl group. Alkanesulfenamides of ammonia ($RSNH_2$) cannot be isolated, but are trapped with aromatic aldehydes and ketones to yield N-alkylidenealkanesulfenamides **2**.

Sulfenamides **1** and N-alkylidenesulfenamides **2** are important intermediates in organic synthesis and have proven useful in investigations of lone pair interactions ("α effect"), bond polarization effects, and (p–d) π conjugation.[2] Sulfenamides have also found important industrial applications.

R–S–NR′R″ — **1a**, R = alkyl; **b**, R = aryl

R–S–N=CR′R″ — **2**, R′, R″ = alkyl, aryl

Sulfenamides (**1**) are used as sulfenyl-transfer reagents in the synthesis of sulfides,[3] disulfides,[4] trisulfides,[4b] sulfenate esters,[5] sulfenamides,[6] alkyl (aryl) dialkylaminosuccinimidosulfonium salts,[7] and aminecarbotrithioates.[8] N-Alkylidenearenesulfenamides, **2b**, can be oxidized to 2-arenesulfonyl-3-phenyloxaziridines[9a] and sulfinamides.[9b] The latter compounds are useful in the synthesis of sulfenic acids.[9b,10]

The possibility that interactions between the lone pairs of electrons on sulfur and nitrogen may destabilize the S–N

Table I. Sulfenamides from Aromatic Disulfides

Entry	Disulfide	Registry no.	Amine	Registry no.	Conditions	Sulfenamide % yield	Registry no.	Bp (mp), °C (mm)	NMR, δ ($CDCl_3$)
1	*p*-Tolyl	103-19-5	Piperidine	110-89-4	$AgNO_3$–MeOH	60	18511-53-0	78–79 (0.005	1.6 (m, 6), 2.4 (s, 3, Me), 2.9 (t, 4), 7.2 (q, 4)
2			Aniline	62-53-3		35		*a*	
3	Phenyl	882-33-7	Ethylamine	75-04-7		75	24380-80-1	54–57 (0.0.04)	1.2 (t, 3, J = 7 Hz), 2.9 (dt, NH, CH_2 7.2 (s, 5)
3			Isopropylamine	75-31-0		76	34690-94-3	61–62 (0.4)	1.1 (d, 6, J = 7 Hz), 2.8 (b, 4, NH), 3.1 (m, 1), 7.26 (m, 5)
4			*tert*-Butylamine	75-64-9		70	19117-31-8	57–60 (0.3)	1.1 (s, 9), 2.7 (b s, 1), 6.9–7.4 (m, 5)
5			Allylamine	107-11-9		88	61076-24-2	61–64 (0.15)	2.85 (b, 1, NH), 3.5 (t, 2, J = 5 Hz), 5.1 (m, 1), 5.8 (m, 1), 7.3 (s, 5)
6			2-Aminoethanol	141-43-5		70	61076-25-3	124 (0.05)	3.0 (b t, 2 H), 3.3 (b, 2 H, OH, NH), 3.6 (m, 2 H), 7.25 (s, 5)
7			Aniline			75–80		*a*	
8			Diethylamine	109-89-7		55	6667-19-2	60–65 (0.65)	1.13 (t, 6, J = 8 Hz), 2.96 (g 4, J = 8 Hz), 7.26 (m, 5)
9			Diisopropylamine	108-18-9		73	19117-30-7	71–73 (0.4)	1.17 (d, 12, J = 7 Hz), 3.4 (m, 2), 7.25 (m, 5)
10	4-Chlorophenyl	1142-19-4	Aniline			75		*b*	
11	4-Bromophenyl	5335-84-2	Aniline			70	32338-03-7	85–89	5.05 (bs, 1, NH), 6.8–7.5 (m, 9)
12	3-Nitrophenyl	537-91-7	Ethylamine			90	34879-73-7	*c*	1.2 (t, 3, J = 6 Hz), 3.0 (q, 2), 7.2–8.4 m, 4)
13					$HgCl_2$–MeOH	61			
14			Allylamine		$AgNO_3$–MeOH	75	61076-26-4	128–130 (0.05)	3.0 (b, 1, NH), 3.6 (t, 2, J = 5 Hz), 5.2 (m, 1), 5.8 (m, 1), 7.3–8.0 (m, 4)
15			2-Aminoethanol			75	61076-27-5	Oil	2.4 (s, 1, OH) 3.1 (t, 2, J = 5 Hz), 3.4 (b, 1, NH), 3.8 (t, 2, J = 5 Hz), 7.5–8.5 (m, 4)
16			Aniline			82		*d*	
17			Dimethylamine	124-40-3		60	61076-28-6	82 (0.015)	2.9 (s, 6), 7.3–8.1 (m, 4)
18					$HgCl_2$–MeOH	60			
19			Bis(2-chloroethyl)amine	334-22-5		23	61076-29-7	Oil[e]	3.6 (m, 8), 7.1–8.5 (m, 4)
20			Diethylamine		$AgNO_3$–MeOH	86	61076-30-0	109 (0.05)	1.2 (t, 6, J = 7 Hz), 3.1 (q, 4, J = 7 Hz), 7.3–8.2 (m,4)
21			2,2-Dimethylaziridine	2658-24-4		45	61076-31-1	123 (0.2)	1.4 (s, 6), 2.0 (s, 2), 7.4–8.4 (m, 4)
22			Di-*sec*-butylamine	626-23-3		70	61076-32-2	134 (0.13)	0.9 (t, 6, J = 7 Hz), 1.2 (d, 3, J = 7 Hz), 1.5 (m, 4), 3.0 (hep, 2), 7.2–8.3 (m, 4)
23	2-Nitrophenyl	1155-00-6	Ethylamine			87[a]	24398-42-3	118 (0.75)	1.2 (t, 3, J = 7 Hz), 2.4 (q, 2, J = 7 Hz), 2.4 (b, 1, NH)
24	4-Nitrophenyl	100-32-3	Aniline			60		*a*	
25	2-Benzothiazolyl	120-78-5	Isopropylamine			90		*f*	
26			Aniline			90		*g*	
27			Piperidine			90		*h*	

[a] Reference 16. [b] Reference 24. [c] Reference 25. [d] F. A. Davis, R. B. Wetzel, T. J. Devon, and J. F. Stackhouse, *J. Org. Chem.*, **36**, 799 (1971). [e] Purified by chloromatography on Florisil (benzene) and silica gel (pentane). [f] N. E. Messer, U.S. Patent 2 370 253; *Chem. Abstr.*, **39**, 3967 (1945). [g] E. Tschunkur and H. Kohler, German Patent 615 580; *Chem. Abstr.*, **29** 8 408 (1935). [h] J. J. D'Amico, *J. Org. Chem.*, **26**, 3436 (1961).

Table II. Sulfenamides from Aliphatic Disulfides

Entry	Disulfide	Registry no.	Amine	Conditions	Sulfenamide % yield	Registry no.	Bp, °C (mm)	NMR, δ
1	Methyl	624-92-0	Piperidine	AgOAc–EtOAc	43	7257-48-9	58 (10)	2.92 (t, 4, J = 6 Hz), 2.2 (s, 3, Me), 1.48 (m, 6)
2			Aniline		Trace[a]			
3			Isopropylamine		Trace[a]			
4	Ethyl	110-81-6	Piperidine		30	25116-55-6	37–38 (0.32)	1.2 (t, 3, J = 7 Hz), 1.5 (m, 6), 2.65 (q, 2, J = 7 Hz), 3.0 (m, 4)
5			Piperidine	$AgNO_3$–MeOH	0			
6			Allylamine	AgOAc–EtOAc	Trace[a]			
7	*n*-Butyl	629-45-8	Piperidine		40	25116-56-7	76 (0.7)	0.93 (t, 3, J = 6 Hz), 1.5 (m, 10), 2.6–3.2 (m, 6)
8	Isopropyl	4253-89-8	Piperidine		45	61076-33-3	36.7 (0.35)	1.3 (d, 6, J = 6 Hz), 1.4 (m, 6), 2.1 (m, 1), 2.8 (m, 4)
9	Benzyl	150-60-7	Isopropylamine		97	59004-78-3	*b*	1.1 (d, 6), 2.33 (broad s, 1), 3.0 (m, 1), 3.75 (s, 2), 7.25 (s, 5)
10			Diethylamine		58	34879-74-8	79–82 (0.07)	1.1 (t, 6, J = 7 Hz), 2.9 (q, 4, J = 7 Hz), 3.77 (s, 2), 7.3 (m, 5)
11			Di-*n*-butylamine[c]		53	61076-34-4	80–81 (0.007)	0.9 (t, 6), 1.4 (m, 8), 2.81 (t, 4, J = 7 Hz), 3.8 (s, 2), 7.27 (m, 5)

[a] As indicated by NMR. [b] Decomposes on heating. [c] Registry no., 111-92-2.

bond[2] and increase the nucleophilicity of the sulfenamide nitrogen has recently been discussed.[11] Bond polarization effects resulting from the difference in electronegativity between sulfur and nitrogen in **1** activate the S–N bond for attack by both nucleophiles and electrophiles and appear to be the factor primarily responsible for the chemistry of these compounds. Recent reports suggest that there is little, if any, (p–d) π conjugation between sulfur and nitrogen when sulfur is attached to an sp^3-hybridized nitrogen.[12,13] Localized (p–d) π bonding exists when sulfur is attachd to an sp^2-hybridized nitrogen, i.e., **2**.[13,14]

Industrial applications of sulfenamide derivatives include use as accelerators in rubber vulcanization, pesticides and fungicides, radioprotective agents, and in polymerization reactions.[15]

The condensation of an aryl or alkyl sulfenyl chloride with an amine has been the only general synthetic route to sulfenamides (eq 1).[2,16,17]

$$R\text{–}S\text{–}Cl + 2R_2NH \rightarrow R\text{–}S\text{–}NR_2 + R_2NH_2{}^+Cl^- \quad (1)$$

Other less satisfactory methods for the synthesis of sulfenamides include the reaction of metal mercaptides with chloro amines,[18] oxidative condensation of thiols with amines,[19] and the displacement of amines on alkylsulfenyl thiocyanates[20] or alkyl thiolsulfonates.[21] A potentially useful synthesis of alkyl and aryl sulfenamides is the substitution of alkyl- and arylamines on thiophthalimides;[6] however, this procedure requires the synthesis of the intermediate thiophthalimide from the sulfenyl chloride and phthalimide.[22]

There are a number of disadvantages in using the sulfenyl chloride method to prepare sulfenamides (eq 1). While the chlorination of a disulfide usually produces the sulfenyl chloride in good yield, side reactions often occur;[16,17] this is particularly true of the lower molecular weight aliphatic disulfides. Sulfenyl chlorides are also thermally unstable, easily hydrolyzed, and react with hydroxyl groups, active methylene groups, and multiple bonds.[17] Sulfenamides containing these functional groups cannot be prepared from the sulfenyl chloride and amine.

Another limitation of the synthesis of sulfenamides from sulfenyl chlorides, which has only recently been recognized, is the difficulty in removing trace amounts of amine hydrochlorides, a by-product in this synthetic procedure (eq 1), which activates the S–N bond toward attack by nucleophiles,[23] markedly lowers the storage lifetime of sulfenamides, and alters the thermal chemistry of arenesulfenanilides.[24]

An important alternative to the synthesis of sulfenamides from amines and sulfenyl chlorides is the metal-assisted synthesis of sulfenamides from disulfides and amines (eq 2).[25] Many of the disadvantages associated with the synthesis of sulfenamides from amines and sulfenyl chloride can be avoided using this procedure (eq 2).

$$R\text{–}S\text{–}S\text{–}R + MX \xrightarrow{2R_2NH} MS\text{–}R + R\text{–}SNR_2 + R_2NH_2{}^+X^- \quad (2)$$

R = alkyl, aryl
MX = $AgNO_3$, AgOAc, $HgCl_2$

In this paper we report on the scope of this method (eq 2) for sulfenamide synthesis.

Results and Discussion

The metal-assisted synthesis of sulfenamides from alkyl and aryl disulfides is a convenient "one-pot" reaction. The metal salt is dissolved in methanol or ethyl acetate followed by addition of the disulfide and an excess of the amine. Removal of the precipitated metal mercaptide yields the sulfenamide. Disulfides can be obtained in high yield (ca. 90%) by oxidation of the thiol with 15% hydrogen peroxide.

Good to excellent yields of sulfenamides from aromatic disulfides (Table I) and moderate yields of sulfenamides from aliphatic disulfides (Table II) were obtained. The sulfenamides were identified by their IR and NMR spectra, comparison with literature values, and elemental analysis where stability of the sulfenamide permitted. The infrared spectra of sulfenamides from primary amines showed a single absorption at 3320–3330 cm^{-1} and sulfenamides of ammonia ($RSNH_2$) absorption at 3280 and 3380 cm^{-1}.

The metal-assisted synthesis of sulfenamides does not require the separate preparation of an unstable intermediate (i.e., sulfenyl chloride) and yields via this method were better than those reported for the sulfenyl chloride method. Furthermore, the sulfenamides obtained by this method (eq 2) were less reactive as indicated by their longer storage time and increased thermal stability.[24] Apparently the amine hydronitrate and -acetate (eq 2) are more easily removed than the corresponding amine hydrochlorides (eq 1).

Using this procedure, sulfenamides containing reactive functional groups such as hydroxyl and double bonds, not accessible from the sulfenyl chloride, can be prepared. Good yields of sulfenamides were obtained from allylamine and 2-aminoethanol and aromatic disulfides (Table I, entries 5, 6, 14, 15), but the procedure failed with aliphatic disulfides.

A disadvantage of the metal-assisted synthesis of sulfenamides is the use of relatively expensive silver salts. This can be overcome to a large extent if the silver is recovered from the silver mercaptide and converted to silver nitrate. This was accomplished with an overall yield of about 70% (see Experimental Section).

Mercuric chloride in methanol gave results similar to silver nitrate–methanol (Table I, entries 13, 18). With mercuric chloride yields were somewhat lower and the thermal stability of the sulfenamide was reduced. No reaction between aliphatic disulfides, amines, and mercuric chloride was detected. Mercuric chloride can also be used in place of silver nitrate where the latter reagent would react with the amine. For example a low yield of bis(2-chloroethyl)-3-nitrobenzenesulfenamide (Table I, entry 19) was obtained using mercuric chloride. This sulfenamide was only moderately stable, decomposing after several weeks at room temperature. Although bis(2-chloroethyl)benzenesulfenamide was apparently formed, it could not be isolated. The reactivity of this sulfenamide may be due to the increased nucleophilicity of the sulfenamide nitrogen (vide infra).

The mechanism for the metal-assisted synthesis of sulfenamides probably involves the complexation of the metal ion with one of the lone pairs of electrons of the disulfide bond. This orientates the S–S bond toward nucleophilic attact by the amine. A similar mechanism has been proposed for the formation of **2** from silver nitrate, disulfides, ammonia, and aldehydes or ketones.[26]

Aromatic Disulfides. Good yields of sulfenamides from aromatic disulfides and a wide variety of aliphatic amines and aniline were obtained using the metal-assisted procedure (eq 2). Hindered amines such as diisopropyl- and di-*sec*-butylamine also gave good yields of the corresponding sulfenamides (Table I, entries 9, 22). Sulfenamides from aliphatic amines were sufficiently stable to be purified by distillation. Sulfenamides from primary aliphatic amines appeared to be less stable than those from secondary amines, the former decomposing over a period of months to yield the disulfide and amine. Since arenesulfenanilides decompose on heating,[2] excess aniline was removed by column chromatography. These results are summarized in Table I.

Amines less basic than aniline failed to yield sulfenamides using this procedure. Disulfides such as 4-hydroxyphenyl disulfide, 2-aminophenyl disulfide, and *N,N'*-piperidinyl disulfide also failed using this procedure.

Aliphatic Disulfides. The metal-assisted synthesis of sulfenamides from aliphatic disulfides and amines required the use of an excess of silver acetate in ethyl acetate. Aliphatic sulfenamides were observed to decompose to disulfide in the presence of silver nitrate–methanol.

The synthesis of aliphatic sulfenamides **1a** using this procedure succeeded with a variety of aliphatic disulfides and amines, but failed with aniline and allylamine. Benzyl disulfide also gave good yields of alkylbenzylsulfenamides with a range of amines using silver acetate–ethyl acetate. These results are summarized in Table II.

Moderate to low yields of aliphatic sulfenamides were obtained from disulfides and aliphatic amines using this method. However, considering the instability of aliphatic sulfenyl chlorides and the inaccessibility of benzylsulfenyl chloride,[27] this method (eq 2) is superior to the sulfenyl chloride method (eq 1).

There appears to be general agreement, but little quantitative evidence, that aryl sulfenamides are more stable than alkyl sulfenamides.[2] A number of workers[28,19] have noted that the thermal stability of alkyl sulfenamides decreases as the basicity of the sulfenamide nitrogen increases, as the electron-donating ability of the group attached to sulfur increases, and when the number of groups attached to the sulfenamide nitrogen decreases. These trends are in the correct order for stabilization of the sulfenyl and amino radicals. Alternatively, increased electron density on nitrogen and sulfur may destabilize the S–N bond and/or increase the nucleophilicity of the sulfenamide nitrogen (vide infra).

The metal-assisted synthesis of alkyl and aryl sulfenamides (Tables I and II) reflects these trends; aromatic sulfenamides were less reactive than aliphatic sulfenamides with the latter obtained in lower yields. Aromatic sulfenamides prepared from primary aliphatic amines were more reactive than those from dialkylamines. With the exception of isopropylbenzylsulfenamide (Table II, entry 9), all attempts to prepare alkanesulfenamides from primary amines failed (see Table II, entry 3).

Disulfides and Ammonia. Sulfenamides of ammonia, **3,** are intermediates in the synthesis of *N*-alkylidenesulfenamides, **2,** from aromatic disulfides, silver nitrate, ammonia, and aldehydes and ketones.[26]

$YY\text{-}C_6H_3S\text{-}NH_2$	$(XY\text{-}C_6H_3S)_2NH$
3a, X = Y = 3,4-Cl_2	**4a,** X = Y = H
b, X = H; Y = 3-NO_2	**b,** X = H; Y = 4-Cl
c, X = H; Y = 4-NO_2	**c,** X = H; Y = 3-NO_2

This provides an alternative synthesis of **2** which avoids an excess of ammonia.

Good yields of arenesulfenamides **3** were obtained from silver nitrate, aromatic disulfides, and ammonia when the disulfide contained electron-attracting groups more powerful than a 4-chlorophenyl group. Both phenyl and 4-chlorophenyl gave the corresponding bis(arenesulfen) imide **4a,b b** as the only isolated product. Ethyl disulfide was recovered when this disulfide was subjected to the reaction conditions. These results are summarized in Table III.

Benzenesulfenyl chloride and *p*-tolylsulfenyl chloride are reported to yield the imide **4** in low yield on reaction with ammonia[16,29] Zincke obtained the sulfenamides **3** from 4- and 2-nitrobenzenesulfenyl chloride and ammonia.[30] When these compounds were heated with dilute acetic acid, imides **4** were obtained in good yield.

We have found that boron trifluoride etherate in ether also effects the rearrangement of 3-nitrobenzenesulfenamide **3c** to **4c** in 70% yield. In attempts to extend this reaction to sulfenamides **5a** and **5b** either boron trifluoride or 20% acetic acid resulted in mixtures of the corresponding disulfide and the imide **6**. The formation of the imide **6** was indicated by the appearance of new methylene absorptions in the NMR at 3.5 and 3.6 ppm, respectively. The imide **6** could not be satisfactorily separated from the disulfide.

$$\underset{\mathbf{5}}{X\text{-}C_6H_4S\text{-}NHC_2H_5} \rightarrow (X\text{-}C_6H_4S)_2 + \underset{\mathbf{6}}{(X\text{-}C_6H_4S)_2NC_2H_5}$$

a, X = H
b, X = 3-NO_2

The mechanism for the formation of the bis(sulfen)imides

Table III. Sulfenamides from Disulfides and Ammonia

Entry	Disulfide	Conditions[e]	Product[f] (% yield)	Mp, °C	NMR, δ
1	Ethyl	$AgNO_3$–MeOH	No reaction		
2	Phenyl	$AgNO_3$–MeOH	**4a** (20)	133–134 (129)[a]	4.7 (bs, 1), 7.35 (s, 10)
3	4-Chlorophenyl		**4b** (50)	138–140	4.6 (bs, 1), 7.3 (s, 8)
4		AgOAc–EtOAc	No reaction		
		$HgCl_2$–MeOH	No reaction		
5	3,4-Dichlorophenyl[d]	$AgNO_3$–MeOH	**3a** (62)	38–40	2.8 (bs, 2, NH_2), 7.0–7.5 (m, 3)
6	3-Nitrophenyl		**3b** (72)	*b*	
7	4-Nitrophenyl		**3c** (84)	*c*	

[a] H. Lecher, F. Holschneider, K. Koberle, W. Speer, and P. Stocklin, *Ber.*, **58**, 409 (1925). [b] Reference 26. [c] T. Zincke and S. Lenhardt, *Justus Liebigs Ann. Chem.*, **400**, 1 (1913). [d] Registry no., 4235-78-3. [e] Registry no.: $AgNO_3$, 7761-88-8; AgOAc, 563-63-3, $HgCl_2$, 7487-94-7. [f] Registry no.: **4a**, 24364-84-9; **4b**, 34583-74-9; **3a**, 61076-35-5.

Table IV. *N*-Alkylidenealkylsulfenamides

Entry	Disulfide	Aldehyde/ ketone	Registry no.	Conditions	$RSN{=}CR_2$ % yield	Registry no.	Bp, °C (mm)	NMR, δ
1	Methyl	Benzaldehyde	100-52-7	$AgNO_3$–MeOH	33	61076-36-5	71–72 (0.11)	2.72 (s, 3, Me), 7.55 (m, 5), 8.35 (s, 1)
2				AgOAc–EtOAc	35			
3		Salicylaldehyde	90-02-8	$AgNO_3$–MeOH	30		*a*	
4		Acetaldehyde	75-07-0		No reaction			
5		Acetone	67-64-1		No reaction			
6	Ethyl	Benzaldehyde			24	61076-37-7	77–78 (0.1)	1.4 (t, 3, J = 7 Hz), 3.2 (q, 2, J = 7 Hz), 7.5 (m, 5), 8.5 (s, 1)
7	*n*-Propyl[b]	Benzaldehyde			30	61076-38-8	79–80 (0.08)	1.1 (t, 3, J = 6 Hz), 1.9 (m, 2), 3.1 (t, 2), 7.5 (m, 5), 8.5 (s, 1)
8				$HgCl_2$–MeOH	No reaction			
9		Salicylaldehyde		$AgNO_3$–MeOH	33	61076-39-9	88–90 (0.08)	1.1 (t, 3, J = 6 Hz), 1.8 (m, 2), 3.1 (t, 2), 6.97 (m, 4), 8.6 (s, 1), 11.0 (s, 1)
10		Acetophenone	98-86-2		26	61076-40-2	103 (0.7)	1.1 (t, 3, J = 6 Hz), 1.9 (m, 2), 2.3 (s, 3, Me), 3.1 (t, 2), 7.5 (m, 5)
11	*n*-Butyl	Salicycaldehyde			17	61076-41-3	137 (0.14)	0.9 (t, 3, J = 6 Hz), 1.6 (m, 4), 2.7 (t, 2, J = 6 Hz), 7.1 (m, 2), 7.6 (m, 2), 10.0 (s, 1), 11.0 (s, 1)
12	Isopropyl	Benzaldehyde			No reaction			
13		Benzaldehyde		AgOAc–EtOAc	No reaction			
14	*tert*-butyl[c]	Benzaldehyde		$AgNO_3$–MeOH	No reaction			

[a] Reference 13. [b] Registry no., 629-19-6. [c] Registry no., 110-06-5.

undoubtedly involves a nucleophilic attack by the sulfenamide nitrogen at the S–N bond of another sulfenamide unit with elimination of an amine (eq 3). Sulfenic acids (RSOH) undergo a similar reaction with formation of a thiolsulfinite [RS(O)SR] and elimination of water.[10]

$$R\text{–}S\text{–}NH_2 + R\text{–}S\text{–}NH_2 \rightarrow (R\text{–}S)_2NH + NH_3 \quad (3)$$

Sulfenamides meet the requirements for "α-effect" nucleophiles in that the nucleophilic atom (nitrogen) is adjacent to a heteroatom (sulfur) containing lone pairs of electrons.[31] In certain cases such nucleophiles display greater nucleophilicity than the parent nucleophile.

As the electronegativity of groups attached to sulfur increases the electron density on sulfur in **3** should decrease. This should reduce the magnitude of the "α effect" and the nucleophilicity of the sulfenamide nitrogen. As reflected in Table III, bis(sulfen)imides **4** were obtained only when the group attached to sulfur was more electron donating than a 3,4-dichlorophenyl group. Similar results have recently been reported by Welch, who observed a regular decrease in the formation of bis(arenesulfen)imides of 6-aminopenicillanic acid as the electronegativity of the group attached to the sulfenyl chloride increased.[11]

The "α effect" could well explain the difference in reactivity between aliphatic and aromatic sulfenamides. However, other factors such as leaving group ability and the effect of electrophiles are also important in determining the reactivity of these compounds.

***N*-Alkylidenealkylsulfenamides.** In a previous paper we reported on the metal-assisted synthesis of *N*-alkylidenear-

enesulfenamides **2** from aromatic disulfides, silver nitrate, ammonia, and aldehydes and ketones,[26] and reported that this procedure failed with benzyl and ethyl disulfide using acetone as the carbonyl compound. We report here that *N*-alkylidenealkylsulfenamides **2** (R = alkyl) can be prepared in certain cases using this method.

N-Alkylidenealkylsulfenamides can only be prepared from aliphatic disulfides using the metal-assisted procedure when the disulfide is straight chain and an aromatic group is attached to the carbonyl carbon. Yields of **2** prepared in this way were generally low, 17–30%. Similar yields of *N*-benzylidenemethylsulfenamides were obtained using silver nitrate–methanol or silver acetate–ethyl acetate. Table IV summarizes these results.

Assuming that an alkylsulfenamide ($RSNH_2$) is an intermediate in the formation of **2**, the low yields of *N*-alkylidenealkylsulfenamides and the inability to prepare **2** from branched-chain disulfides is readily explained. For the reasons discussed above, an alkanesulfenamide of ammonia ($RSNH_2$) should be very unstable with the instability increasing as the degree of branching of the disulfide increases. Furthermore, steric hindrance to attack by ammonia on the silver–disulfide complex would be anticipated to be greater for the branched-chain disulfides.

Experimental Section

Melting points were measured on a Mel-Temp apparatus. ^1H NMR spectra were obtained on a Varian A-60A spectrometer and IR spectra on a Perkin-Elmer 457 spectrometer. Disulfides obtained commercially were used without further purification. Solvents were purified by standard methods. *N*-Alkylidenealkanesulfenamides **2** were prepared as described previously for *N*-alkylidenearenesulfenamides.[26]

Oxidation of Thiols to Disulfides. The thiol was dissolved in 70% ethanol containing 1 equiv of NaOH. The solution was cooled and an equivalent amount of 15% hydrogen peroxide added dropwise. The precipitated disulfide was collected and crystallized from ethanol.

General Synthesis of Sulfenamides from Aromatic Disulfides. In a 1000-ml three-necked flask equipped with overhead stirrer was placed 7.8 g (0.045 mol) of silver nitrate in 400 ml of methanol. After solution had taken place an equivalent amount of disulfide was added and the reaction mixture cooled in an ice bath. An excess of the appropriate amine (usually 5 equiv) was added and the reaction mixture allowed to stir overnight. The silver mercaptide was filtered and the solvent removed at reduced pressure, at a temperature of 35–40 °C. The resulting residue was dissolved in ether, washed with water (4 × 100 ml), and dried over $MgSO_4$. Removal of the ether solvent gave the sulfenamide which was distilled or crystallized. Sulfenanilides were purified prior to crystallization by chromatography on Florisil. This same procedure was used with mercuric chloride. To prepare sulfenamides of ammonia, dry ammonia gas was passed through the metal–disulfide solution for 10–15 min at 0 °C.

General Synthesis of Sulfenamides from Aliphatic Disulfide. In a 1000-ml three-necked flask equipped with overhead stirrer were placed 8.38 g (0.05 mol) of silver acetate and 0.025 mol of the appropriate alkyl disulfide in 300 ml of ethyl acetate. The solution was cooled, an excess of the appropriate amine (5 equiv) was added, and the reaction mixture was stirred for 23 h at room temperature in the dark. The silver mercaptide was removed by filtration and the filtrate evaporated under reduced pressure at 40 °C. The residue was extracted with ether, washed with water (3 × 100 ml), and dried over $MgSO_4$. Evaporation of the ether yielded a yellow oil which was distilled.

Bis(3-nitrobenzenesulfen)imide (4c). In a 50-ml round-bottom flask equipped with magnetic stirring bar was placed 0.5 g (0.00294 mol) of 3-nitrobenzenesulfenamide **3b** in 25 ml of water or 35 ml of ethyl ether. Acetic acid (5 ml), or 0.417 g (0.00294 mol) of boron trifluoride etherate (Aldrich) was added and the reaction mixture allowed to stir for 12 h at room temperature. The precipitated solid was removed by filtration, washed with water, dried, and crystallized from chloroform to yield 0.35–0.4 g (72–84%) of orange needles; mp 166–168 °C; IR (KBr) 3230 cm^{-1} (NH); NMR ($CDCl_3$) δ 2.7 (broad s, 1), 7.4–8.3 (m, 8)

Anal. Calcd for $C_{12}H_9N_3O_4S$: C, 44.58; N, 2.79. Found: C, 44.44; H, 2.82.

Silver Recovery. The silver mercaptide was burned to yield a dark ash which was further combusted to silver metal using an oxygen-gas torch. The silver metal was dissolved in concentrated nitric acid and filtered. The filtrate was concentrated by boiling and on cooling yielded crystals of silver nitrate. Additional silver nitrate can be obtained by further concentration of the filtrate. Overall recovery of silver nitrate by this method is 65–75%.

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Registry No.—**3b**, 40576-93-0; **4c**, 61076-42-4; ammonia, 7664-41-7.

References and Notes

(1) Part 11: F. A. Davis and E. B. Skibo, *J. Org. Chem.*, **41**, 1333 (1976).
(2) For a recent review on the chemistry of the S–N bond see F. A. Davis, *Int. J. Sulfur Chem.*, **8**, 71 (1973).
(3) T. Kumamoto, S. Kobayashi, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **45**, 866 (1972); T. Mukaiyama, S. Kobayashi, and T. Kumamoto, *Tetrahedron Lett.*, 5115 (1970).
(4) (a) K. S. Boustany and A. B. Sullivan, *Tetrahedron Lett.*, 3547 (1970); (b) D. N. Harpp, D. K. Ash, T. G. Back, J. G. Gleason, B. A. Owig, W. F. Van-Horn, and J. P. Snyder, *ibid.*, 3551 (1970); (c) D. N. Harpp and T. G. Back, *J. Org. Chem.*, **36**, 3828 (1971); (d) D. A. Armitage, M. J. Clark, and C. C. Tso, *J. Chem. Soc., Perkin Trans. 1*, 680 (1972).
(5) D. H. R. Barton, G. Page, and D. A. Widdowson, *Chem. Commun.*, 1406 (1970).
(6) D. N. Harpp and T. G. Back, *Tetrahedron Lett.*, 4953 (1971).
(7) M. Haake and H. Benack, *Synthesis*, 308 (1976).
(8) J. E. Dunbar and J. H. Rogers, *J. Org. Chem.*, **35**, 279 (1970).
(9) (a) F. A. Davis, U. K. Nadir, and E. W. Kluger, *J. Chem. Soc., Chem. Commun.*, in press; (b) F. A. Davis, A. J. Friedman, and E. W. Kluger, *J. Am. Chem. Soc.*, **96**, 5000 (1974).
(10) F. A. Davis and A. J. Friedman, *J. Org. Chem.*, **41**, 897 (1976).
(11) W. M. Welch, *J. Org. Chem.*, **41**, 2220 (1976).
(12) D. Kost and A. Zeichner, *Tetrahedron Lett.*, 3239 (1975).
(13) F. A. Davis, J. M. Kaminski, E. W. Kluger, and H. S. Freilich, *J. Am. Chem. Soc.*, **97**, 7085 (1975).
(14) F. A. Davis and E. W. Kluger, *J. Am. Chem. Soc.*, **98**, 302 (1976).
(15) C. Brown and B. T. Grayson, *Mech. React. Sulfur Compd.*, **5**, 93 (1970).
(16) N. Kharasch, S. J. Potempa, and H. H. Wehrmeister, *Chem. Rev.*, **39**, 269 (1946).
(17) (a) E. Kuhle, *Synthesis*, 561 (1970); (b) *ibid.*, 617 (1971).
(18) T. J. Hurley and M. A. Robinson, *J. Med. Chem.*, **8**, 888 (1965).
(19) J. J. D'Amico, M. W. Harmon, and R. H. Cooper, *J. Am. Chem., Soc.*, **79**, 5270 (1957); E. L. Carr, G. E. P. Smith, Jr., and G. Allinger, *J. Org. Chem.*, **14**, 921 (1949).
(20) R. T. Major and L. H. Peterson, *J. Am. Chem. Soc.*, **78**, 6181 (1956).
(21) J. E. Dunbar and J. H. Rogers, *J. Org. Chem.*, **31**, 2848 (1966).
(22) M. Bhforouz and J. E. Kerwood, *J. Org. Chem.*, **34**, 51 (1969).
(23) F. A. Davis and J. M. Kaminski, unpublished results.
(24) F. A. Davis, E. R. Fretz, and C. J. Horner, *J. Org. Chem.*, **38**, 690 (1973).
(25) M. D. Bentley, I. B. Douglass, J. A. Lacadie, D. C. Weaver, F. A. Davis, and S. J. Eitelman, *Chem. Commun.*, 1625 (1971).
(26) F. A. Davis, W. A. R. Slegeir, S. Evans, A. Schwartz, D. L. Goff, and R. Palmer, *J. Org. Chem.*, **38**, 2809 (1973).
(27) I. B. Douglass, K. R. Brower, and F. T. Martin, *J. Am. Chem. Soc.*, **74**, 5770 (1952).
(28) N. E. Heimer and L. Field, *J. Org. Chem.*, **35**, 3012 (1970).
(29) H. Lecher, F. Holschneider, K. Koberle, W. Speer, and P. Stocklin, *Ber.*, **58**, 409 (1925).
(30) (a) T. Zincke and F. Farr, *Justus Liebigs Ann. Chem.*, **391**, 55 (1912); (b) T. Zincke and S. Lenhardt, *ibid.*, **400**, 1 (1913).
(31) (a) G. Klopman, K. Tsuda, J. B. Louis, and R. E. Davis, *Tetrahedron*, **26**, 4549 (1970); (b) J. D. Aubort and R. F. Hudson, *Chem. Commun.*, 937, 938, 1378 (1970).

Preparation and Reaction of Compounds Related to 2,2,4,4-Tetramethylpentane-3-thiol [Di(*tert*-butyl)methanethiol]

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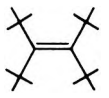
Reduction with lithium aluminum hydride of 2,2,4,4-(tetramethyl)pentane-3-thione (**3**) gives the thiol (**2**). Treatment of **2** with chlorine affords 2,2,4,4-(tetramethyl)pentane-3-sulfenyl chloride (**4**), the reactions of which were investigated. Substitution of **4** on sulfur proceeds normally with diazomethane, phthalimide, and methanol. Hydrolysis of **4** likely provides the corresponding sulfenic acid (**11**), which dimerizes to a thiol sulfoxide (**7**). Reaction of **4** with ozone gives 2,2,4,4-(tetramethyl)pentane-3-sulfinyl chloride (**8**). This compound can be converted to the sulfine (**13**) by treatment with pyridine at −30 °C. Several substitution reactions on sulfinic sulfur were investigated. Alkylation of **2** with benzyl bromide and oxidation of this product gave benzyl[2,2,4,4-(tetramethyl)-3-pentyl] sulfone (**17**) that was converted to a dianion on treatment with excess *n*-butyllithium. Some reactions of this dianion were investigated.

We, and others,[1] have been interested for some time in devising a synthesis of tetra-*tert*-butylethylene (**1**). Although our experiences in this area parallel those of other workers, namely failure to obtain **1**, we have during this effort devel-



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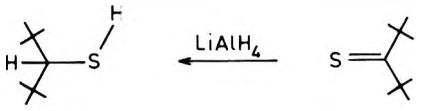
oped a considerable amount of chemistry centered around the thiol **2**, which we viewed as a possible intermediate in a synthesis of **1**. We now report some of the chemistry of this hindered thiol.

Thiol **2** was prepared in excellent yield by reduction (eq 1) of di(*tert*-butyl)thione (**3**), which has recently become avail-



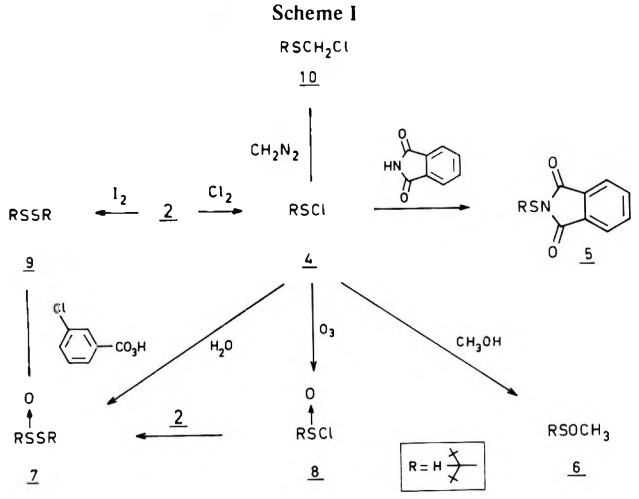
(1)

2 **3**

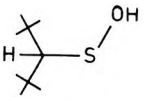
able.[1a,2] This thiol proved more susceptible to chemical manipulation than its oxygen analogue, di(*tert*-butyl)carbinol, which enters cleanly into relatively few reactions other than esterification.[3,4]

Reaction of **2** with chlorine[5] proceeded smoothly to give in essentially quantitative yield the sulfenyl chloride (**4**). This compound was not stable enough for analysis and was characterized by spectral data and reactions as outlined in Scheme I. Attempts to add **4** to olefins failed to give characterizable

Scheme I

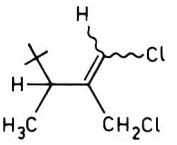


products. However, the reactions with phthalimide[6] and methanol[7] to form respectively the *N*-(alkylthio)phthalimide **5** and the sulfenate ester **6** are characteristic for reasonably stable sulfenyl chlorides. The corresponding sulfoxide and sulfone derivatives of **5** were also prepared. With water **4** reacted cleanly to give the thiosulfinate **7**, which is the expected condensation product of the sulfenic acid **11**.[8] Attempts to trap **11** by addition to conjugated systems were



11

unsuccessful, however. Oxidation of **4** with ozone was extremely clean and gave the sulfinyl chloride **8**; all attempts to force the reaction further failed. The same was true with *m*-chloroperbenzoic acid (MCPBA) as oxidant, which gave again, even under the most forcing conditions, only **8**. We were unable to obtain the sulfonyl chloride. The samples of **8** prepared by oxidation with MCPBA were for unknown reasons not stable and on attempted purification by chromatography on silica gel the product decomposed readily to give chiefly the unsaturated chloride **12**. A mechanism involving the formation



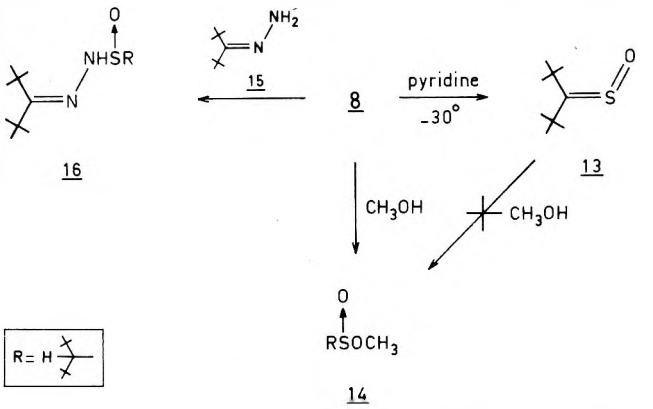
12

of the di(*tert*-butyl) carbonium ion is likely involved in the formation of **12**.[3]

The thiolsulfinate **7** was also obtained by oxidation with MCPBA of disulfide **9**, formed by the (rather sluggish) oxidation of **2**. The combination of **2** with **8** afforded also the thiolsulfinate. Reaction of **2** with diazomethane[9] proceeded normally to give chloromethyl compound **10**.

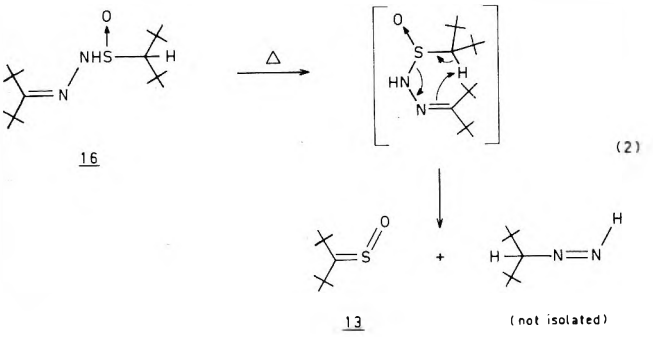
Some additional reactions as shown in Scheme II were carried out on sulfinyl chloride **8**. Dehydrohalogenation with pyridine at −30 °C gave cleanly the sulfine **13**, which has been prepared previously by Barton and co-workers by oxidation of the thione **3**.[10,2] No or only a very poor yield of **13** was obtained on treating **8** with pyridine at temperatures higher than −30 °C, with triethylamine, diisopropylamine, or calcium hydroxide.[11]

Scheme II



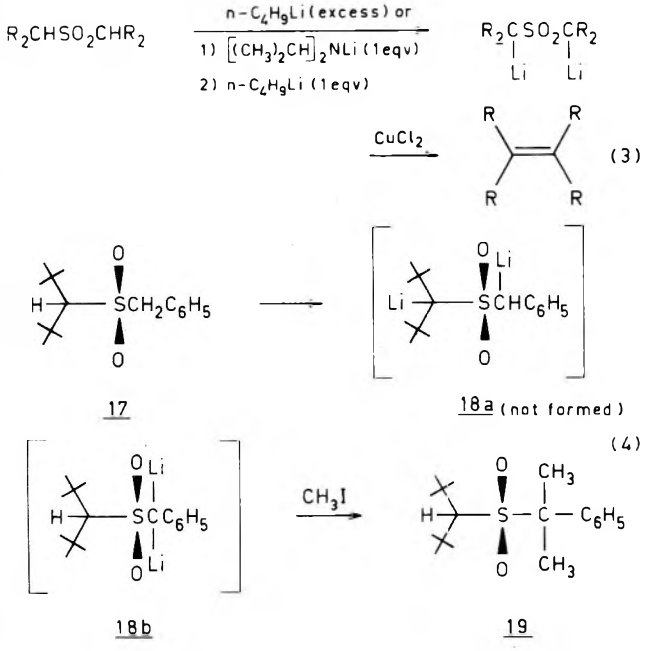
Since reaction with methanol gave the sulfinate ester **14**, whereas sulfine **13** fails to react with methanol, we suspect that there is a competition in the reactions of **8** between catalyzed elimination leading to sulfine formation and attack at sulfur to form sulfinates, which can be isolated when suitable nucleophiles like methanol or **2** are used.

A rather interesting reaction of **8** was with the hydrazone of di-*tert*-butyl ketone (**15**)[17] as shown in eq 2. The condensation product **16** was isolated in good yield; attempts to couple by pyrolytic means the two di(*tert*-butyl)methyl (or methylene) units resulted in the formation of the sulfine **13** as the only isolated product. A possible sigmatropic rearrangement that could lead to **13** is shown in eq 2. Other paths involving initial homolysis of a bond can, of course, be suggested.



(2)

Brief examination was made of the feasibility of preparing 1,1-di(*tert*-butyl)alkenes by the route of eq 3 previously developed for simple alkenes.[13] Reaction of **2** with benzyl bromide gave the alkylated product, which was oxidized to the sulfone **17**. Treatment of **17** with excess *n*-butyllithium or alternatively first with 1 equiv of diisopropylamide followed by 1 equiv of *n*-butyllithium gave a light yellow solution thought to contain a dicarbanion.[14] Oxidation with $CuCl_2$ gave, however, no isolable amounts of alkene and swamping of the solution with methyl iodide gave in good yield **19**. This suggests that not the α,α' dianion **18a** but rather α,α dianion **18b** is formed (eq 4).



(3)

(4)

Experimental Section

All melting points were determined with a calibrated melting point block or with a Mettler automatic melting point apparatus. UV, IR ^{1}H NMR, and mass spectra were obtained using common laboratory instruments. ^{13}C NMR measurements were made at 25.2 MHz and chemical shifts are relative to Me_4Si.

Chemicals cited without reference were either in stock or were prepared following well-described procedures. Elemental analyses were carried out in the analytical laboratory of this university.

2,2,4,4-Tetramethylpentane-3-thiol (2) was prepared by the reduction of 2,2,4,4-tetramethyl-3-pentanethione (3.0 g, 19 mmol) in dry ether (50 ml) added dropwise to a stirred suspension of $LiAlH_4$ (0.34 g, 10 mmol) in dry ether (70 ml). The solution was let stand for 2 h. After neutralization with dilute H_2SO_4 and workup there was obtained 285 mg (17.8 mmol, 94%) of thiol: bp (43 mm) 96–98 °C; IR (CCl_4) 1150, 1205, 1360, 1395, and 1480 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.10 [s, 18, $(CH_3)_3C$], 1.22 (d, J = 8 Hz, SH), and 2.60 (d, J = 8 Hz, CH).

Anal. Calcd for $C_9H_{20}S$: C, 67.43; H, 12.67; S, 20.00. Found: C, 67.62; H, 12.63; S, 19.75.

2,2,4,4-Tetramethylpentane-3-sulfenyl chloride (4) was prepared by treating a stirred solution of **2** (1.6 g, 10 mmol) in 10 ml of dry CCl_4 with a stream of dry Cl_2 at 0 °C. The reaction was followed by ^{1}H NMR and was stopped once conversion was complete. The material had ^{1}H NMR δ 1.20 [s, 18, $(CH_3)_3C$] and 2.75 (s, 1, CH). The material was only moderately stable and was used without further purification save that excess Cl_2 was blown out of solution with a stream of N_2. Addition of excess Cl_2 gave no evidence for the addition of a second mole of Cl_2 to the sulfur atom. Although the point is not rigorously proven, we believe that exclusively RSCl and not $RSCl_3$ is the compound formed.

***N*-[(2,2,4,4-Tetramethyl)-3-pentyl]thiophthalimide (5)** was prepared by allowing a freshly prepared solution of **4** (10 mmol) in CCl_4 to react with a stirred slurry of phthalimide (1.47 g, 10 mmol) and triethylamine (1.5 g, 15 mmol) in 20 ml of CCl_4 over a period of one night. Water (25 ml) was added, and the organic layer was separated and dried over $MgSO_4$. The product was recrystallized from CH_3OH affording 3.02 g (10 mmol, 99% yield) of **5** as a white solid: mp 118–120 °C; ^{1}H NMR (CCl_4) δ 1.22 [s, 18, $(CH_3)_3C$], 3.10 (s, 1, CH), and 7.70 (complex, 4, C_6H_4); IR (KBr) 1720, 1700, 1470, 1290, 1050, 870, and 700 cm^{-1}.

Anal. Calcd for $C_{17}H_{23}NO_2S$; C, 66.85; H, 7.59; N, 4.59; S, 10.50. Found: C, 66.89; H, 7.67; N, 4.55; S, 10.53.

Oxidation of **5** to the sulfinamide was carried out by treating **5** (102 mg, 0.35 mmol) dissolved in $CHCl_3$ with *m*-chloroperbenzoic acid (67 mg, 0.33 mmol) at room temperature. Workup gave 103 mg (0.32 mmol, 92% yield) of the sulfinamide: mp 155–160 °C; ^{1}H NMR δ 1.17 [s, 9, $(CH_3)_3C$], 1.40 [s, 9, $(CH_3)_3C$], 4.35 (s, 1, CH), and 7.80 (complex 4, C_6H_4); IR (KBr) 1020 cm^{-1} (S–O).

Anal. Calcd for $C_{17}H_{23}NO_3S$: C, 63.53; H, 7.21; N, 4.35; S, 9.98. Found: C, 63.61; H, 7.12; N, 4.34; S, 9.82.

The sulfonamide of **5** was prepared by treating **5** (102 mg, 0.35 mmol) dissolved in $CHCl_3$ with *m*-chloroperbenzoic acid (134 mg, 0.66 mmol). Workup gave 109 mg (0.32 mmol, 92% yield) of the sulfonamide as a white solid: mp 167–169 °C; IR (KBr) 1300 cm^{-1} (SO_2); ^{1}H NMR (CCl_4) δ 1.42 [s, 18, $(CH_3)_3C$], 3.85 (s, 1, CH), and 7.58 (complex, 4, C_6H_4).

Anal. Calcd for $C_{17}H_{23}NO_4S$: C, 60.51; H, 6.87; N, 4.15; S, 9.50. Found: C, 60.70; H, 6.90; N, 4.13; S, 9.52.

The sulfinamide **5** was also prepared in 73% isolated yield from the reaction of **4** with phthalimide in CCl_4 at −15 °C with added triethylamine.

***O*-Methyl[2,2,4,4-(tetramethyl)-3-pentyl] sulfenate (6)** was prepared by allowing freshly prepared **4** (300 mg, 1.5 mmol) in CCl_4 to react with excess methanol and triethylamine (200 mg, 2 mmol) with stirring at room temperature. After disappearance of the yellow color the precipitated triethylamine hydrochloride was removed by

filtration to give 244 mg (1.28 mmol, 85% yield) of crude **6**: bp (0.2 mm) 48 °C; IR (neat) 1430–1490, 1390, 1365, 1220, and 1000 cm^{-1}; ^1H NMR (CCl_4) δ 1.15 [s, 18, $(CH_3)_3C$], 2.63 (s, 1, CH), and 3.58 (s, 3, CH_3O); mass spectrum *m/e* 190 (parent) (calcd for $C_{10}H_{22}SO$, 190). An acceptable elemental analysis could not be obtained.

2,2,4,4-(Tetramethyl)-3-pentylsulfinyl chloride (8) was best prepared by leading for several hours a stream of ozone through a solution of **4** (5 mmol) dissolved in CCl_4. The course of reaction was followed by ^1H NMR and reaction was stopped once the absorption for **8** had disappeared. As judged by ^1H NMR the sulfinyl chloride was formed in quantitative yield: ^1H NMR (CCl_4) δ 1.27 [s, 9, $(CH_3)_3C$], 1.35 [s, 9, $(CH_3)_3C$], and 3.18 (s, 1, CH); IR (neat) 1300, 1260, 1215, 1150 cm^{-1}. A satisfactory elemental analysis could not be obtained.

Alternatively **4** could be oxidized with *m*-chloroperbenzoic acid to give **8** in 65% yield. On attempted purification by chromatography over silica gel a product was isolated to which structure **12** was assigned: bp (45 mm) 120 °C; IR (neat) 1625, 1460, 1365, 1375, and 825 cm^{-1}, ^1H NMR (CCl_4) δ 0.93[s, 9, $CH_3)_3C$], 1.14 (d, J = 7 Hz, 3, CH_3), 2.32 (q, J = 7 Hz, 1, CH_3CH), 3.91 (d, J = 11 Hz, 1, CH_aH_bCl), 4.43 (d, J = 11 Hz, 1, CH_aH_bCl), and 6.02 (s, 1, vinyl H); ^{13}C NMR ($CDCl_3$, δ relative to Me_4Si) δ 15.5 (q, J = 128 Hz, CH_3CH), 27.7 [q, J = 128 Hz, $(CH_3)_3C$], 33.9 [s, $(CH_3)_3C$], 42.5 (t, J = 152 Hz, CH_2Cl), 47.7 ppm (d, J = 120 Hz, CH_3CH), 120.1 ppm (d, J = 192 Hz, CHCl), and 142.2 (s, CCH_2Cl).

Di[2,2,4,4-(tetramethyl)-3-pentyl] disulfide (9) was prepared by dissolving thiol **2** (1.69, 10 mmol) in 3 ml of 15% NaOH solution and allowing this to react with I_2 (1.09 g, 4 mmol) added in portions. The reaction was carried out in an ice bath and the mixture was allowed to stir for 12 h thereafter. The upper layer was separated, the lower layer was extracted three times with ether, and the organic layers were combined and dried over $MgSO_4$. Filtration and removal of the solvent gave 1.65 *g* (5 mmol, 100% yield) of crude **9**: mp 75.5–76 °C; IR (KBr) 2900–3000, 1475, 1390, 1365, 1250, and 1220 cm^{-1}; ^1H NMR (CCl_4) δ 1.17 [s, 18, $(CH_3)_3C$] and 2.53 (s, 1, CH).

Anal. Calcd for $C_{18}H_{38}S_2$: C, 67.85; H, 12.02; S, 20.13. Found: C, 67.89; H, 11.94; S, 20.04.

The disulfide was also obtained in quantitative yield by allowing **4** (387 mg, 2 mmol) to react with **2** (320 mg, 2 mmol) in pyridine at room temperature.

Hydrolysis of 2,2,4,4-(tetramethyl)-3-pentylsulfenyl chloride (4) was carried out with a solution of **4** (684 mg, 1.75 mmol), which was allowed to react with ice–water. After stirring for 2 h, the solution was extracted with ether and the organic layer was dried over $MgSO_4$. Removal of the solvent gave 438 mg (1.25 mmol, 70% yield) of 2,2,4,4-(tetramethyl)-3-pentylthiol[2,2,4,4-(tetramethyl)-3-pentyl] sulfinate (**7**): mp 113.5–114.5 °C (from CH_3OH); IR (KBr) 1440–1480, 1390, 1370, and 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 [s, 8, $(CH_3)_3C$], 1.22 [s, 9, $(CH_3)_3C$], 1.40 [s, 9, $(CH_3)_3C$], 2.97 (s, 2, CH, absorptions overlap).

Anal. Calcd for $C_{18}H_{38}S_2O$: C, 64.61; H, 11.45; S, 19.16. Found: C, 64.95; H, 11.51; S, 19.17.

The thiolsulfinate **7** was also obtained in nearly quantitative yield by oxidation of disulfide **9** with 1 equiv of *m*-chloroperbenzoic acid. All attempts to oxidize this further afforded only uncharacterizable products.

Reaction of sulfinyl chloride **8** with thiol **2** in pyridine gave also thiolsulfinate **7** in 40% yield.

Di(*tert*-butyl)sulfine (13) was obtained by adding slowly to 10 ml of dry pyridine held at −29 to −30 °C sulfinyl chloride **8** (500 mg, 2.38 mmol) with stirring. After standing with stirring at room temperature for 1 h, the pyridinium hydrochloride was removed by filtration, and the solvent removed to give 400 mg (2.37 mmol, 100% yield) of crude sulfine, pure by ^1H NMR spectroscopy and with physical constants identical with those described previously.[10]

2,2,4,4-(Tetramethyl)-3-pentylmethyl sulfinate (14) was obtained by allowing sulfinyl chloride **8** (0.89 g, 5 mmol) to reflux in 15 ml of absolute CH_3OH. Removal of methanol left exclusively **14**: bp (1 mm) 100 °C; IR (neat) 1450–1500, 1400, 1370, 1125, and 1000 cm^{-1}; ^1H NMR (C_6D_6) δ 1.12 [s, 9, $(CH_3)_3C$], 1.28 [s, 9, $(CH_3)_3C$], 2.32 (s, 1, CH), and 3.30 (s, 3, CH_3O).

Anal. Calcd for $C_{10}H_{22}SO_2$: C, 58.21; H, 10.74; S, 15.54. Found: C, 58.48; H, 10.69; S, 15.22.

Di-*tert*-butyl ketone [2,2,4,4-(tetramethyl)-3-pentyl] sulfinylhydrazone (16) was prepared from the reaction of sulfinyl chloride **8** (2.58 g, 12.4 mmol) and 2,2,4,4-(tetramethyl)-3-pentanone ketazine (1.92 g, mmol, 12.3 mmol) at 0 °C in pyridine (30 ml). After 1 h at this temperature followed by 2 h at room temperature pyridine hydrochloride was filtered off, the solvent removed, and the residue recrystallized from *n*-heptane to give 2.42 g (7.38 mmol, 60% yield) of **16** as a white solid: mp 93.5–95 °C; IR (KBr) 3170, 2800–3000 (br), 1460, 1390, 1375, 1370, 1360, 1220, 1190, 1140, 1075, 1040, 995, and 880 cm^{-1}; NMR (CCl_4) δ 1.30 [s, 9, $(CH_3)_3C$], 1.37 [s, 9, $(CH_3)_3C$], 1.42 [s, 18, $(CH_3)_3C$], 2.50 (s, 1, CH), and 7.52 (s, 1, NH).

Anal. Calcd for $C_{18}H_{38}N_2OS$: C, 65.40; H, 11.59; N, 8.47; S, 9.70. Found: C, 65.39; H, 11.63; N, 8.44; S, 9.75.

Pyrolysis of **16** dissolved in toluene in a sealed tube at 150 °C gave a mixture of products from which sulfine **13** was characterized (70% yield).

Benzyl[2,2,4,4-(tetramethyl)-3-pentyl] sulfide was prepared by allowing a mixture of thiol **2** (1.6 g, 10 mmol), benzyl bromide (1.71 g, 10 mmol), and sodium (250 mg, 10.9 mmol) dissolved in ethanol (4 ml) to stir at room temperature overnight. The solution was diluted with saturated NaCl solution and extracted with ether. After drying, removal of the solvent, and distillation there was obtained 2.5 g (10 mmol, 100% yield) of the sulfide: bp (10 mm) 165–167 °C; IR (neat) 1600, 1500, 1475, 1455, 1390, 1360, and 700 cm^{-1}; ^1H NMR (CCl_4) δ 1.12 [s, 18 $(CH_3)_3C$], 1.25 (s, 1, CH), 3.68 (s, 2, CH_2), and 7.21 (complex, 5, C_6H_5).

Anal. Calcd for $C_{16}H_{26}S$: C, 76.73; H, 10.46. Found: C, 76.40; H, 10.42.

An acceptable analysis for sulfur was not obtained.

The sulfoxide of benzyl [2,2,4,4(tetramethyl)-3-pentyl] sulfide was prepared in the usual fashion by oxidation with 1 equiv of *m*-chloroperbenzoic acid: mp 97–98 °C (from CH_3OH); IR (KBr) 1010–1030 cm^{-1} (S–O); ^1H NMR (CCl_4) δ 1.00 [s, 9, $(CH_3)_3C$], 1.35 [s, 9, $(CH_3)_3C$], 2.25 (s, 1, CH), 4.15 (s, 2, CH_2), and 7.28 (complex, 5, C_6H_5).

Anal. Calcd for $C_{16}H_{26}SO$: C, 72.13; H, 9.84; S, 12.03. Found: C, 61.68; H, 9.70; S, 11.76.

The sulfone **17** was prepared by oxidation of the sulfide with 2 equiv of *m*-chloroperbenzoic acid: mp 71.5–73.5 °C (from CH_3OH); IR (KBr) 700, 1120, and 1300 cm^{-1}; ^1H NMR (CCl_4) δ 1.28 [s, 18, $(CH_3)_3C$], 2.63 (s, 1, CH), 4.19 (s, 2, CH_2), and 7.36 (complex, 5, C_6H_5). The sulfone was characterized as a derivative (see below).

Reaction of Benzyl[2,2,4,4-tetramethyl)-3-pentyl] sulfone (17) with Strong Base. To **17** (213 mg, 0.755 mmol) dissolved in 20 ml of pure, dry dimethoxyethane under dry nitrogen at 0 to −5 °C was added *n*-butyllithium (4.4 mmol). A light brown color developed rapidly; the resulting solution was stirred for 1 h. Methyl iodide (426 mg, 3 mmol) was added rapidly and the solution was stirred for 1 h more at 0 °C and kept overnight at room temperature. Quenching with water and straightforward workup gave 308 mg of crude material that was recrystallized from CH_3OH to give 97 mg (0.313 mmol, 41% yield) of **19**: mp 110–111 °C; IR (KBr) 1470, 1370, 1270, 1110, 1090, 780, and 650 cm^{-1}; ^1H NMR (CCl_4) δ 1.09 [s, 18, $(CH_3)_3C$], 1.77 (s, 6, CH_3), 2.82 (s, 1, CH), and 7.25 (complex, 5, C_6H_5).

Anal. Calcd for $C_{18}H_{30}SO_2$: C, 69.63; H, 9.74; S, 10.33. Found: C, 69.63; H, 9.84; S, 10.24.

Various attempts to oxidize a dianion from **17** following procedures described in ref 13 gave only recovered starting material and/or uncharacterized products.

Chloromethyl[2,2,4,4-(tetramethyl)-3-pentyl] sulfide (10) was prepared by allowing **4** (200 mg, 1.02 mmol) dissolved in ether to react with a slight excess of a diazomethane solution in ether. Stirring was continued for 15 h at room temperature. Any remaining diazomethane was destroyed and the solution was concentrated under reduced pressure. Distillation gave 149 mg (0.717 mmol, 70% yield) of **10**: bp (0.1 mm) 50 °C; IR (neat) 1475, 1395, 1370, 1260, 1230, 1080, 1020, 800 (br), and 725 cm^{-1}; ^1H NMR (CCl_4) δ 1.18 [s, 18, $(CH_3)_3C$], 2.49 (s, 1, CH), and 2.76 (s, 2, CH_2).

Anal. Calcd for $C_{10}H_{21}SCl$: C, 57.53; H, 10.14; S, 15.35; Cl, 16.98. Found: C, 57.43; H, 10.17; S, 15.05.

An acceptable analysis for chlorine was not obtained.

Registry No.—**2**, 57602-97-8; **3**, 54396-69-9; **4**, 61258-91-1; **5**, 61258-92-2; **5** sulfinamide analogue, 61258-93-3; **5** sulfonamide analogue, 61258-94-4; **6**, 61258-95-5; **7**, 61258-96-6; **8**, 61258-97-7; **9**, 58712-15-5; **10**, 61258-98-8; **12**, 61258-99-9; **14**, 61259-00-5; **15**, 33420-22-3; **16**, 61259-01-6; **17**, 61259-02-7; **19**, 61259-03-8; phthalimide, 85-41-6; *m*-chloroperbenzoic acid, 937-14-4; methanol, 67-56-1; ozone, 10028-15-6; benzyl bromide, 100-39-0; benzyl[2,2,4,4-(tetramethyl)-3-pentyl] sulfide, 61259-04-9; benzyl[2,2,4,4-(tetramethyl)-3-pentyl] sulfoxide, 61259-05-0; diazomethane, 334-88-3.

References and Notes

(1) See, for example (a) D. H. R. Barton, F. S. Guziec, Jr., and I. Shahak, *J. Chem. Soc., Perkin Trans. 1*, 1794 (1974); (b) D. H. R. Barton in "Organic Sulphur Chemistry, Structure, Mechanism, and Synthesis", C. J. M. Stirling, Ed., Butterworths, London, 1975, pp 229–235; (c) J. A. Boerma, thesis, Groningen, 1972; there has over the years been much interest in the synthesis of *tert*-butyl substituted alkenes. For representative references on

tert-butylethenes, see (d) W. H. Puterbaugh and M. S. Newman, *J. Am. Chem. Soc.*, **81**, 1611 (1959); (e) G. J. Abruscato and T. T. Tidwell, *ibid.*, **92**, 4125 (1970); (f) R. B. Turner, D. E. Nettleton, Jr., and M. Perelman, *ibid.*, **80**, 1430 (1958); (g) M. S. Newman in "Steric Effects in Organic Chemistry", Wiley, New York, N.Y., 1956, p 248; (h) N. L. Allinger and J. T. Sprague, *J. Am. Chem. Soc.*, **94**, 5734 (1972); (i) M. B. Robin, G. N. Taylor, and N. A. Kuebler, *J. Org. Chem.*, **38**, 1049 (1973).

(2) (a) A. Ohno, K. Nakamura, Y. Nakazima, and S. Oka, *Bull. Chem. Soc. Jpn.*, **48**, 2403 (1975); (b) A. Ohno, K. Nakamura, M. Uohama, and S. Oka, *Chem. Lett.*, 983 (1975).

(3) A typical reference for esterification reactions is G. J. Karabatsos, N. Hsi, and C. E. Orzech, Jr., *Tetrahedron Lett.*, 4639 (1966). Substitution at oxygen in di-*tert*-butylcarbinol is very difficult. Virtually the only example is the reaction with phosgene, which affords di-*tert*-butylcarbinyl chloride: M. S. Kharasch, Y. C. Liu, and W. Nudenberg, *J. Org. Chem.*, **19**, 1150 (1954); F. Brown, T. D. Davies, I. Dostrovsky, O. J. Evans, and E. D. Hughes, *Nature (London)*, **167**, 987 (1951). The only report of ^{1}H NMR spectral data seemingly compatible with this structure is that of S. H. Liggero, J. J. Harper, P. v. R. Schleyer, A. P. Krapcho, and D. E. Horn, *J. Am. Chem. Soc.*, **92**, 3789 (1970), who obtained the compound in unreported yield. The oxidation of di-*tert*-butylcarbinol has also been studied. See, for example, H. Kwart and J. H. Nickle, *J. Am. Chem. Soc.*, **95**, 3394 (1973).

(4) Thiol **2** shows in the ^{1}H NMR spectrum C-**H**/S-**H** coupling (8.0 Hz) reminiscent of the well-studied C-**H**/O-**H** coupling in di-*tert*-butylcarbinol. See L. K. Patterson and R. M. Hammaker, *J. Phys. Chem.*, **70**, 3745 (1966), and succeeding papers.

(5) (a) M. Behforour and J. E. Kerwood, *J. Org. Chem.*, **34**, 51 (1969); (b) I. B. Douglass, B. S. Farah, and E. O. Thomas, *ibid.*, **26**, 1996 (1966).

(6) D. H. R. Barton, G. Page, and D. A. Widdowson, *J. Chem. Soc., Chem. Commun.*, 1466 (1970).

(7) See, for example, L. Goodman and N. Kharasch, *J. Am. Chem. Soc.*, **77**, 6541 (1955).

(8) See, for a recent compilation of references, (a) F. A. Davis and A. J. Friedman, *J. Org. Chem.*, **41**, 897 (1976). (b) Rearrangements of penicillin sulfoxides: P. G. Sammes, *Chem. Rev.*, **76**, 113 (1976).

(9) (a) A. Schönberg and T. Stolpp, *Chem. Ber.*, **63**, 3102 (1930). (b) For a review of the reactions of sulfenyl chlorides and sulfenic acids, see E. Kühle, "The Chemistry of the Sulfenic Acids", Georg Thieme Verlag, Stuttgart, 1973.

(10) T. G. Back, D. H. R. Barton, M. R. Britten-Kelly, and F. S. Guziec, Jr., *J. Chem. Soc., Chem. Commun.*, 539 (1975).

(11) J. H. Boyer and J. Kooi, *J. Am. Chem. Soc.*, **98**, 1099 (1976).

(12) H. D. Hartzler, *J. Am. Chem. Soc.*, **93**, 4527 (1971).

(13) J. S. Grossert, J. Buter, E. W. H. Asveld, and R. M. Kellogg, *Tetrahedron Lett.*, 2805 (1974).

(14) (a) W. E. Truce and L. W. Christensen, *J. Chem. Soc., Chem. Commun.*, 588 (1971); E. M. Kaiser, L. E. Solter, R. A. Schwarz, R. D. Beard, and C. R. Hauser, *J. Am. Chem. Soc.*, **93**, 4237 (1971); (c) V. Pascali, N. Tangari, and A. Umani-Ronchi, *J. Chem. Soc., Perkin Trans. 1*, 1166 (1973); (d) E. M. Kaiser and C. R. Hauser, *Tetrahedron Lett.*, 3341 (1967); (e) L. A. Paquette, R. H. Meisinger, and R. Gleiter, *J. Am. Chem. Soc.*, **95**, 5414 (1973).

Reactions of Cation Radicals of EE Systems. 5. Acid–Base Equilibria in Nucleophilic Reactions of Pyridine and Water with Thianthrene Cation Radical[1a]

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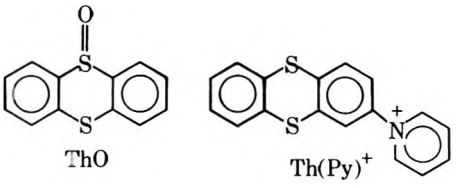
The role of cation radical/nucleophile adduct deprotonation equilibria in the reactions of thianthrene cation radical (Th·$^+$) with pyridine and water in acetonitrile solution has been examined using stopped-flow and electrochemical techniques. In both reactions reversible nucleophilic attack and adduct formation at a sulfur site on Th·$^+$ is proposed as the first step in a general half-regeneration scheme. Rate-determining electron transfer involves reaction between adduct (oxidant) and deprotonated adduct in the case of a protic nucleophile (e.g., water). In the case of an aprotic nucleophile (e.g., pyridine) the rate-determining encounter is between a nonadducted cation radical and adduct with the adduct functioning here as the reducing agent. The formation of the product of *both* reactions, thianthrene 5-oxide, is discussed in terms of the relative stabilities of the oxidized forms of these cation radical/nucleophile adducts.

Recent studies of the kinetics and mechanisms of the reactions of the 9,10-diphenylanthracene (DPA) cation radical (DPA·$^+$) with various nucleophiles and reducing agents[1] suggest that a half-regeneration mechanism[2] predominates in all cases where addition products are observed. Although this scheme is operative in the cases examined thus far, reactions of DPA·$^+$ with certain nucleophiles (e.g., chloride)[1d] have exhibited reaction dynamics which are second order in cation radical concentration. These observations are accounted for within the half-regeneration pathway in terms of rapid, reversible cation radical/nucleophile adduct formation which precedes rate-determining electron transfer from this adduct to a second ion radical. By comparison protic nucleophiles (e.g., water) in reaction with DPA·$^+$ show a first-order dependence of rate on both nucleophile and cation radical concentration,[3,4] indicative of rate-determining adduct formation. Such observations invite speculation concerning the role of ion radical/nucleophile adduct deprotonation steps and the extent to which processes of this type may influence the observed dynamics of a particular reaction.

An ideal system through which this role can be probed is afforded by the cation radical derived from thianthrene (Th). While the hydrolysis of the thianthrene cation radical (Th·$^+$) is known to be second order with respect to radical ion,[5,6] the corresponding anisylation of this species has been accounted for via a half-regeneration mechanism which exhibits concentration-dependent reaction order.[7] This mechanism involves adduction equilibria of the type noted in the chlorination of DPA.[1d]

The reaction of pyridine with Th·$^+$ in neat pyridine affords the *ring-substituted* product[8] Th(Py)$^+$ in which charge relief for this two-electron deficient species has occurred via substrate proton loss. Alternatively, the hydrolysis (protic nucleophile) of Th·$^+$ affords the addition product, thianthrene 5-oxide (ThO),[5,6] in which charge relief has been attained by



discharge of nucleophile protons. The nucleophiles pyridine and water were therefore selected for a comparative evaluation of the mechanistic effects exerted by protic and aprotic nucleophiles upon their respective reactions with the cation radical of thianthrene.

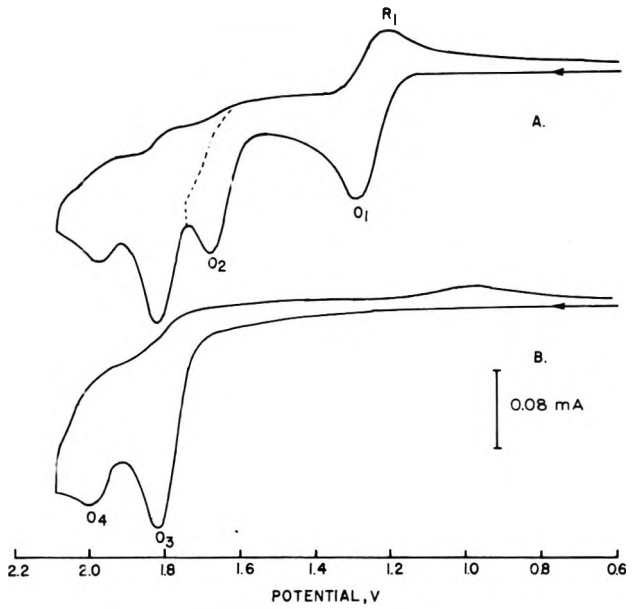


Figure 1. Anodic voltammetry of acetonitrile containing 0.10 M tetraethylammonium perchlorate (TEAP) and 1.0 mM Th (curve A) or 1.0 mM ThO (curve B). Scan rate 150 mV/s.

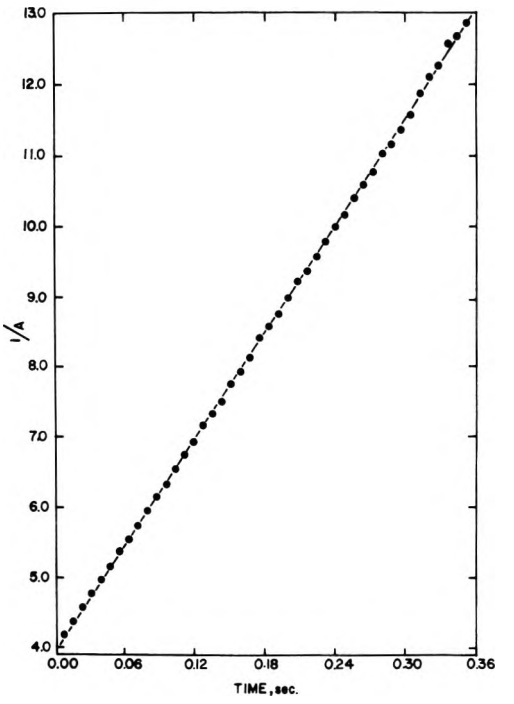


Figure 2. Second-order kinetic plot for the reaction of electrochemically generated $Th^{\cdot+}$ with water (0.20 M) in acetonitrile containing 0.10 M TEAP and 1.50 mM Th. T = 25.0 (± 0.1) °C.

This report details kinetic results and product analyses which offer insight into the role of acid–base reactions of cation radical/nucleophile adducts and points to the necessity of such considerations in the study of the addition reactions of cation radicals derived from EE substrates.[9]

Results and Discussion

Reaction of $Th^{\cdot+}$ with Water. The cyclic voltammetric behavior of Th at a platinum electrode in anhydrous acetonitrile is shown in Figure 1. The oxidative process observed at a potential of +1.25 V (O_1, curve A) is attributed to the oxidation of Th to $Th^{\cdot+}$ (eq 1).

$$Th \rightleftharpoons Th^{\cdot+} + e^- \quad (1)$$

$$Th^{\cdot+} \rightleftharpoons Th^{2+} + e^- \quad (2)$$

Upon scanning to more anodic potentials a second monoelectronic oxidation wave is observed with a peak at +1.65 V (O_2) corresponding to the formation of dication (Th^{2+}) from cation radical (eq 2). Scan reversal at this point shows no peak for the reduction of the dication formed at O_2; however, the stability of the cation radical in this medium is noted by the presence of the cathodic wave (R_1) for cation radical reduction. The absence of the wave corresponding to dication reduction may be taken as a measure of its reactivity in this solvent-supporting electrolyte system. Although residual water is present at very low concentrations (ca. 1–3 mM) in this rigorously dried solvent, a sufficient quantity is present to cause the rapid formation of the monoxide (ThO, eq 3)

$$Th^{2+} + H_2O \xrightarrow{\text{fast}} ThO + 2H^+ \quad (3)$$

from dication. The ThO species is characterized by its oxidative electrochemistry[10] (O_3 and O_4) which is evident in both voltammograms of Figure 1. As water is incrementally added to the solution, O_1, O_3, and O_4 increase in height at the expense of O_2 and R_1.[11] O_1 is enhanced due to the regenerative nature of the overall reaction (eq 4).[5,6]

$$2Th^{\cdot+} + H_2O \rightarrow ThO + Th + 2H^+ \quad (4)$$

By carrying out exhaustive electrolyses of wet acetonitrile solutions of Th at a potential of +1.40 V, one notes the passage of charge corresponding to 2 Faradays/mol of Th originally present (eq 5).

$$Th + H_2O \rightarrow ThO + 2H^+ + 2e^- \quad (5)$$

Following electrolysis, the anolyte shows the characteristic response of ThO (Figure 1, curve B).

Either of two possible mechanisms for the reaction of $Th^{\cdot+}$ with H_2O can account for the aforementioned observations. Scheme I, the disproportionation mechanism, has been argued by Murata and Shine[5,6] on the basis of kinetic results indicating an experimental rate law of the form[13]

$$-\frac{d[Th^{\cdot+}]}{dt} = k_{app}\frac{[Th^{\cdot+}]^2[H_2O]}{[Th]} \quad (6)$$

Scheme I

$$2Th^{\cdot+} \underset{\text{fast}}{\overset{K_d}{\rightleftharpoons}} Th^{2+} + Th \quad (7)$$

$$Th^{2+} + H_2O \xrightarrow{k_{rds}} ThO + 2H^+ \quad (8)$$

According to this scheme the oxidized form of Th which undergoes nucleophilic attack by H_2O is the *dication*. Parker and Eberson subsequently presented evidence which indicated that the *cation radical* reacts directly with the nucleophile.[14] Their observations support the half-regeneration mechanism[3,4] shown in Scheme II.

Scheme II

$$Th^{\cdot+} + H_2O \rightarrow Th(OH_2)^{\cdot+} \quad (9)$$

$$Th(OH_2)^{\cdot+} + Th^{\cdot+} \rightarrow Th + ThO + 2H^+ \quad (10a)$$

$$Th(OH_2)^{\cdot+} \xrightarrow[\text{electrode}]{\text{via}} ThO + 2H^+ + e^- \quad (10b)$$

Included here are two routes for the oxidation of the $Th(OH_2)^{\cdot+}$ intermediate. The first (eq 10a) represents the homogeneous pathway (half-regeneration mechanism) while the second (eq 10b) shows the oxidation of $Th(OH_2)^{\cdot+}$ as proceeding heterogeneously (ECE mechanism).[2]

Table I. Stopped-Flow Kinetic Results for the Hydrolysis of Thianthrene Cation Radical at 25.0 (± 0.1) °C

Series	$[H_2O]$, M	Source[a] of Th·$^+$	[Th], × 10^3 M	[ThO], × 10^3 M	Replicates	k_{obsd},[b] A^{-1} s^{-1}
1	0.050	E	0.61	0.00	9	0.427 (±0.023)[c]
2	0.056	S	0.00	0.00	5	0.365 (±0.007)
3	0.100	E	0.61	0.00	8	3.42 (±0.23)
4	0.150	E	0.60	0.00	7	7.53 (±0.33)
5	0.150	E	0.06	0.00	6	7.23 (±0.33)
6	0.200	E	1.50	0.00	7	25.3 (±1.5)
7	0.200	E	0.61	0.00	5	19.3 (±0.6)
8	0.200	E	0.06	0.00	10	17.9 (±1.5)
9	0.200	E	0.00	0.00	10	20.4 (±0.7)
10	0.200	S	0.00	0.00	10	26.4 (±2.8)
11	0.200	S	0.61	0.52	8	26.5 (±0.9)
12	0.333	S	0.00	0.00	6	105 (±9)
13	0.400	E	0.61	0.00	7	195 (±5)
14	0.500	E	3.00	0.00	5	397 (±13)
15	0.556	S	0.00	0.00	10	312 (±23)
16	1.00	E	0.61	0.00	8	3430 (±80)

[a] Source of Th·$^+$ either via electrolysis (E) of Th solution or from solution of Th·$^+$ ClO_4^- salt (S). Both Th·$^+$ and H_2O reactant solutions contained 0.10 M tetraethylammonium perchlorate to maintain constant ionic strength. Initial [Th·$^+$] ranged between 1×10^{-5} and 5×10^{-5} M. [b] k_{obsd} defined as the slope of a plot of $1/A_{546}$ vs. time. All data treated for at least 2 half-lives. Correlation coefficients were typically 0.9995, and in all cases exceeded 0.9990. [c] Parentheses contain one standard deviation.

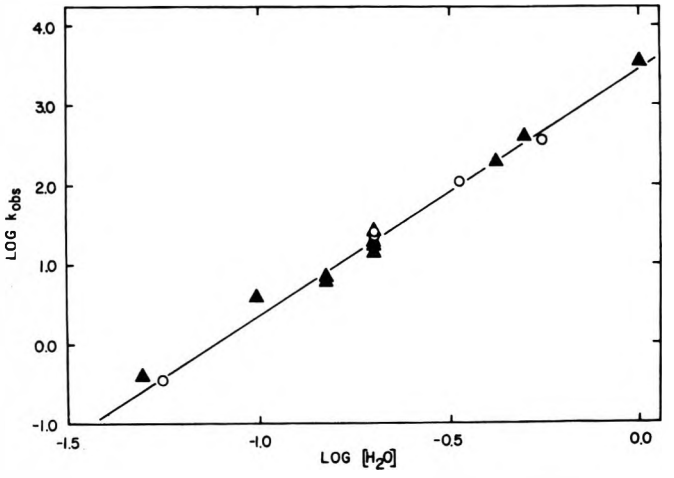


Figure 3. Dependence of second-order rate constant on water concentration for the reaction of Th·$^+$ with aqueous acetonitrile. k_{obsd} defined as slope of second-order kinetic plot (Figure 2). ▲, Th·$^+$ from electrogeneration; ○, Th·$^+$ from Th·$^+$·ClO_4^- salt. T = 25.0 (± 0.1) °C.

Scheme III outlines a half-regeneration pathway which affords a rate law of a form which accounts for the observed kinetics.[4,5]

Scheme III

$$\text{Th}\cdot^+ + H_2O \overset{K_1}{\rightleftharpoons} \text{Th}(OH_2)\cdot^+ \quad (11)$$

$$\text{Th}(OH_2)\cdot^+ + \text{Th}\cdot^+ \overset{K_2}{\rightleftharpoons} \text{Th} + \text{Th}(OH_2)^{2+} \quad (12)$$

$$\text{Th}(OH_2)^{2+} \xrightarrow{k_{rds}} \text{Th}(OH)^+ + H^+ \quad (13)$$

$$\text{Th}(OH)^+ \xrightarrow{\text{fast}} \text{ThO} + H^+ \quad (14)$$

As depicted in Figure 2, stopped-flow experiments gave data indicative of a clean second-order decay of Th·$^+$ upon reaction with aqueous acetonitrile. However, description of the hydrolysis of Th·$^+$ in terms of Scheme III was soon abandoned for reasons which become obvious upon close examination of the data presented in Table I. As reflected in series **6–10**, there can be no statistically significant dependence of reaction rate on the concentration of Th.[15] Series **11** provides evidence that the same is true for ThO, the second product of the reaction.

The most striking feature of the data presented in this table is, however, the unusual dependence of Th·$^+$ consumption on the concentration of water. A plot of log k_{obsd} vs. log $[H_2O]$ is given in Figure 3. The relationship is linear and gives rise to a slope of 2.99 (± 0.10) indicating a third-order dependence of reaction rate on water concentration. In concert, these observations result in an experimental rate law (eq 15)

$$-\frac{d[\text{Th}\cdot^+]}{dt} = k_{app}[\text{Th}\cdot^+]^2[H_2O]^3 \quad (15)$$

which is second order in Th·$^+$, third order in H_2O, and independent of precursor and ThO concentrations.

Since a single molecule of water ultimately undergoes addition to one of the cation radicals consumed in the reaction, it must be concluded that the others perform some transient function to promote the progress of the reaction. The following pathway is proposed:

Scheme IV

$$\text{Th}\cdot^+ + H_2O \overset{K_1}{\rightleftharpoons} \text{Th}(OH_2)\cdot^+ \quad (16)$$

$$\text{Th}(OH_2)\cdot^+ + H_2O \overset{K_2}{\rightleftharpoons} \text{Th}(OH)\cdot + H_3O^+ \quad (17)$$

$$\text{Th}(OH_2)\cdot^+ + \text{Th}(OH)\cdot \xrightarrow{k} \text{Th} + H_2O + \text{Th}(OH)^+ \quad (18)$$

$$\text{Th}(OH)^+ + H_2O \xrightarrow{\text{fast}} \text{ThO} + H_3O^+ \quad (19)$$

The thianthrene cation radical is rapidly and reversibly complexed by water to form the Th$(OH_2)\cdot^+$ adduct. This adduction equilibrium (eq 16) very strongly favors the complex, which in turn is involved in yet another rapid equilibrium in which adduct is deprotonated to form the Th(OH)· radical. The rate-determining step, then, consists of electron transfer from Th(OH)· to cation radical–nucleophile adduct (eq 18). The products of this rate-determining redox reaction are precursor, water, and protonated oxide which in the presence of excess base (H_2O) is rapidly deprotonated (eq 19).[16]

On a stoichiometric basis two cation radicals are consumed

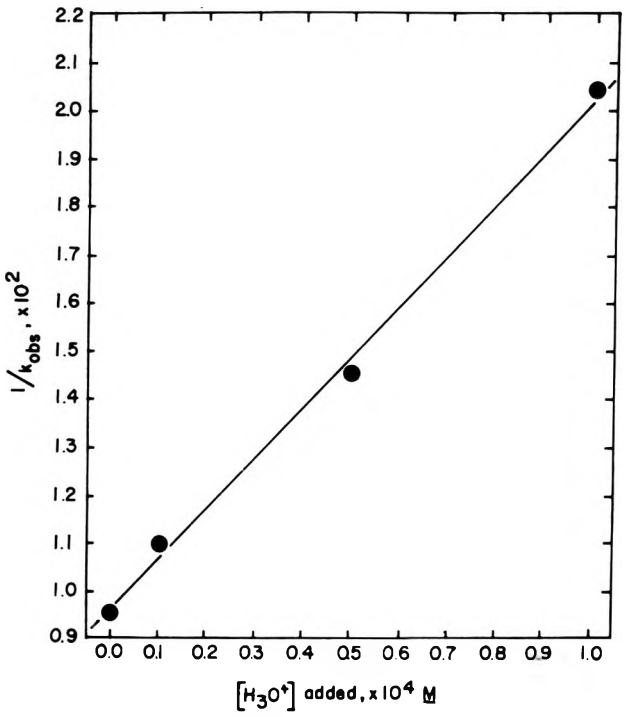


Figure 4. Dependence of second-order rate constant on added acid concentration. Added acid was $HClO_4$. $Th^{\cdot+}$ from $Th^{\cdot+}ClO_4^-$ salt and $[H_2O]$ = 0.33 M in all cases. T = 25.0 (± 0.1) °C.

for each Th(OH)· which is involved in a rate-determining encounter, i.e., one from which the Th(OH)· species was formed and a second from which the oxidizing agent, $Th(OH_2)\cdot^+$, was formed. One may write

$$-\frac{d[Th\cdot^+]}{dt} = -2\frac{d[Th(OH)\cdot]}{dt} \qquad (20)$$

By virtue of its involvement in the rate-determining step, eq 18, the rate of disappearance of Th(OH)· may be expressed as

$$-\frac{d[Th(OH)\cdot]}{dt} = k[Th(OH)\cdot][Th(OH_2)\cdot^+] \qquad (21)$$

The equilibrium expressions for the processes preceding the rate-determining step are given by

$$K_1 = \frac{[Th(OH_2)\cdot^+]}{[Th\cdot^+][H_2O]} \qquad (22)$$

$$K_2 = \frac{[Th(OH)\cdot][H_3O^+]}{[Th(OH_2)\cdot^+][H_2O]} \qquad (23)$$

Appropriate rearrangement of eq 22 and 23 and substitution with eq 20 into eq 21 results in a form of the rate law for Scheme IV which is compatible with the experimental results.

$$-\frac{d[Th\cdot^+]}{dt} = \frac{2kK_1^2K_2[Th\cdot^+]^2[H_2O]^3}{[H_3O^+]} \qquad (24)$$

Thus, for the 131 experiments reported in Table I, $kK_1^2K_2/[H_3O^+]$ evaluates to 4.64 (± 1.04) × 10^7 M^{-4} s^{-1}.

If the hydrolysis of $Th^{\cdot+}$ is correctly accounted for by Scheme IV, then a depression of reaction rate should be noted upon the addition of hydronium ion to the reaction mixture. Such experiments were conducted and the results are shown in Figure 4. The inverse first-order dependence of reaction rate on added H_3O^+ is clearly evident from these data and lends further credence to the proposed mechanism.

Reaction of $Th^{\cdot+}$ with Pyridine. The cyclic voltammetric behavior of Th in the presence of a twofold excess of pyridine

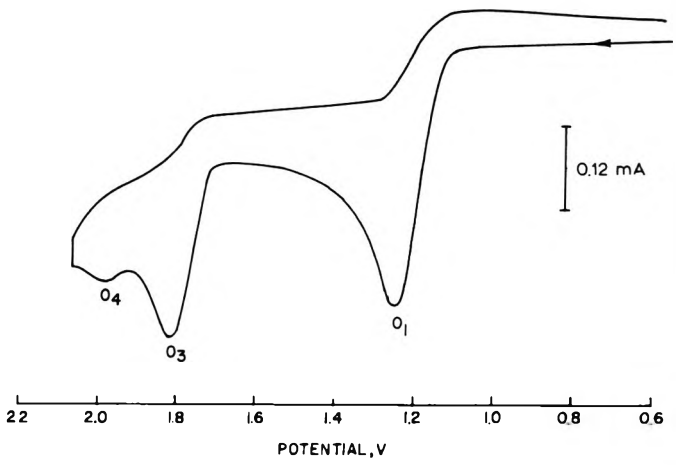


Figure 5. Anodic voltammetry of Th (1.0 mM) in the presence of excess Py (3.0 mM) and TEAP (0.10 M) in acetonitrile. Scan rate 150 mV/s.

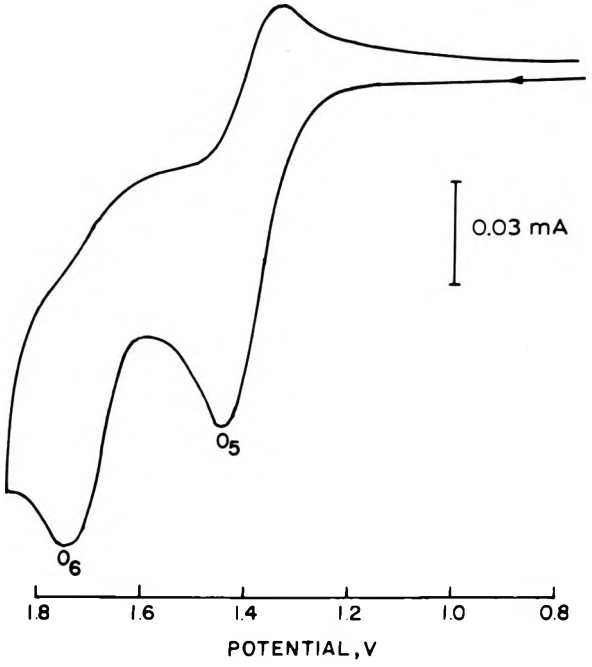


Figure 6. Anodic voltammetry of 1.0 mM $Th(Py)^+ClO_4^-$ and 0.10 M TEAP in acetonitrile. Scan rate 110 mV/s.

at moderate scan rate is shown in Figure 5. A catalytic current[12] indicative of Th regeneration as a consequence of $Th^{\cdot+}$ reaction is noted at O_1 where Th is oxidized to $Th^{\cdot+}$ and the characteristic voltammetry of the monoxide is also observed (O_3 and O_4). Seemingly, the product of the anodic oxidation of Th where Py is present is the oxide, yet Shine et al. have reported the reaction of $Th^{\cdot+}$ with Py in both nitromethane and neat Py to yield the *N*-(2-thianthrenyl)pyridinium ion $[Th(Py)^+]$.[8] Since the assignment of voltammetric peaks to particular intermediates or products is often tenuous, authentic $Th(Py)^+$ was prepared[8] and isolated as the perchlorate salt for use in cyclic voltammetric characterization of this species. The voltammetry of acetonitrile solutions of this ion is shown in Figure 6. One observes a morphology similar to that of Th; however, the two anodic peaks (O_5 and O_6) appear at decidedly different potentials (+1.45 and +1.74 V) than the corresponding peaks (O_1 and O_2) of Th. Reexamination of Figure 5 shows the $Th(Py)^+$ ion to be absent in this scan and it is apparent that this species is not detected under these conditions. Analysis of the products isolated from the reaction

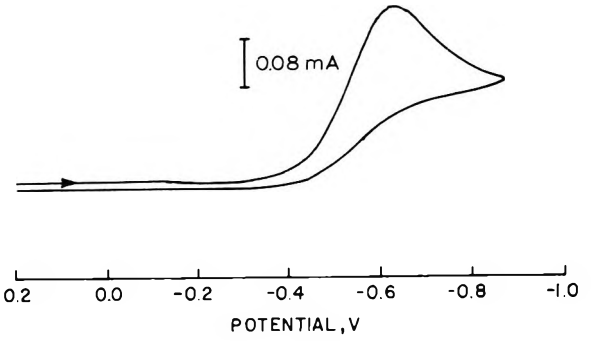


Figure 7. Cathodic voltammetry of $PyHClO_4$ (1.0 mM) and TEAP (0.10 M) in acetonitrile. Scan rate 120 mV/s.

of the perchlorate salt of $Th^{\cdot+}$ with Py (0.50 M) carried out in acetonitrile also revealed the lack of a detectable quantity of the $Th(Py)^+$ ion (as perchlorate). ThO and Th, in addition to pyridinium perchlorate ($PyHClO_4$), were the products isolated.

This ambiguity between the reaction conducted in acetonitrile and that carried out in neat pyridine or nitromethane was probed further using controlled potential coulometric procedures to elucidate the stoichiometry of the acetonitrile reaction. Exhaustive electrolysis (+1.40 V) of acetonitrile solutions containing both Th and Py revealed the release of 1.99 (± 0.01) electrons per molecule of Th present in the anolyte. The anodic voltammetry of this solution following electrolysis showed only the presence of the ThO waves while excursions to cathodic potentials showed the presence of a wave (Figure 7) for the reduction of pyridinium ion (PyH^+). It was found that this cathodic wave could be used to quantitate the PyH^+ formed during the electrolysis conducted at +1.40 V by carrying out a subsequent, reductive electrolysis of the anolyte from the aforementioned electrolysis at a potential of −0.80 V.[18] Such procedures were performed and after electrolysis at +1.40 V, 2.02 (± 0.01) mol of PyH^+ was found to be present per mole of Th originally taken. In toto, these observations lead to the formulation of the stoichiometry given by eq 25 for the electrolysis of Th in acetonitrile solution containing Py.

$$Th + 2Py + H_2O \rightarrow ThO + 2PyH^+ + 2e^- \qquad (25)$$

These results suggested that residual water (ca. 1–3 mM) present in the "anhydrous" acetonitrile employed for these studies contributed to the absence of the $Th(Py)^+$ ion. A series of experiments was then undertaken in which trifluoroacetic anhydride (TFAn) was added to the solvent to scavenge the residual water.[20] However, reaction of the perchlorate salt of $Th^{\cdot+}$ with 0.50 M pyridine in acetonitrile containing 4% TFAn (v/v) again failed to afford a detectable quantity of $Th(Py)^+$ ion. Rather, workup of this reaction mixture indicated the stoichiometry of eq 26

$$2Th^{\cdot+}\ ClO_4^- + H_2O + 2Py \rightarrow Th + ThO + 2PyHClO_4 \qquad (26)$$

where the respective yields of Th, ThO, and $PyHClO_4$ were 76, 79, and 74%.

It had been assumed that residual water in the acetonitrile would be irreversibly *reacted* upon addition of TFAn. However, subsequent gas chromatographic analysis of the mixed solvent showed the presence of water. Furthermore, its concentration in the TFAn/acetonitrile was at essentially the same level noted in acetonitrile free of TFAn and leads to the conclusion that the water-scavenging properties of the TFAn are attributable to the *selective solvation* (i.e., complexation) of water by the TFAn in this medium.[22]

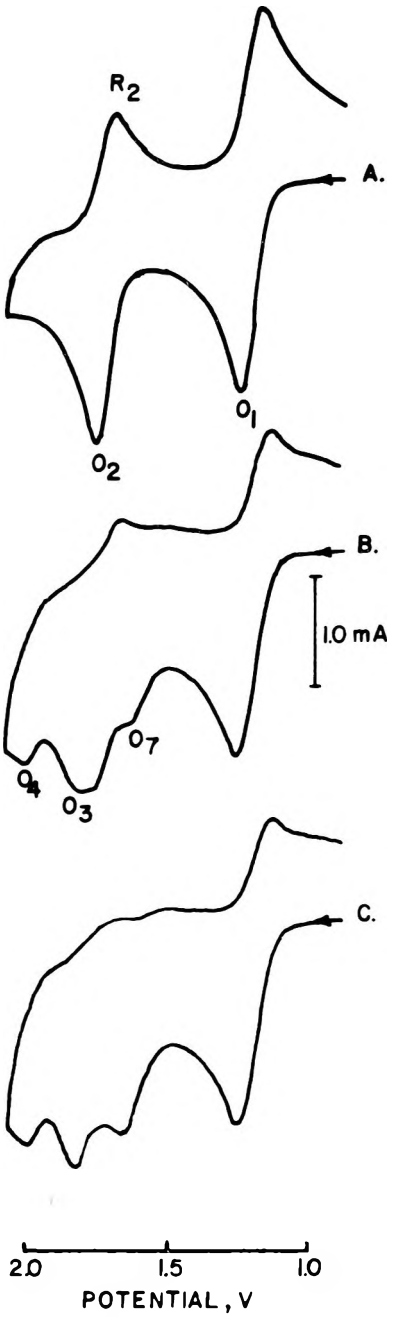


Figure 8. Fast cyclic voltammetry of 1.0 mM Th and 0.20 M TEAP in 4% TFAn/acetonitrile: (A) no Py added; (B) 0.93 mM Py added; (C) 1.55 mM Py added. Scan rate 35 V/s.

A series of fast (high scan rate) cyclic voltammetric experiments was conducted in the TFAn/acetonitrile mixture in order to elucidate the role of Py in this reaction. The voltammograms shown in Figure 8 summarize the results of these investigations. In the absence of Py, the voltammetric behavior of Th in this medium is depicted in curve A of this figure. The presence of the cathodic wave (R_2) for the reduction of the relatively stable dication formed during the oxidative scan (O_2) is indicative of the ability of the TFAn to effectively reduce the activity of water in the acetonitrile.[20] In the absence of TFAn, R_2 is not observed at these scan rates.

The effect of added Py is shown in Figure 8, curves B and C. Firstly, it should be noted that there is no enhancement of the anodic wave due to the oxidation of Th to $Th^{\cdot+}$ (O_1) upon addition of Py. This indicates that *no* Th is regenerated during the time scale of the experiment. Secondly, a new anodic peak appears at O_7 and grows with incremental addition of Py as

Table II. Stopped-Flow Kinetic Results for the Reaction of Thianthrene Cation Radical with Pyridine in 4% (v/v) TFAn-Acetonitrile at 25.0 (± 0.1) °C

[Th], × 10^3 M	[Th·$^+$]$_0$, × 10^5 M	[Py], × 10^3 M	Replicates	k_{obsd},[a] A^{-1} s^{-1}
0.0	2.95	0.574	10	25.0 (±0.6)[b]
0.0	3.64	3.44	9	178 (±4)
0.0	6.09	3.76	5	178 (±8)
0.0	4.64	5.74	10	282 (±13)
0.419	3.41	5.74	8	302 (±8)

[a] k_{obsc} defined as slope of $1/A_{546}$ vs. time. All data treated for 2 half-lives. Correlation coefficients were typically 0.9990 and in all cases exceeded 0.9980. [b] Parentheses contain one standard deviation.

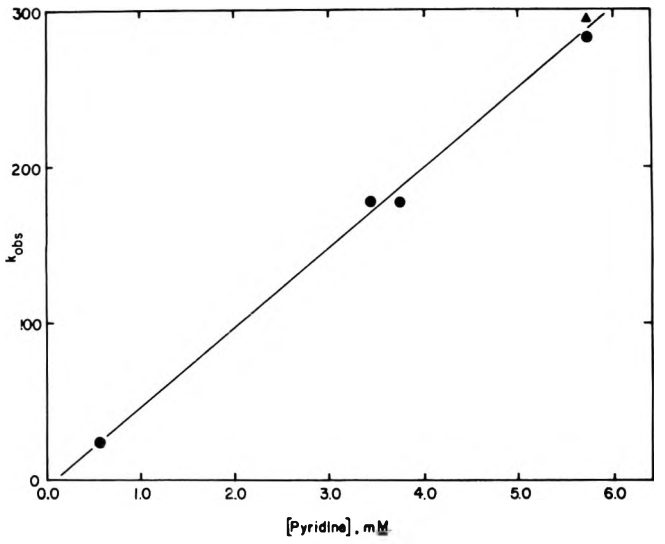
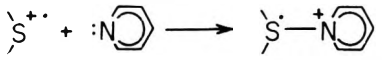


Figure 9. Dependence of observed second-order rate constant for the reaction of Th·$^+$ with Py on concentration of Py. k_{obsd} defined as slope of second-order kinetic plot. In all cases, solvent was 4% TFAn/acetonitrile. Source of Th·$^+$ was Th·$^+$$ClO_4^-$ salt. ●, [Th] = 0.0 mM; ▲, [Th] = 0.42 mM.

do the ThO waves (O_3 and O_4). These enhancements proceed at the expense of the height of the waves corresponding to the oxidation of Th·$^+$ to Th^{2+} (O_2) and its reverse process (R_2). These results are interpreted as follows. The species whose oxidation proceeds at O_7 is the *sulfur* bonded adduct resulting from reaction of Th·$^+$ with Py:



Following *heterogeneous* oxidation (O_7), this species is *rapidly* converted to ThO observed at O_3 and O_4. It is important to note the absence of the peaks attributable to the Th(Py)$^+$ (*carbon* bonded) species (O_5 and O_6, Figure 6). One must conclude that formation of Th(Py)$^+$ is overwhelmingly less likely than the observed generation of ThO, even in this medium where the reactivity of water has been minimized.

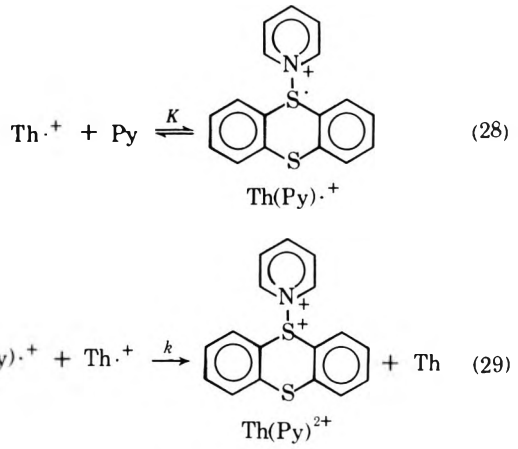
Stopped-flow determination of the Th·$^+$/Py reaction rate in the absence of TFAn clearly indicated second-order dependence on Th·$^+$ concentration. However, rate parameters arising from analysis of these experiments were extremely irreproducible. Reproducibility in these measurements was attained when reactant solutions were prepared in the TFAn/acetonitrile mixed solvent. These data, together with the Py dependence shown in Figure 9, indicate that the experimental rate law takes the form

$$-\frac{d[Th\cdot^+]}{dt} = k_{app}[Th\cdot^+]^2[Py] \qquad (27)$$

The kinetic parameters for the Th·$^+$/Py system, summarized in Table II, attest to the validity of this rate law over a range of Th, Th·$^+$, and Py concentrations.

These stopped-flow results in combination with the observations obtained from the fast cyclic voltammetry of this system lead to the proposition of Scheme V as the mechanism operative in this reaction.

Scheme V



$$Th(Py)^{2+} + H_2O \xrightarrow{fast} Th(OH)^+ + PyH^+ \qquad (30)$$

$$Th(OH)^+ + Py \xrightarrow{fast} ThO + PyH^+ \qquad (31)$$

The rate-determining step (eq 29) involves electron transfer from a pyridine/cation radical sulfur bonded adduct to a nonadducted cation radical. The product of this step [the N–S dication, Th(Py)$^{2+}$] is extremely reactive (more so toward water than is Th^{2+}), undergoing rapid hydrolysis to the protonated oxide [Th(OH)$^+$] and PyH$^+$. Subsequent fast deprotonation by a second Py molecule yields the ultimate addition product, ThO.

In conclusion, the results detailed here suggest the general applicability of a half-regeneration scheme in describing the reactions of thianthrene cation radical with pyridine *and* water in acetonitrile. As carried out in acetonitrile solutions, kinetic results and product analyses support the hypothesis that in both reactions attack of nucleophile occurs at a sulfur site on this cation radical. The inability of the N–S bonded adduct to achieve charge relief via proton loss following further oxidation ultimately leads to the rapid hydrolysis of the oxidized form to yield the monoxide. In both reactions studied, complications of acid–base reactions between cation radical/nucleophile adducts (acids) and nucleophiles (bases) are noted within the framework of the proposed mechanism.

Experimental Section

Materials. The purification procedures for acetonitrile (Burdick and Jackson Laboratories, UV grade) and tetraethylammonium perchlorate (TEAP, Eastman Organic Chemicals) have been described previously.[1d] TEAP was employed as supporting electrolyte in electrochemical measurements and included in all solutions used in kinetic determinations to maintain a constant ionic strength of 0.10

M. Reagent grade pyridine (J. T. Baker) was distilled at atmospheric pressure from KOH (bp 114–114.5 °C). The concentration of pyridine in acetonitrile solutions was determined by potentiometric titration with perchloric acid in glacial acetic acid.[23] Trifluoroacetic anhydride (TFAn, Fluka A. G., purum grade) was used as received. All solutions used in voltammetry, coulometry, and stopped-flow kinetic measurements were freshly prepared in an inert atmosphere and degassed with prepurified nitrogen.

Pyridinium perchlorate ($PyHClO_4$) was prepared by the combination of stoichiometric amounts of perchloric acid and pyridine in glacial acetic acid,[24] mp 287–289 °C (lit. 287 °C). Thianthrene (Th, Aldrich Chemical Co.) was twice recrystallized from absolute EtOH, mp 156–156.5 °C (lit.[17] 155–157 °C).

Thianthrene 5-oxide (ThO) was prepared according to Fries and Vogt,[25] mp 142.5–143.5 °C (lit. 143 °C). Synthesis of thianthrene cation radical perchlorate ($Th^{\cdot+}ClO_4^-$) was carried out according to Murata and Shine.[5,6] *N*-(2-Thianthrenyl)pyridinium perchlorate [$Th(Py)^+ClO_4^-$] was prepared by the gradual addition of $Th^{\cdot+}ClO_4^-$ to pyridine with stirring,[8] affording golden yellow crystals, mp 204–206 °C (lit. 206–207 °C). All other chemicals were reagent grade or equivalent.

Reaction of $Th^{\cdot+}ClO_4^-$ with Pyridine in 4% (v/v) TFAn/Acetonitrile. Reaction and product analyses were performed in a manner analogous to that employing neat pyridine.[8] To a 100-ml volume of 0.50 M pyridine in 4% (v/v) TFAn/acetonitrile was added 0.625 g (1.98 mmol) of $Th^{\cdot+}ClO_4^-$. The solvent was stripped and ca. 25 ml of nitromethane added. The solids and nitromethane solution were repeatedly extracted with cyclohexane (solids soluabilized during first extraction) until TLC of the extract showed absence of Th and ThO. The combined cyclohexane extracts were concentrated and chromatographed (silica gel/cyclohexane and 95:5 benzene/EtOH). Removal of solvent from the respective fractions yielded 0.163 g of Th (0.75 mmol, 76%) and 0.182 g of ThO (0.78 mmol, 79%). The nitromethane fraction was found to contain 0.262 *g* (1.46 mmol, 74%) of pyridinium perchlorate.

Apparatus. Electrochemical measurements were carried out using a conventional potentiostat[26] and a two-compartment cell.[1c] All electrode potentials are referred to the aqueous saturated calomel electrode.

A dedicated minicomputer (Data General Corp. NOVA 1200) was interfaced to both the potentiostat and the Durrum Model D-110B stopped-flow spectrophotometer for experimental control as well as data acquisition and subsequent reduction.[1d] Modification of the stopped-flow apparatus to accommodate electrolytic generation of reactants is described elsewhere.[1d] Kinetic determinations were carried out at 25.0 (± 0.1) °C. The molar absorptivity of $Th^{\cdot+}$ (acetonitrile) was taken to be $8.5 \times 10^3\ M^{-1}\ cm^{-1}$ at the analytical wavelength (546 nm, λ_{max}) employed for kinetic measurements.[5,6]

Registry No.—$Th^{\cdot+}$, 34507-27-2; Py, 110-86-1.

References and Notes

(1) (a) Part 4: J. F. Evans and H. N. Blount, *J. Phys. Chem.*, **80**, 1011 (1976); (b) H. N. Blount, *J. Electroanal. Chem.*, **42**, 271 (1973); (c) D. T. Shang and H. N. Blount, *ibid.*, **54**, 305 (1974); (d) J. F. Evans and H. N. Blount, *J. Org. Chem.*, **41**, 516 (1976).

(2) See ref 1b for a synopsis of mechanisms. The ECE and ECC mechanisms as they apply to electrochemical studies are distinguished on the basis of whether the oxidation of the intermediate (formed upon homogeneous reaction of nucleophile with electrogenerated cation radical) is achieved predominantly by means of *a heterogeneous* (via electrode, ECE) or a *homogeneous* (via a second cation radical, ECC) redox step. In stopped-flow experiments, the absence of the electrode necessarily denies the applicability of the ECE scheme and the half-regeneration mechanism becomes synonomous with its electrochemical counterpart (ECC).

(3) R. E. Sioda, *J. Phys. Chem.*, **72**, 2322 (1968).

(4) H. N. Blount and T. Kuwana, *J. Electroanal. Chem.*, **27**, 464 (1970).

(5) H. J. Shine and Y. Murata, *J. Am. Chem. Soc.*, **91**, 1872 (1969).

(6) Y. Murata and H. J. Shine, *J. Org. Chem.*, **34**, 3368 (1969).

(7) U. Svanholm, O. Hammerich, and V. D. Parker, *J. Am. Chem. Soc.*, **97**, 101 (1975).

(8) H. J. Shine, J. J. Silver, R. J. Bussey, and T. Okuyama, *J. Org. Chem.*, **37**, 2691 (1972).

(9) An EE substrate is defined as a species capable of undergoing two distinct monoelectronic oxidation (or reduction) steps at successively more anodic (or cathodic) potentials. E.g., for the oxidative EE system:

$$A \rightarrow A^{\cdot+} + e^- \qquad (E_1)$$

$$A^{\cdot+} \rightarrow A^{2+} + e^- \qquad (E_2)$$

where $E_2 > E_1$.

(10) The processes giving rise to the oxidative currents at O_3 and O_4 are beyond the scope of this paper. Although they are definitive for ThO in this medium, these are complex processes, e.g., O_3 is a 1.24 (± 0.01) electron process per ThO molecule.

(11) O_2 is also noted to shift to more cathodic potentials upon incremental addition of water. This phenomenon is indicative of irreversible homogeneous chemical reaction following electron transfer.[12]

(12) R. S. Nicholson and I. Shain, *Anal. Chem.*, **36**, 706 (1964).

(13) k_{app} necessarily incorporates the equilibrium constant for disproportionation which may be determined from the separation of O_1 and O_2 under conditions where both oxidation steps are chemically reversible (i.e., Th^{2+} is stable). See ref 20 and 21.

(14) V. D. Parker and L. Eberson, *J. Am. Chem. Soc.*, **92**, 7488 (1970).

(15) This observation conflicts with that of Murata and Shine.[5,6] For the reaction conditions reported ($1–5 \times 10^{-5}$ M initial concentrations of $Th^{\cdot+}$), no inverse dependence of rate on Th concentration has been observed in these laboratories.

(16) The process embodied in eq 19 most probably possesses some degree of reversibility. The protonation of the oxide in strong acid and subsequent $Th^{\cdot+}$ formation have been noted in these and other[17] laboratories.

(17) H. J. Shine and L. Piette, *J. Am. Chem. Soc.*, **84**, 4798 (1962); H. J. Shine and C. F. Dais, *J. Org. Chem.*, **30**, 2145 (1965).

(18) Authentic $PyHClO_4$ was found to require 0.97 (± 0.01) Faraday/mol for complete reduction at −0.80 V; ostensibly the product is a bipyridyl.[19]

(19) M. S. Spritzer, J. M. Costa, and P. J. Elving, *Anal. Chem.*, **37**, 211 (1965).

(20) O. Hammerich and V. D. Parker, *Electrochim. Acta*, **18**, 537 (1973).

(21) K. W. Fung, J. Q. Chambers, and G. Mamantov, *J. Electroanal. Chem.*, **47**, 81 (1973).

(22) The nature of the interaction between water and TFAn which lowers the activity of water in acetonitrile is currently under investigation in these laboratories.

(23) J. S. Fritz, "Acid-Base Titrations In Non-Aqueous Solvents", Allyn and Bacon, Boston, Mass., 1973.

(24) A. I. Popov and R. T. Pflaum, *J. Am. Chem. Soc.*, **79**, 570 (1957).

(25) K. Fries and W. Vogt, *Justus Liebigs Ann. Chem.*, **381**, 312 (1911).

(26) A. A. Pilla, *J. Electrochem. Soc.*, **118**, 702 (1971).

Reactions of Cation Radicals of EE Systems. 6. The Pyridination of 10-Phenylphenothiazine: Heteroatom Effects on Rates and Mechanisms of Pyridinations[1]

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The kinetics of the reaction of 10-phenylphenothiazine (PH) cation radical ($PH^{\cdot+}$) with pyridine (Py) have been examined. Electrochemical characterization of the $PH/PH^{\cdot+}$ couple in neat Py showed $PH^{\cdot+}$ to be of sufficiently low reactivity to permit kinetic investigation in this medium. The results of these kinetic determinations, together with those obtained in acetonitrile solutions of Py, indicate the applicability of a half-regeneration mechanism. The reaction gives rise to only the pyridinated product in neat Py while both hydrolysis (sulfoxide) and pyridination products are observed in acetonitrile solutions. Formation of the sulfoxide is accounted for by the hydrolysis of an N–S bonded dicationic intermediate in the proposed pyridination mechanism. The product distributions observed in the pyridinations of the cation radicals derived from PH and other EE substrates reflect the relative reactivities of the corresponding dicharged intermediates.

A half-regeneration mechanism[2] has been shown to be tenable for the reaction of pyridine with thianthrene cation radical ($Th^{\cdot+}$) in acetonitrile.[1a] Although this reaction afforded thianthrene 5-oxide rather than the *N*-(2-thianthrenyl)pyridinium ion formed in neat pyridine,[3] the rate of radical ion consumption was nonetheless first order in pyridine concentration.[1a] It was concluded that the N–S bond in the oxidized form of the pyridine adduct of thianthrene cation radical was hydrolyzed by residual water present in the acetonitrile.[1a] The mechanism by which the pyridinated product is formed in neat pyridine was not elucidated owing to the high reactivity of the cation radical in this medium.[3]

Reactions of phenothiazine cation radical with neat pyridine have been shown to afford product types and distributions similar to those noted in the case of thianthrene.[3] Since the presence of the nitrogen heteroatom diminishes the reactivity of the sulfur site in the cation radical, it was envisioned that the pyridination of phenothiazine would proceed more slowly, thereby permitting convenient mechanistic investigation. Moreover, this examination would allow the comparison of mechanisms by which carbon centered,[4,5] sulfur centered,[1a] and mixed nitrogen–sulfur centered cation radicals of EE systems react with pyridine.

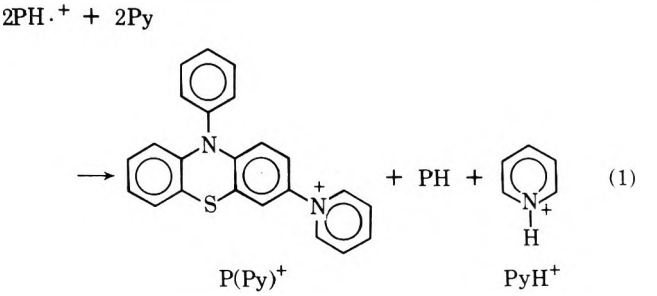
The chemistry of the phenothiazine cation radical is, however, complicated by the ease with which it may be deprotonated.[6] The free radical resulting from this deprotonation dimerizes and undergoes further oxidation.[3,7-9] Such a reaction sequence represents a pathway for the consumption of cation radical which is parallel to and competes with the nucleophilic addition/substitution reactions which are of primary interest in this study. To circumvent these complications so that this present investigation might focus on the nucleophile/cation radical reaction, the *N*-phenyl substituted phenothiazine (PH) was chosen as a representative dibenzenoid EE system containing both nitrogen and sulfur heteroatoms.

This paper reports the electrochemical and spectroscopic characterization of the reaction dynamics of 10-phenylphenothiazine cation radical ($PH^{\cdot+}$) in both neat pyridine and pyridine/acetonitrile solutions. Together with product characterizations, these results provide the basis for a general mechanism which accounts for the kinetics and product distributions observed for the two sulfur-containing EE systems, thianthrene[1a,3] and 10-phenylphenothiazine, in reactions with Py.

Results and Discussion

The anodic voltammetric behavior of PH at platinum in acetonitrile under conditions of slow potential scan (0.10 V s^{-1}) is shown in Figure 1A. The wave at O_1 (+0.68 V) corresponds to the oxidation of PH to $PH^{\cdot+}$ and the wave at O_2 (+1.37 V) results from further oxidation of $PH^{\cdot+}$ to the dication, PH^{2+}. The dication is not sufficiently stable in this medium to be detected upon scan reversal at this rate of potential sweep.[10] At higher scan rate (20 V s^{-1}), the reduction of the dication in the same solvent-supporting electrolyte system is readily observed (R_2, Figure 1B).

Stoichiometry of the $PH^{\cdot+}$/Py Reaction. The perchlorate salt of $PH^{\cdot+}$, prepared after the manner of Shine,[3] was reacted in neat pyridine and afforded stoichiometric quantities of *N*-[3-(10-phenylphenothiazinyl)]pyridinium perchlorate,[12] phenothiazine, and pyridinium perchlorate (eq 1). These reaction products are exactly analogous to those observed for the reactions of the perchlorate salts of the cation radicals of both thianthrene and unsubstituted phenothiazine in neat pyridine.[3]



(1)

The electrooxidation (+0.80 V) of PH in acetonitrile solutions of pyridine show the release of two Faradays of charge per mole of PH consumed and gives rise to the formation of both $P(Py)^+$ and 10-phenylphenothiazine 5-oxide [PH(O)] in addition to PH and PyH^+. The formation of PH(O) in this medium (eq 2)

$$2PH^{\cdot+} + 2Py + H_2O \rightarrow PH(O) + PH + 2PyH^+ \quad (2)$$

is analogous to the formation of thianthrene 5-oxide from the corresponding cation radical under similar reaction conditions.[1a]

The voltammetry of $P(Py)^+$, isolated as the perchlorate salt from reactions in both neat Py and acetonitrile solutions of

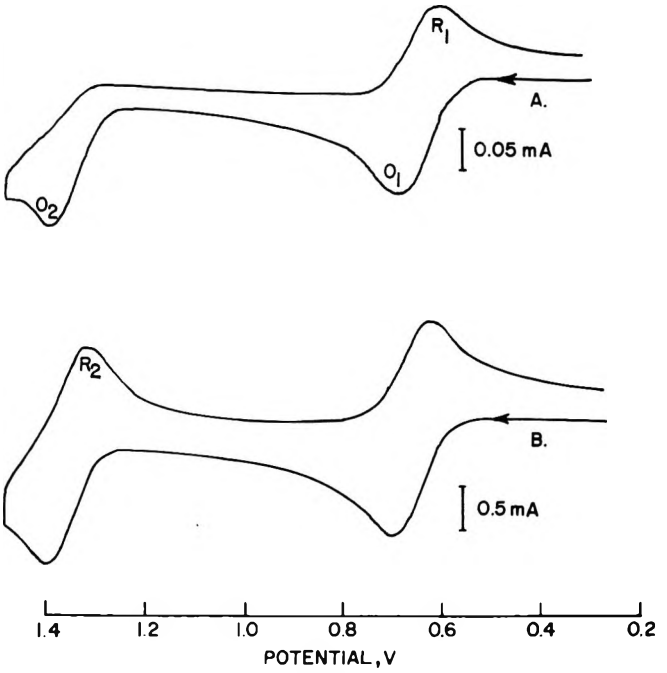


Figure 1. Cyclic voltammetric behavior of PH at a platinum electrode (0.36 cm^2) in acetonitrile containing TEAP. (A) [PH] = 1.0 mM, [TEAP] = 0.10 M, sweep rate 0.10 V s^{-1}; (B) [PH] = 1.1 mM, [TEAP] = 0.20 M, sweep rate 20 V s^{-1}.

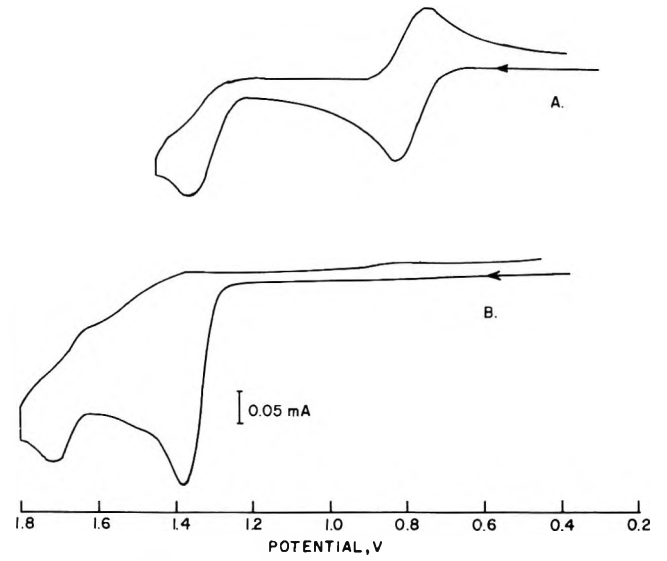


Figure 2. Cyclic voltammetric behavior of 1.0 mM (A) $P(Py)^+$ and (B) PH(O) at a platinum electrode (0.3 cm^2) in acetonitrile containing 0.10 M TEAP, sweep rate 0.10 V s^{-1}.

Py, is shown in Figure 2A. The monoelectronic oxidation wave at +0.81 V corresponds to the reversible formation of a dication radical (eq 3).

$$P(Py)^+ \rightleftharpoons P(Py)\cdot^{2+} + e^- \qquad (3)$$

As expected, the oxidation potential of the pyridinium substituted 10-phenylphenothiazine is observed to be anodic of that observed for PH.[13]

The voltammetry of PH(O), isolated from the reaction in acetonitrile, is shown in Figure 2B. This electrochemical behavior is identical with that observed for authentically prepared PH(O).[15] From the voltammetry shown in Figure 2, it can be seen that the formation of $P(Py)^+$ could be monitored electrochemically during the reaction of $PH\cdot^+$ with Py. This was not the case for PH(O) since its oxidation potential occurs

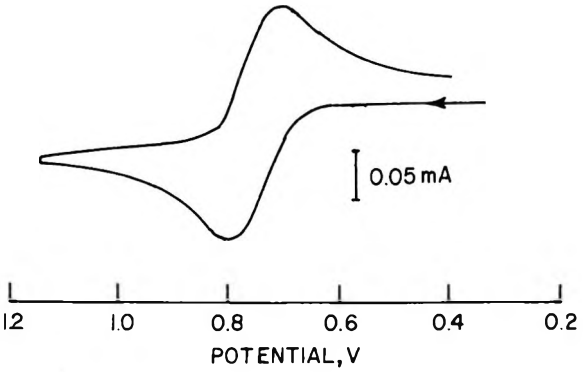


Figure 3. Cyclic voltammetric behavior of 1.0 mM PH at a platinum electrode (0.36 cm^2) in neat Py containing 0.10 M TEAP, sweep rate 0.10 V s^{-1}.

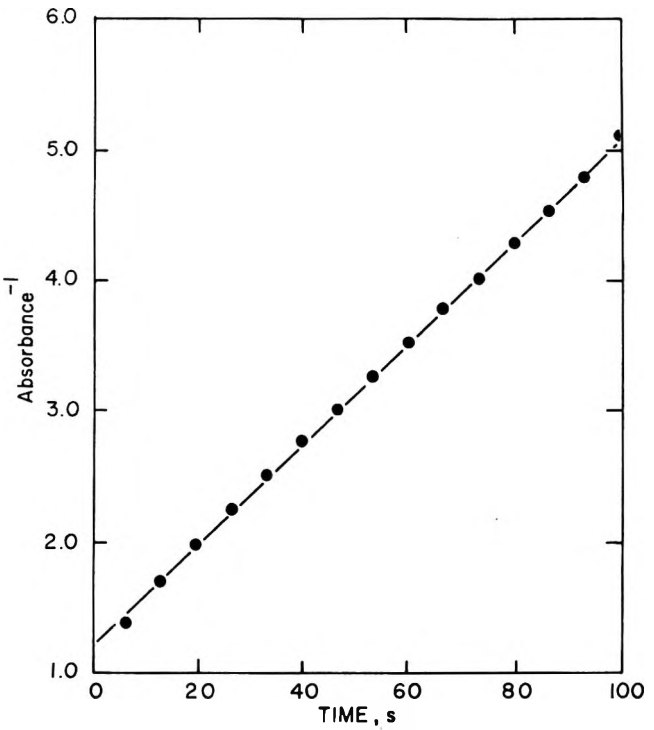


Figure 4. Second-order kinetic plot for reaction of $PH\cdot^+$ in neat Py. $[PH\cdot^+]_0 = 1.02 \times 10^{-4}$ M, $[PH]_0 = 5.0 \times 10^{-3}$ M, slope = 3.90 (± 0.03) $\times 10^{-2}$ A^{-1} s^{-1}, coefficient of correlation = 0.9997.

more anodically than that of Py. Isolation of PH(O) from the acetonitrile reaction mixture showed it and $P(Py)^+$ to be found in approximately a 1:3 ratio.

The Reaction in Neat Pyridine. The low reactivity of $PH\cdot^+$ toward Py is indicated by the voltammetry of the $PH/PH\cdot^+$ couple *in neat pyridine* shown in Figure 3. In this medium, the disappearance of $PH\cdot^+$ proceeds with a seond-order dependence on cation radical concentration (Figure 4). The apparent pseudo-second-order rate constant, k_{app}, for this process was found to be inversely dependent on precursor (PH) concentration in the manner shown in Figure 5. These data are of the form

$$1/k_{app} = C_1[PH] + C_2 \qquad (4)$$

and afford linear regression values of 4.38 (±0.03) $\times 10^{-1}$ s and 1.37 (± 0.27) $\times 10^{-3}$ M s for C_1 and C_2 (eq 4), respectively. The kinetics of this reaction are then appropriately described by

$$-\frac{d[PH\cdot^+]}{dt} = \left(\frac{2.28}{[PH] + 3.13 \times 10^{-3}}\right)[PH\cdot^+]^2 \qquad (5)$$

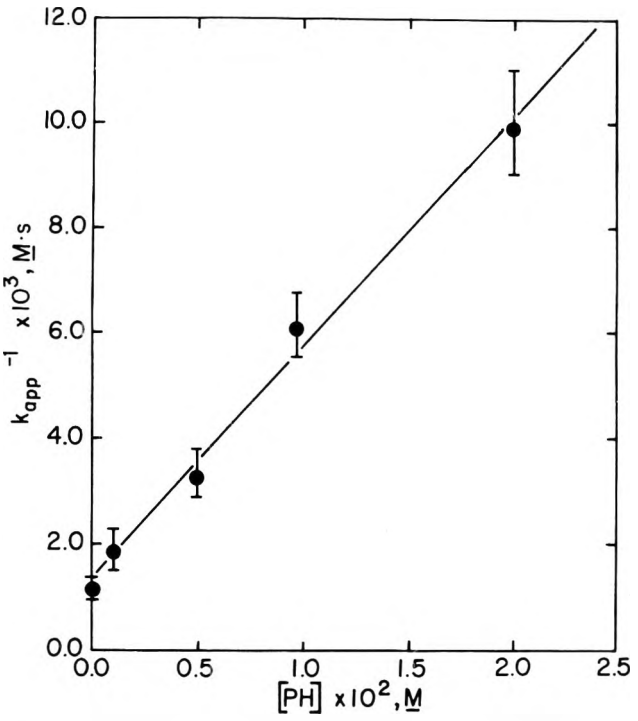


Figure 5. Dependence of the apparent pseudo-second-order rate constant on [PH] for the reaction of PH·$^+$ in neat Py. Vertical bars indicate $\pm 1\sigma$ in k_{app}. Solid line from linear regression (eq 4); coefficient of correlation = 0.985.

The second-order dependence of rate on cation radical concentration and inverse first-order dependence on neutral precursor concentration together with the observed stoichiometry suggests the involvement of a disproportionation step[16] (eq 6) prior to rate-determining encounter of dication with Py.

Scheme I

$$PH^{\cdot+} + PH^{\cdot+} \underset{k_{-6}}{\overset{k_6}{\rightleftharpoons}} PH^{2+} + PH \quad (6)$$

$$PH^{2+} + Py \underset{k_{-7}}{\overset{k_7}{\rightleftharpoons}} PH(Py)^{2+} \quad (7)$$

$$PH(Py)^{2+} + Py \xrightarrow{k_8} P(Py)^{+} + PyH^{+} \quad (8)$$

Assuming that the disproportionation step is fast and reversible and that the rate-determining attack of nucleophile on dication (eq 7) is irreversible, one derives an expression for the disappearance of cation radical given by eq 9.

$$-\frac{d[PH^{\cdot+}]}{dt} = \frac{2k_7K_{dis}[PH^{\cdot+}]^2[Py]}{[PH]} \quad (9)$$

While the appropriate reaction orders for PH·$^+$ and PH are embodied in eq 9, this rate law predicts that a plot of $1/k_{app}$ vs. PH concentration should afford a straight line with a *zero intercept* (i.e., from eq 4, $C_1 = \frac{1}{2}k_7K_{dis}[Py]$, $C_2 = 0$). Clearly the intercept of Figure 5 is nonzero. Moreover, if one assumes that some systematic error in the kinetic analyses gave rise to the nonzero intercept of Figure 5 and then proceeds to evaluate k_7 from the slope of this plot, a value of 4.18 ($\pm$0.03) $\times$ 10^{10} M^{-1} s^{-1} is calculated. This value of k_7 exceeds the diffusion controlled rate constant (k_{diff}) in pyridine which is estimated[17] to be 7.4 $\times$ 10^9 M^{-1} s^{-1}. Clearly Scheme I, constrained by the assumptions outlined above, does not adequately account for the observed data.

If it is again assumed that the attack by nucleophile on dication (eq 7) is irreversible and rate determining but that the disproportionation process (eq 6) is not a rapidly established equilibrium, then application of steady-state kinetics to [PH^{2+}] affords the rate expression

$$-\frac{d[PH^{\cdot+}]}{dt} = \frac{k_6k_7[Py]}{k_{-6}[PH] + k_7[Py]}[PH^{\cdot+}]^2 \quad (10)$$

from which

$$\frac{1}{k_{app}} = \frac{k_{-6}[PH]}{k_6k_7[Py]} + \frac{1}{k_6} \quad (11)$$

From the numerical value of $1/k_6$ (the intercept of Figure 5) and the experimentally determined value of K_{dis},[16] k_{-6} is evaluated to be 3.3 ($\pm$0.6) $\times$ 10^{14} M^{-1} s^{-1}, *which is in excess of the diffusion limit.* Even if the comproportionation reaction (the reverse of eq 6) were diffusion controlled, no linear dependence of k_{app} on [PH] would be observed.

A third possibility is that eq 6 is a rapidly established, reversible equilibrium and eq 7 is a reversible equilibrium or pseudoequilibrium process. Taking eq 8 to be rate determining yields the rate expression given by eq 12.

$$-\frac{d[PH^{\cdot+}]}{dt} = \frac{2k_8K_7K_{dis}[PH^{\cdot+}]^2[Py]^2}{[PH]} \quad (12)$$

Like eq 9, this rate law does not account for the experimental observations in that it predicts a *zero intercept* for a plot of $1/k_{app}$ vs. [PH].

A fourth possibility is that the disproportionation step (eq 6) is a rapidly established equilibrium, eq 7 is reversible, and the rates of reactions 7 and 8 are of comparable magnitudes such that neither is rate determining. With these stipulations, steady-state kinetics can be applied to [$PH(Py)^{2+}$], giving rise to the rate expression given in eq 13.

$$-\frac{d[PH^{\cdot+}]}{dt} = \frac{2k_7k_8K_{dis}[PH^{\cdot+}]^2[Py]^2}{(k_8[Py] + k_{-7})[PH]} \quad (13)$$

This form is also unacceptable in that it, too, predicts a *zero intercept* for a plot of $1/k_{app}$ vs. [PH].

Lastly, the possibility that both the disproportionation process (eq 6) and the addition of Py to the dication (eq 7) are not rapidly established equilibria must be addressed. If no reactive intermediates build up, then application of steady-state kinetics to *both* [PH^{2+}] and [$PH(Py)^{2+}$] affords the rate expression

$$-\frac{d[PH^{\cdot+}]}{dt} = \frac{2k_6k_7k_8[PH^{\cdot+}]^2[Py]^2}{k_{-6}[PH](k_{-7} + k_8[Py]) + k_7k_8[Py]^2} \quad (14)$$

for which

$$\frac{1}{k_{app}} = \frac{k_{-6}(k_{-7} + k_8[Py])}{2k_6k_7k_8[Py]^2}[PH] + \frac{1}{2k_6} \quad (15)$$

Under these constraints a plot of $1/k_{app}$ vs. [PH] yields a nonzero intercept. However, the numerical value of k_{-6}, calculated from the intercept of Figure 5 and the experimentally determined value of K_{dis}[16] to be 1.7 ($\pm$.0.3) $\times$ 10^{14} M^{-1} s^{-1}, is in *excess of the diffusion limit.*

An alternative to the disproportionation pathway is the half-regeneration mechanism,[2] Scheme II, which retains the proper overall stoichiometry.

Scheme II

$$PH^{\cdot+} + Py \underset{k_{-16}}{\overset{k_{16}}{\rightleftharpoons}} PH(Py)^{\cdot+} \quad (16)$$

$$PH(Py)^{\cdot+} + PH^{\cdot+} \underset{k_{-17}}{\overset{k_{17}}{\rightleftharpoons}} PH(Py)^{2+} + PH \quad (17)$$

$$PH(Py)^{2+} + Py \xrightarrow{k_{18}} P(Py)^{+} + PyH^{+} \quad (18)$$

The required dependencies of reaction rate on PH·$^+$ and PH concentrations may be shown to arise from treatment of

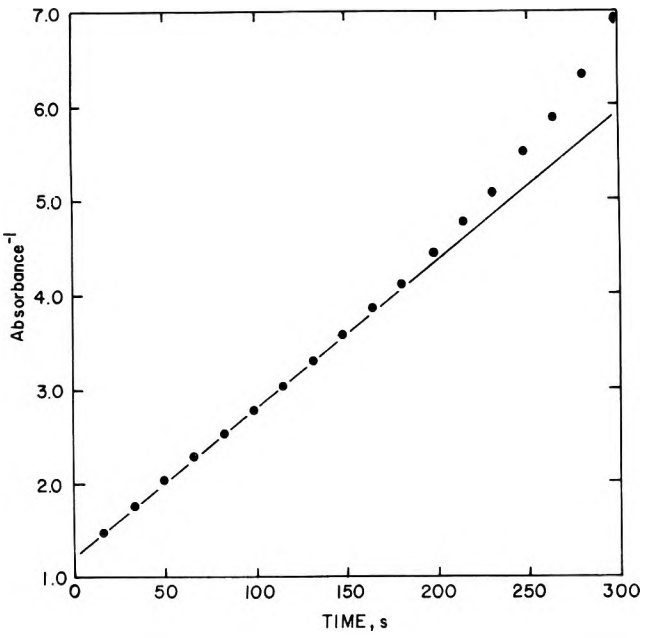


Figure 6. Representative kinetic plot for the reaction of $PH^{\cdot+}$ with Py in acetonitrile. $[PH^{\cdot+}]_0 = 1.00 \times 10^{-4}$ M, [Py] = 7.45 M, $[PH]_0$ = 0.00 M. For first half-life: slope = 1.55 (± 0.01) × 10^{-2} A^{-1} s^{-1}; coefficient of correlation = 0.9998.

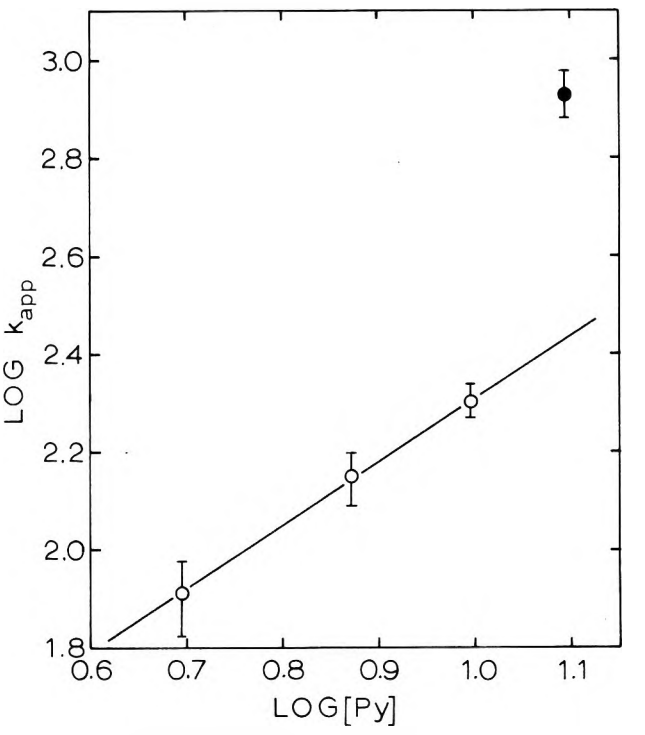


Figure 7. Dependence of the apparent rate constant (eq 20) for the reaction of $PH^{\cdot+}$ with Py on [Py]. Regression line for data obtained in acetonitrile/pyridine mixture (open circles), slope = 1.30 (± 0.04), coefficient of correlation = 0.9989. Solid circle is for reaction in neat Py (see text). $[PH]_0$ = 0.00 M in all cases.

the kinetic equations describing Scheme II provided that (1) the adduction equilibrium between $PH^{\cdot+}$ and Py (eq 16) is fast, (2) the electron transfer step (eq 17) is fast and reversible, and (3) steady-state kinetics may be applied to the concentration of the $PH(Py)^{2+}$ species. Under these conditions, eq 18 [deprotonation of $PH(Py)^{2+}$] is rate determining and eq 19 may be derived for the disappearance of $PH^{\cdot+}$.

$$-\frac{d[PH^{\cdot+}]}{dt} = \frac{2k_{16}k_{17}k_{18}[PH^{\cdot+}]^2[Py]^2}{k_{-16}(k_{-17}[PH] + k_{18}[Py])} \quad (19)$$

A *nonzero* intercept is predicted here for the data treatment of Figure 5.

Scheme II is offered as a tenable mechanism for this reaction.[20] The form of k_{app} (eq 4) becomes

$$k_{app} = \frac{2k_{16}k_{17}k_{18}[Py]^2}{k_{-16}(k_{-17}[PH] + k_{18}[Py])} \quad (20)$$

The slope (C_1, eq 4) of this plot may be assigned to the expression

$$C_1 = \frac{k_{-16}k_{-17}}{2k_{16}k_{17}k_{18}[Py]^2} = 4.38\ (\pm 0.03) \times 10^{-1}\ s \quad (21)$$

and the intercept (C_2, eq 4) to

$$C_2 = \frac{k_{-16}}{2k_{16}k_{17}[Py]} = 1.37\ (\pm 0.27) \times 10^{-3}\ M\ s \quad (22)$$

From these results and the concentration of neat Py (12.4 M) the kinetic parameters $k_{16}k_{17}k_{18}/k_{-16}k_{-17}$ and $k_{16}k_{17}/k_{-16}$ evaluate to 7.41 (±0.16) × 10^{-3} M^{-1} s^{-1} and 2.94 (±0.60) × 10^{+1} M^{-2} s^{-1}, respectively.

The Reaction in Acetonitrile Solutions. From eq 19, it can be seen that the dependence of reaction rate on Py concentration is bounded by the relative magnitudes of the two parenthetical denominator terms, $k_{-17}[PH]$ and $k_{18}[Py]$. In the limit of $k_{-17}[PH] \gg k_{18}[Py]$, a second-order dependence of reaction rate on Py concentration is predicted. In the other limit, i.e., $k_{-17}[PH] \ll k_{18}[Py]$, a first-order dependence should be observed. If the magnitudes of $k_{-17}[PH]$ and $k_{18}[Py]$ are similar, then an intermediate apparent reaction order is expected.

To evaluate the dependence of reaction rate on Py concentration, kinetic determinations were carried out in acetonitrile solutions containing various concentrations of Py. In this medium, however, multiple reaction pathways contribute to the consumption of cation radical and hence to complex observed kinetics.

The data presented in Figure 6 are typical of kinetic experiments conducted in this mixed solvent system. Although deviation from second-order dependence is reflected at sufficiently long times of observation, the initial rate of reaction is clearly dependent on $PH^{\cdot+}$ concentration in a second-order fashion. This is true for at least the first half-life. The dependence of this initial rate of reaction on concentration of Py in this solvent system, shown in Figure 7, is that predicted by eq 19, wherein $k_{-17}[PH]$ and $k_{18}[Py]$ are of similar magnitudes. That the apparent rate constant noted in neat Py is considerably higher than predicted from this figure is most probably a manifestation of the gross change in solvent character.[21]

The competing reaction in the acetonitrile solvent system is the formation of PH(O). This occurs via hydrolysis of $PH(Py)^{2+}$, this reaction being competitive with the deprotonation step in Scheme II (eq 18).

$$PH(Py)^{2+} + H_2O \rightarrow PH(OH)^+ + PyH^+ \quad (23)$$

$$PH(OH)^+ + Py \rightarrow PH(O) + PyH^+ \quad (24)$$

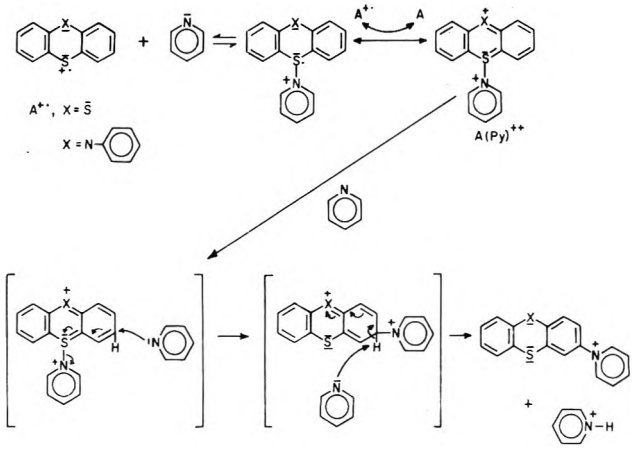
The hydrolysis of $PH(Py)^{2+}$ observed here is analogous to that noted in the reaction of thianthrene cation radical ($TH^{\cdot+}$) with Py in acetonitrile.[1a] In the $Th^{\cdot+}$ case, the hydrolysis of the analogous dicharged intermediate, $Th(Py)^{2+}$, proceeds with complete exclusion of pyridination. The relative reactivity of $PH(Py)^{2+}$ toward water is much less, however, and in this case the formation of both $P(Py)^+$ and PH(O) is observed. In fact, if hydrolysis of $PH(Py)^{2+}$ were the dominant pathway, then a first-order dependence of initial rate on Py concentration would be expected. Both the data shown in Figure 7 and the

product distribution reflect the initial dominance of the pyridination rather than the hydrolysis process.

Conclusions

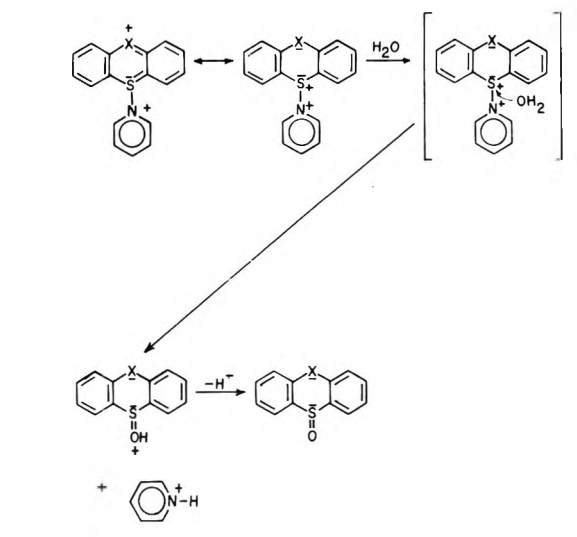
While it is known that the pyridinations of the cation radicals of thianthrene and phenothiazine[3] give rise to nucleophilic *substitution* products (carbon ring site), it is also established that the reactions of the cation radicals of thianthrene, 10-methylphenothiazine, and 10-phenylphenothiazine with protic nitrogen centered nucleophiles (viz., ammonia,[24] primary and secondary amines[25,26]) afford nucleophilic *addition* products (sulfur site). That pyridine should behave in this anomalous way toward sulfur-containing cation radicals is explicable in terms of the necessary product stability attainable through charge relief via release of protons borne by the nitrogen centered nucleophile.[3] Such stabilization has been found to be unnecessary in the case of the carbon centered 9,10-diphenylanthracene cation radical ($DPA^{\cdot+}$) in reaction with Py and triethylamine.[5]

The formation of thianthrene 5-oxide (ThO)[1a,3] and PH(O) in the course of the reaction of the respective cation radicals with pyridine, together with the observation that the rate of ThO formation is proportional to Py concentration, leads to the conclusion that the initial encounter of Py with these sulfur-centered cation radicals occur *at a sulfur site*. The following general mechanism is offered to account for the pyridination of $Th^{\cdot+}$ and $PH^{\cdot+}$:

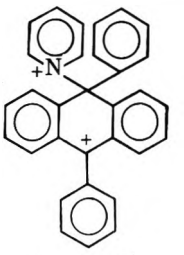


The attack of Py at the 3 position in this case is consistent with nucleophilic aromatic substitution under the direction of X^+.

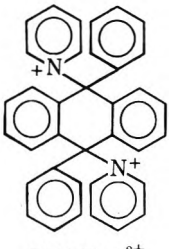
It is suggested that the 5-oxide is formed from hydrolysis of the dicationic $A(Py)^{2+}$ as follows:



The extent to which 5-oxide formation competes with pyridination is reflective of the relative reactivities of the $A(Py)^{2+}$ species. From the product distributions observed in acetonitrile, it is clear that $PH(Py)^{2+}$ is far less reactive than the corresponding $Th(Py)^{2+}$. The analogous intermediate in the case of the pyridination of $DPA^{\cdot+}$, $DPA(Py)^{2+}$, is also highly



$DPA(Py)^{2+}$



$DPA(Py)_2^{2+}$

reactive. This species, however, affords the dipyridinated ion[5], $DPA(Py)_2^{2+}$. Like $Th(Py)^{2+}$ and $PH(Py)^{2+}$, the pyridinium substituents in $DPA(Py)_2^{2+}$ are also labile,[5] but unlike the sulfur-containing species, reaction with protic nucleophiles (hydrolysis) does not kinetically favor the irreversible formation of the hydroxylated products.

Experimental Section

Materials. Acetonitrile (Burdick and Jackson Laboratories, UV grade) was purified as previously described.[27] Butyronitrile (Eastman) was purified in a similar manner. Py (J. T. Baker, reagent grade) was distilled from KOH at atmospheric ressure (bp 114–114.5 °C) and dried immediately prior to use by passage through activated alumina. Tetraethylammonium perchlorate (TEAP) was purified as reported elsewhere.[28] Phenothiazine (Aldrich) and iodobenzene (Aldrich) were used as received.

PH was prepared according to Gilman et al.[29] and purified by column chromatography (silica gel, CCl_4 eluent) followed by double recrystallization from glacial acetic acid (mp 94.5–95.5 °C, lit.[29] 94.5 °C). The perchlorate salt of the cation radical ($PH^{\cdot+}ClO_4^-$) was prepared in a manner analogous to that used by Shine et al.[3] for the synthesis of phenothiazine cation radical perchlorate. To a solution of 550 mg (2.00 mmol) of PH and 270 mg (1.06 mmol) of iodine in 40 ml of CH_2Cl_2 was added 3 ml of acetonitrile containing 420 mg (2.02 mmol) of $AgClO_4$. After stirring for 0.5 h, the AgI precipitate was filtered off and the filtrate added dropwise to 200 ml of anhydrous ether. The reddish-brown crystals formed were collected and dried in vacuo (25 °C) to yield 517 mg (1.38 mmol, 69%) of $PH^{\cdot+}ClO_4^-$, mp 250 °C dec. Anal. Calcd for $C_{18}H_{13}NSClO_4$: C, 57.68; H, 3.50; N, 3.74; S, 8.55; Cl, 9.46; O, 17.07. Found: C, 57.69; H, 3.48; N, 3.77; S, 8.57; Cl, 9.30; O, 17.19 (by difference).

PH(O) was prepared via oxidation of PH with hydrogen peroxide in refluxing EtOH[15] (mp 171–172 °C, lit. 172–173 °C).

Reaction of $PH^{\cdot+}$ ClO_4^- with Py. A solution of 590 mg (1.57 mmol) of $PH^{\cdot+}ClO_4^-$ in 40 ml of dry Py was stirred for 48 h. The solvent was removed and the resulting red solids dissolved in 200 ml of CH_3NO_2. This solution was repeatedly extracted with cyclohexane until TLC of the extract showed the absence of PH. The CH_3NO_2 fraction was evaporated to dryness, and the residue crushed and washed repeatedly with cold water to remove pyridinium perchlorate. The remaining orange crystals were dried in vacuo (25 °C), yielding 324 mg (0.72 mmol, 91% by eq 1) of *N*-[3-(10-phenylphenothiazinyl)]pyridinium perchlorate,[12] mp 110 °C dec, λ_{max} (acetonitrile) 255 nm (ϵ 3.22×10^4 M^{-1} cm^{-1}), 414 (3.10×10^3 M^{-1} cm^{-1}). Anal. Calcd for $C_{23}H_{17}N_2SClO_4$: C, 60.99; H, 3.78; N, 6.18; S, 7.08; Cl, 7.82; O, 14.13. Found: C, 61.18; H, 3.78; N, 6.18; S, 7.07; Cl, 7.58; O, 14.21 (by difference).

The cyclohexane extracts were combined and evaporated to yield 193 mg (0.701 mmol, 89% by eq 1) of PH. Removal of water from aqueous washings and subsequent recrystallization of the solids from aqueous MeOH gave 17 mg (0.652 mmol, 83% by eq 1) of pyridinium perchlorate, mp 286.5–288 °C (lit.[30] 287 °C).

The PH(O) formed when the reaction was carried out in acetonitrile/pyridine mixtures was isolated from the cyclohexane extracts by column chromatography (silica gel, CCl_4 and EtOH elution). Identification was by mixture melting point with authentic[15] material (171–173 °C) and comparison of UV spectra (EtOH).

Apparatus. Electrochemical measurements were carried out using

a conventional potentiostat[31] and cells described elsewhere.[4,5] Potentials are referred to the aqueous saturated calomel electrode. Working electrodes were fabricated from platinum foil (cyclic voltammetry) and platinum gauze (coulometry).

Spectra and kinetic transients were recorded on a Beckman Acta III spectrophotometer. The procedure employed for kinetic determinations consisted of pipetting 3.0 ml of Py or Py/acetonitrile solution into each of two matched cuvettes. The experiment was initiated by injection of a 10–20-μl volume of a stock $PH^{\cdot+}ClO_4^-$ solution (butyronitrile) into the sample cell, followed by rapid mixing. The molar absorptivity of $PH^{\cdot+}ClO_4^-$ in Py [$8.32\ (\pm.0.05) \times 10^3\ M^{-1}\ cm^{-1}$, 523 nm] was determined by extrapolation of the absorbance transient to zero time and comparison of the initial absorbance with that obtained from addition of an identical volume of the stock solution to 3.0 ml of butyronitrile [λ_{max} 515.5 nm, ϵ $8.70\ (\pm0.07) \times 10^3\ M^{-1}\ cm^{-1}$]. All kinetic determinations were performed at 24.7 (±0.3) °C.

Registry No.—$PH^{\cdot+}ClO_4^-$, 52156-15-7; Py, 110-86-1; *N*-[3-(10-phenylphenothiazinyl)]pyridinium ClO_4^-, 61047-42-5; $PH^{\cdot+}$, 38130-02-8.

References and Notes

(1) (a) Part 5: J. F. Evans and H. N. Blount, *J. Org. Chem.*, preceding paper in this issue. (b) Part 4: J. F. Evans and H. N. Blount, *J. Phys. Chem.*, **80,** 1011 (1976).
(2) C. Barry, G. Cauquis, and M. Maurey, *Bull. Soc. Chim. Fr.*, 2510 (1966).
(3) H. J. Shine, J. J. Silber, R. J. Bussey, and T. Okuyama, *J. Org. Chem.*, **37,** 2691 (1972).
(4) H. N. Blount, *J. Electroanal. Chem.*, **42,** 271 (1973), and references cited therein.
(5) D. T. Shang and H. N. Blount, *J. Electroanal. Chem.*, **54,** 305 (1974).
(6) Aqueous pK_a ca. 4–5; see S. A. Alkaitis, G. Beck, and M. Grätzel, *J. Am. Chem. Soc.*, **97,** 5723 (1975).
(7) (a) Y. Tsujino, *Tetrahedron Lett.*, 2445 (1968); (b) *ibid.*, 411 (1968); (c) *ibid.*, 763 (1969).
(8) P. Hanson and R. O. C. Norman, *J. Chem. Soc., Perkin Trans. 2,* 264 (1973).
(9) G. Cauquis, A. Deronzier, and D. Serve, *J. Electroanal. Chem.*, **47,** 193 (1973).
(10) Most probably, PH^{2+} reacts with residual nucleophilic impurities (e.g., H_2O) which escape removal during solvent pretreatment. This reaction is much slower than the analogous reactions of thianthrene dication (Th^{2+}) and 9,10-diphenylanthracene dication (DPA^{2+}) since Th^{2+} may be electrochemically detected only in the presence of addec nucleophile scavengers[11] while DPA^{2+} is not observed even under these conditions.
(11) O. Hammerich and V. D. Parker, *Electrochim. Acta,* **18,** 537 (1973).
(12) The site of substitution by Py at the ring system is assigned by analogy to the corresponding product from reaction of Py with phenothiazine cation radical[3]
(13) The presence of an electron-withdrawing substituent (e.g., pyridinium) renders oxidation more difficult.[14] Although a 135-mV shift is noted in this case, a shift of 200 mV is noted for the analogous *N*-(2-thianthrenyl)pyridinium ion compared to its precursor.[1a]
(14) P. Zuman, "Substituent Effects in Organic Polarography", Plenum Press, New York, N.Y., 1967.
(15) H. Gilman and R. O. Ranck, *J. Org. Chem.*, **23,** 1903 (1958).
(16) For an EE system involving two reversible couples

$$A \rightarrow A^{\cdot+} + e^- \quad (E_1)$$

$$A^{\cdot+} \rightarrow A^{2+} + e^- \quad (E_2)$$

the equilibrium constant for disproportionation, K_{dis}, may be calculated by[4]

$$2A^{\cdot+} \underset{}{\overset{K_{dis}}{\rightleftharpoons}} A^{2+} + A$$

$$K_{dis} = \exp\left(\frac{RT}{nF}|E_2 - E_1|\right)$$

From the data of Figure 1B, K_{dis} evaluates to be 2.2×10^{-12}.
(17) Calculated from the combined Stokes–Einstein and Smolunchousky equations:[18]

$$k_{diff} = \frac{8RT}{3000\eta}$$

For Py at 25 °, $\eta = 8.78 \times 10^{-3}$ P.[19]
(18) E. F. Caldin, "Fast Reactions in Solutions", Wiley, New York, N.Y., 1964, p 10.
(19) A. Cisak and P. J. Elving, *Electrochim. Acta,* **10,** 935 (1965).
(20) An analogous pathway involving rate-determining deprotonation of an oxidized cation radical/nucleophile intermediate has been proposed in the anisylation of thianthrene cation radical; see U. Svanholm, O. Hammerich, and V. D. Parker, *J. Am. Chem. Soc.*, **97,** 101 (1975).
(21) The dielectric constant of neat Py is considerably lower[22] than that of even the most concentrated solution of Py in acetonitrile used in this work. This lower dielectric solvent stabilizes the transition state (see Conclusion section) more so than the reactants, thereby affording a higher reaction rate. A comprehensive examination of solvent effects on reactions of radical cations of EE systems is in progress.[23]
(22) At 25°, ϵ 12.3 and 36.0 for P and acetonitrile, respectively. For 9.4 M Py in acetonitrile, ϵ 23.4.
(23) H. N. Blount et al., to be published.
(24) H. J. Shine and J. J. Silber, *J. Am. Chem. Soc.*, **94,** 1026 (1972).
(25) H. J. Shine and K. Kim, *Tetrahedron Lett.*, 99 (1974).
(26) B. K. Bandlish, A. G. Padilla, and H. J. Shine, *J. Org. Chem.*, **40,** 2590 (1975).
(27) T. Osa and T. Kuwana, *J. Electroanal. Chem.*, **22,** 389 (1969).
(28) J. F. . Evans and H. N. Blount, *J. Org. Chem.*, **41,** 516 (1976).
(29) H. Gilman, P. R. Van Ess, and D. A. Shirley, *J. Am. Chem. Soc.*, **66,** 1214 (1944).
(30) A. I. Popov and R. T. Pflaum, *J. Am. Chem. Soc.*, **79,** 570 (1957).
(31) A. A Pilla, *J. Electrochem. Soc.*, **118,** 702 (1971).

Structure and Rearrangement of the Reduction Dimers of *N*-Alkyl Pyridinium Cations[1]

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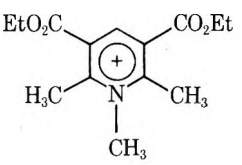
Reduction of the 1,2,6-trimethyl-3,5-dicarboethoxypyridinium cation (1) both chemically and electrochemically yields a mixture of isomeric reduction dimers. The less stable of these isomers, namely the 2,4′ dimer (8), undergoes rearrangement to yield the thermally more stable 4,4′ dimer **3** in a first-order reaction [$k = 1.1 \times 10^{12} \exp(-28.5/RT)\ s^{-1}$]. A mechanism is proposed for the rearrangement that involves the thermal dissociation of the 2,4′ dimer **8** into two pyridinyl radicals (**5**) which recombine to yield the 4,4′ dimer **3.**

The reduction of the 1,2,6-trimethyl-3,5-dicarboethoxypyridinium cation **1** by sodium amalgam in aqueous acetic acid was reported by Mumm and his co-workers[2] to yield a dimeric reduction product that melted at 168 °C. Heating this material, which Mumm called "Primaester" ("primary ester"), resulted in its rearrangement to a higher melting isomer (mp 192 °C) referred to by Mumm as "Umwandlungester" ("transformation ester"). Mumm assigned the structure of the 2,2′ dimer **2** (1,1′,2,2′,6,6′-hexamethyl-3,3′,5,5′-tetracarboethoxy-1,1′,2,2′-tetrahydro-2,2′-bipyridine) to the "primary ester" and that of the 4,4′ dimer **3** (1,1′,2,2′,6,6′-hexamethyl-



1

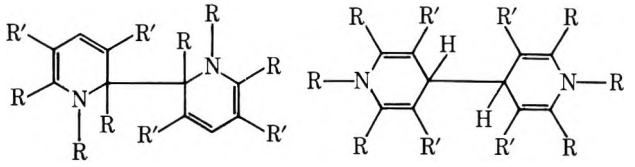
$$\xrightarrow[AcOH]{Na(Hg)} C_{28}H_{40}N_2O_8$$

"primary ester"
mp 168 °C

$$\xrightarrow{Heat} C_{28}H_{40}N_2O_8 \quad (1)$$

"transformation ester"
mp 192 °C

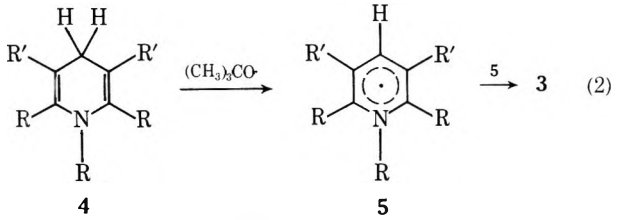
3,3′,5,5′-tetracarboethoxy-1,1′,4,4′-tetrahydro-4,4′-bipyridine) to the "transformation ester". Only the higher melting 4,4′



2 3

(R = CH_3; R′ = CO_2Et)

dimer **3** was obtained from the oxidation of 1,2,6-trimethyl-1,4-dihydro-3,5-dicarboethoxypyridine (**4**) with di-*tert*-butyl peroxide at 125 °C.[3] This reaction product was presumed to result from dimerization of two hybrid monohydropyridyl radicals **5** (1,2,6-trimethyl-3,5-dicarboethoxymonohydropyridyl) formed by abstraction of hydrogen atom from the 4 carbon of **4** by a *tert*-butoxyl radical obtained from the py-



4 5

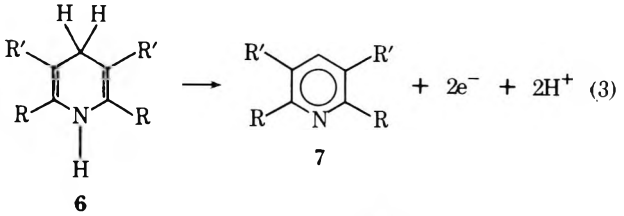
(R = CH_3; R′ = CO_2Et)

rolysis of the peroxide. The fact that no significant amounts of the lower melting "primary ester" were observed in this reaction, however, did not preclude its formation since the reaction temperature was sufficiently high and reaction time sufficiently long to have allowed for its rearrangement to the higher melting "transformation ester".

Our cyclic voltammetric studies of dihydropyridine derivatives reported in this article led to the observation that cathodic reduction of **1** yields the same reduction dimer obtained in its chemical reduction, namely the lower melting "primary ester". However, the NMR spectra of both the "primary ester" and "transformation ester" indicated that the structure assignment of the 2,2′ dimer **2** made previously for the "primary ester" was not correct. Determination of the correct composition of this lower melting reduction dimer made it possible to determine a mechanism for the rearrangement of the "primary ester" to the more stable "transformation ester" based on the kinetic parameters of the reaction.

Electrochemistry of Pyridine Derivatives in Acetonitrile. The anodic oxidation of various dihydropyridine derivatives to the corresponding pyridine and pyridinium derivatives has been the object of many investigations.[4] We have found that cyclic voltammograms of **4** and the corresponding dihydropyridine having no *N*-alkyl substituent, namely 2,6-dimethyl-1,4-dihydro-3,5-dicarboethoxypyridine (**6**), in acetonitrile at a platinum electrode to be informative, particularly with regard to the cathodic behavior of the anodic oxidation products of these dihydropyridine derivatives.

The dihydropyridine **6** undergoes anodic oxidation at a platinum electrode ($E_{p/2}$ = 0.81 V vs. SCE) to yield 2,6-dimethyl-3,5-dicarboethoxypyridine (**7**). Coulombic measure-



6 7

(R = CH_3; R′ = CO_2Et)

Table I. Summary of Electrochemical Data for Pyridine Derivatives[a]

Compd	$E_{p/2}$, V[b] Cathodic	$E_{p/2}$, V[b] Anodic	Coulometric measurement[c]
6		0.81	1.10
6 (+ γ-picoline)		0.81	1.99
4		0.75	1.05
4 (+ γ-picoline)		0.75	1.98
1 (ClO_4^-)	0.98		1.01
"Transformation ester"		0.20	2.05

[a] At a platinum electrode in acetonitrile, 0.10 M in tetraethylammonium perchlorate. [b] $E_{p/2}$ vs. a standard calomel electrode. [c] Number of faradays per mole of reagent initially present.

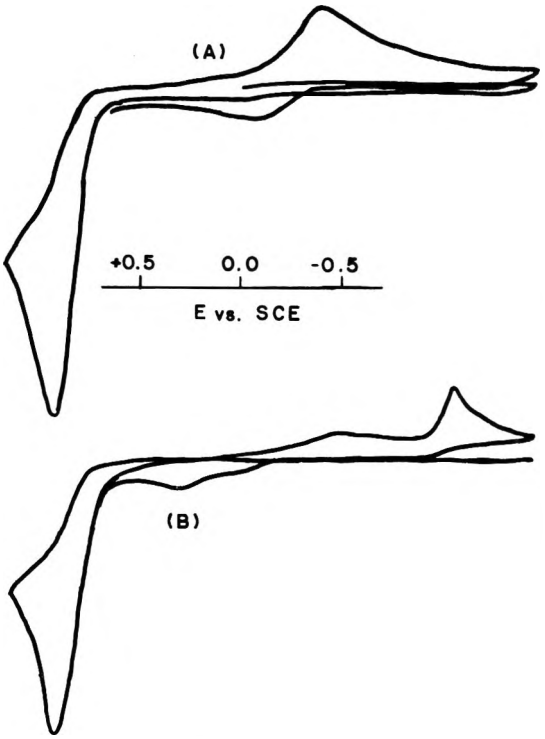


Figure 1. Cyclic voltammograms of (a) 2,6-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine (**6**) and (b) 1,2,6-trimethyl-3,5-dicarboethoxy-1,4-dihydropyridine (**4**) in acetonitrile (0.1 M TEAP).

ment of the oxidation of **6** (Table I) indicated that only half of the dihydropyridine was reduced because the protons formed in the oxidation interact with **6** to yield the protonated amine which is not oxidized at this potential. However, in the presence of an excess of the base γ-picoline, the reduction proved to be a 1.99-electron process (see Table I). The cyclic voltammogram of **6** (Figure 1a) shows a cathodic peak ($E_{p/2}$ = −0.23) that corresponds to the reduction of the protonated amine to yield molecular hydrogen. The reversible character of this peak as well as the appearance of a peak at the same potential observed in the cathodic sweep of **6** in the presence of a small amount of perchloric acid supports the assignment of reaction 4 for the cathodic peak in the cyclic voltammogram **6**. A cathodic sweep of **6** in acetonitrile in the absence of acid shows no peaks.

$$6\,H^+ + e^- \rightarrow 6 + \tfrac{1}{2}H_2 \qquad (4)$$

Anodic oxidation of the *N*-alkyl dihydropyridine derivative **4** occurs at $E_{p/2}$ = 0.75 V. Coulombic measurements show the oxidation is a two-electron process if γ-picoline is present to react with the protons formed in the reaction. The cyclic

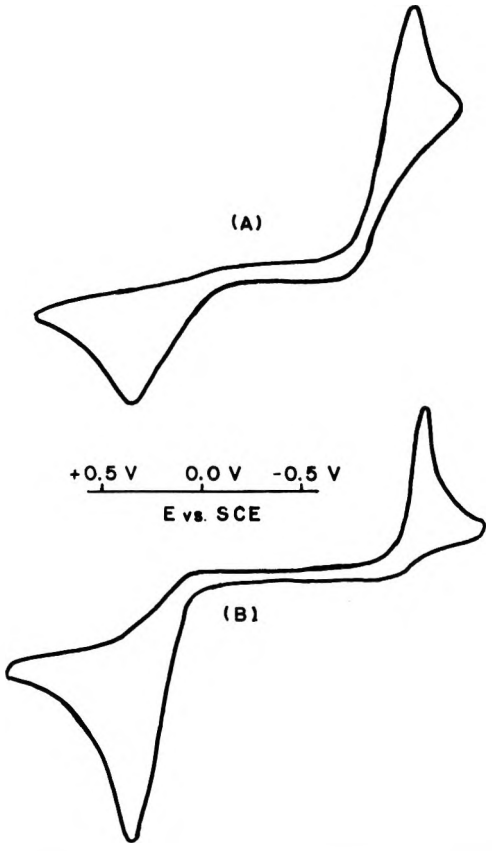


Figure 2. Cyclic voltammograms of (a) 1,2,6-trimethyl-3,5-dicarboethoxypyridinium perchlorate (1) and (b) the 4,4′-bipyridine 3 in acetonitrile (0.1 M TEAP).

voltammogram (Figure 1b) reveals that in addition to the expected cathodic peak at $E_{p/2} = -0.28$ V for the protonated amine, a second cathodic peak ($E_{p/2} = -0.98$ V) appears, a peak not observed in a cathodic sweep of 4 prior to anodic oxidation. The half-potential of this peak is identical with that observed in the cyclic voltammogram of an authentic sample of the perchlorate salt of the pyridinium cation 1 (Figure 2a).

$$4 \rightarrow 2 + H^+ + 2e^- \quad (5)$$

An anodic sweep *after* reduction of the cation 1 reveals oxidation ($E_{p/2} = 0.20$ V) of a material that is not present in the initial anodic sweep of 4. The coulometric data obtained for the reduction of the pyridinium cation 1 at −1.1 V (see Table I) correspond to a one-electron process which would be consistent with the formation of a reductive dimer of the pyridinium cation 1. The cyclic voltammogram of an acetonitrile solution of an authentic sample of the "transformation ester" (Figure 2b) prepared by rearrangement of the "primary ester" obtained by sodium amalgam reduction of 1 gave a peak with the same $E_{p/2}$ ascribed to the reductive dimer observed in the cyclic voltammogram of 4 and, subsequent to the oxidation of the dimer, a cathodic peak that can be ascribed to 1. Coulometric measurement of the anodic oxidation of the reductive dimer indicated the reaction to be a two-electron process (Table I).

Several attempts were made to reduce the pyridine 7 cathodically to a reductive dimer in acetonitrile. In no case was there evidence of any current flow or of a yellow coloration at the electrode, a phenomenon characteristic of the cathodic reduction of the pyridinium cation 1 to the yellow reduction dimer. Cathodic reduction of the pyridine 7 in the presence of $HClO_4$ showed only a peak at −0.32 V corresponding to the reduction of the protonated pyridine to yield hydrogen.

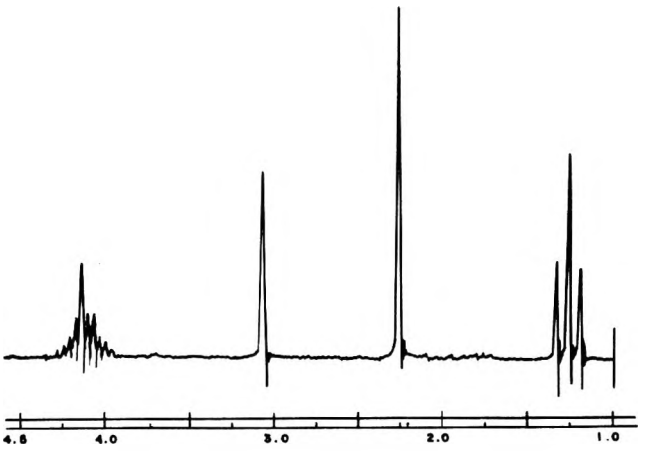


Figure 3. NMR spectrum of 1,1′,2,2′,6,6′-hexamethyl-3,3′,5,5′-tetracarboethoxy-1,1′,4,4′-tetrahydro-4,4′-bipyridine (3).

Structures of Reductive Dimers. We found that reduction of the sulfate salt of 1 by 3% sodium amalgam in acetic acid in the manner reported by Mumm and his co-workers yielded a material ("primary ester") that melted over a 3 °C range (162–165 °C). The same material could be isolated from the electrochemical reduction at a platinum electrode of the perchlorate salt of 1 in anhydrous acetonitrile at a potential of −1.1 V (vs. a standard calomel electrode). The "transformation ester" (mp 193 °C) was formed in 91% yield of recrystallized material by refluxing a toluene solution of the "primary ester" for about 24 h. A 40% yield of the "transformation ester" was obtained simply by heating the "primary ester" for 10 min at 180 °C.

The mass spectra of both the "primary ester" and "transformation ester" had parent peaks at *m/e* 532 and base peaks at *m/e* 266. The parent and the base peaks strongly support the suggested dimeric character of these reductive dimers of 1 (mol wt 266).

One apparent difference in the two materials is that the higher melting "transformation ester" can be isolated readily as crystalline material whereas the lower melting "primary ester" was obtained from reaction mixtures only as powder. However, on standing for several days at room temperature, a methanolic solution of the "primary ester" yielded a crop of crystals which melted sharply at 176.5–177 °C. These observations suggested that the "primary ester" formed in the reduction reactions is actually a mixture, the main component of which is the material that melts at 176.5–177 °C.

The NMR spectrum (Figure 3) of the "transformation ester" confirmed the assignment of 4,4′-tetrahydrobipyridine structure 3 for this compound made by Mumm and Beth.[2a] The triplet centered at 1.52 ppm (12 protons) can be assigned to the methyl protons of the four ethyl groups, the singlet at 2.52 ppm to the 3,3′,5,5′-methyl groups, and the singlet at 3.08 ppm (6 protons) to the two *N*-methyl groups. The multiplet centered at 4.20 ppm (10 protons) consists of a singlet at 4.25 ppm that can be assigned to the 4,4′ protons and a multiplet consisting of ten peaks resulting from the eight methylene protons of the four ethyl groups. The complexity of the signal (four overlapping quartets) is due to the nonequivalence of the two protons of each methylene group owing to the chiral character introduced in the molecule because of the restricted rotation at the 4,4′ linkage.[5]

The NMR spectrum of the crystalline material obtained from the "primary ester" is more complex (Figure 4) but is consistent with the assignment of the 2,4′ dimer 8 for this compound. The *N*-methyl groups appear as two singlets (unassigned) at 3.06 and 3.12 ppm, the 2-methyl as a singlet at 1.75 ppm. the 2′,6,6′-methyls as three singlets (unassigned)

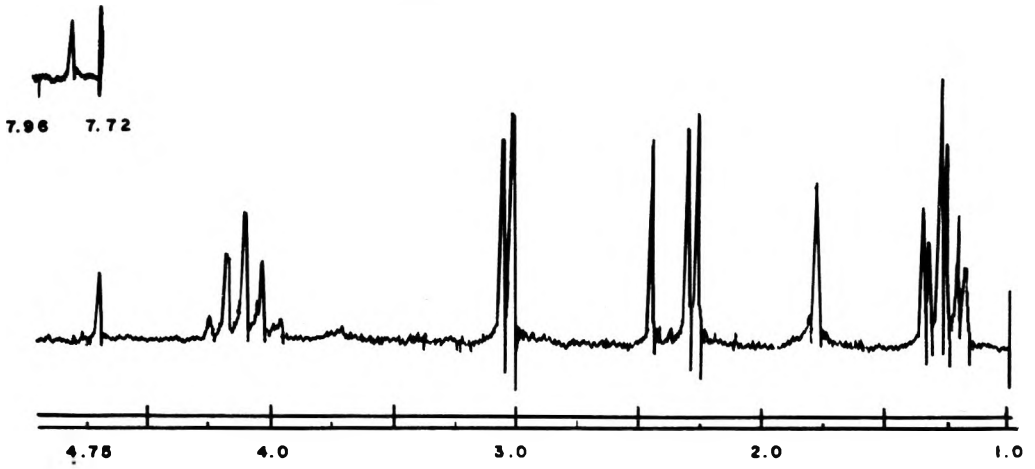
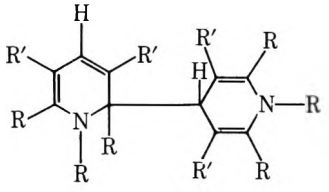


Figure 4. NMR spectrum of 1,1′,2,2′,6,6′-hexamethyl-3,3′,5,5′-tetracarboethoxy-1,1′,2,4′-tetrahydro-2,4′-bipyridine (8).

at 2.27, 2.32, and 2.45 ppm, the 4′ proton at 4.70 ppm, and the 4 proton at 7.85 ppm. The resonances centered at 1.50 and 4.15



8

(R = CH_3; R′ = CO_2ET)

ppm can be ascribed to the triplets and quartets of the four ethyl groups of the carboethoxy groups.

The NMR spectrum of the "primary ester" is a composite of the spectra of the 4,4′ dimer **3** and the 2,4′ dimer **8**. Missing in the NMR spectrum of the "primary ester" is any evidence of the 2,2′ dimer **2**, the structure assigned by Mumm to the "primary ester". Although **2** would be expected to exist as a mixture of the meso and racemic diastereoisomers and therefore display the same number of singlet methyl group resonances (four singlets for the 2,2′,6,6′-methyls and two singlets for the *N*-methyls), the observed chemical shifts are not consistent with the assignment of the 2,2′ dimer to either the low-melting "primary ester" or the crystalline material obtained from it. The chemical shifts of the 2- and 2′-methyl groups of the two diastereomers of **2** would be expected to appear as singlets upfield relative to the singlets of the 6- and 6′-methyl groups. Furthermore, the signals of the 4 and 4′ protons would appear in the downfield region expected for vinyl protons. The absence of any observable amounts of the 2,2′ dimer **2** in the "primary ester" mixtures is discussed subsequently in this article.

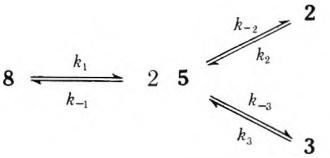
Integration of the resonance signal at 3.17 ppm for the *N*-methyl groups of **3** and those at 3.06 and 3.12 ppm for the *N*-methyl groups of **8** (see Experimental Section) allows for determination of the amounts of the two isomers that comprise the "primary ester" mixture. Employing this method, we found that the "primary ester" prepared by sodium amalgam reduction of **1** consisted of 81% of the 2,4′ dimer **8** and 19% of the 4,4′ dimer **3**.

Mechanism of the Rearrangement of the 2,4′ Dimer to the 4,4′ Dimer. The kinetics of the isomerization of the 2,4′ dimer **8** to the 4,4′ dimer **3** are informative of the mechanism of this rearrangement. The rates of the rearrangement in chlorobenzene were determined by measuring the NMR integrations of the *N*-methyl protons after appropriate intervals of heating. Chlorobenzene was used as the solvent for these reactions because it did not show any observable amounts of reaction with either **8** or **3** at the reaction temperatures used in our kinetic studies. Extensive coloration of the solution and formation of insoluble reaction products (not identified) were encountered when both **8** and **3** were heated for short times (10 min) in deuteriochloroform and 1,1,2,2-tetrachloroethane. Chlorobenzene was not a suitable solvent for the NMR determinations, however, because neither **3** nor **8** is sufficiently soluble in chlorobenzene at room temperature to allow for reliable NMR measurements. Therefore, after removal of the chlorobenzene under vacuum, solutions of the reaction mixtures in 1,1,2,2-tetrachloroethane were prepared for NMR analysis. Table II lists the first-order rate constants obtained for the rearrangement from which the rate constant $k = 1.1 \times 10^{12} \exp(-28.6/RT)\ s^{-1}$ can be calculated.

Table II. First-Order Rate Constants for Rearrangement of 8 to 3

Temp, °C	Rate constant $\times 10^5$, s^{-1}	Std dev $\times 10^5$
99.8	1.85	0.07
119.4	7.86	0.32
131.9	39.5	2.34

A mechanism consistent with the kinetic parameters for the rearrangement is one in which the 2,4′ dimer **8** undergoes unimolecular homolysis to form a pair of the hybrid radicals **5**, the same radical that is formed in the one-electron reduction of the pyridinium cation **1** or by abstraction of a 4-hydrogen atom from **4**. Two of the hybrid radicals **5** can recombine to form the 2,2′ dimer **2**, the 4,4′ dimer **3**, or the 2,4′ dimer **8**. Both **2** and **3** may also undergo homolysis to form the hybrid radi-



(6)

cals **5**, the former considerably faster than **8** ($k_2 \gg k_1$) because of greater steric crowding in the region of the bond undergoing cleavage and the latter more slowly than **8** ($k_3 \ll k_1$) because of less steric crowding. In the temperature region of our studies (100–130 °C), **3** apparently does not decompose to any significant extent whereas **2** does so rapidly. Indeed, our failure to observe any evidence of the 2,2′ dimer **2** in the "primary ester" mixture very likely arises from the fact that this isomer is not stable even at the temperatures used to "work up" the reaction mixtures (refluxing methanol) and rearranges to **3** and **8**.

The steady-state concentration for the intermediate hybrid radical **5** is shown in eq 7.

$$\left(\frac{k_1[8] + k_2[2] + k_3[3]}{k_{-1} + k_{-2} + k_{-3}}\right)^{1/2} = 5 \quad (7)$$

If it is assumed that the 2,2′ dimer decomposes at the temperatures of our reactions essentially as fast as it is formed ($k_2[2] = k_{-2}[5]^2$), that $k_3 \ll k_1$, and that the rate of the formation of the 4,4′ dimer **3** by dimerization of two of the hybrid radicals **5** is given by $d[3]/dt = k_{-3}[5]^2$, then the rate law of rearrangement of **8** to **3** is that shown in eq 8, a rate law consistent with the first-order kinetics observed for the reaction.

$$\frac{d[3]}{dt} = \frac{k_1[8]}{1 + k_{-1}/k_{-3}} \quad (8)$$

The activation parameters for the rearrangement of **8** to **3** are determined by the rate-limiting step of the reaction sequence, namely the unimolecular decomposition of **8**. Although the activation energy is consistent for a reaction involving rupture of a single σ bond between two carbon atoms to yield two resonance stabilized radicals at the rates observed for the rearrangement, the preexponential (frequency) factor A (1.1×10^{12} s^{-1}) is unexpectedly low for such a reaction.[6] In general, unimolecular fragmentation reactions that involve breaking of a single σ bond (e.g., peroxide decompositions) have A values that are greater than 10^{13} ($\Delta S^{\ddagger} > 0$). A values less than 10^{13} ($\Delta S^{\ddagger} < 0$) are more often encountered in unimolecular decompositions that proceed by simultaneous bond breaking and bond making at two or more sites in the molecule (e.g., ester and anhydride pyrolyses). Severe conformational restrictions are encountered in the transition states of the latter reactions accounting for the low frequency factors or negative entropies of activation.

The low A values for the rearrangement of **8** to **3** must be ascribed to the decomposition of the 2,4′ dimer **8** and consequently reflect a conformational requirement for the transition state of the homolysis of the σ bond between the 2 and 4′ carbon atoms of this molecule. Since the resonance stabilization of the monohydropyridyl radicals (**5**) is the principal reason that homolysis of this carbon–carbon bond occurs at these moderate temperatures, the transition state likely has considerable productlike character, namely that of the resonance stabilized radicals. The bond breaking would therefore be expected to occur most readily if the p orbitals generated at the 2 and 4′ carbon atoms are parallel to those of the π bonds in the two ring systems in order to allow for maximum overlap of the p orbitals of the resonance stabilized radical. Such would be the case only if the fragmenting molecule assumes the proper conformation in the transition state of the homolysis, namely that in which the σ bond that is broken is in an axiallike position with respect to both rings. Although not the preferred conformation for **C** (the equatorial–equatorial, the equatorial–axial, and axial–equatorial all likely more stable), it is only in (he axial–axial conformation that the σ bond undergoes homolysis since it is only in this conformation that the resonance stabilization of the radicals being formed can lower the activation energy requirement for the reaction.

Homolysis of the σ bond between the two rings of other tetrahydrobipyridyls has been proposed for various thermal reactions of these compounds.[7] In gereral, the products of these reactions are pyridine derivatives or rearrangement products and can be accounted for in terms of reactions of the monohydropyridyl radicals formed in the fragmentation.

Experimental Section

2,6-Dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine (6) was prepared by the method of Singer and McElvain[8] and **2,6-dimethyl-3,5-dicarboethoxypyridine (7)** by oxidation of **6** with sodium nitrite.[9] The perchlorate salt of the **1,2,6-trimethyl-3,5-dicarboethoxypyridinium** cation **1** was obtained by reaction of **7** with dimethyl sulfate followed by precipitation of the perchlorate salt by addition of sodium perchlorate in the manner described by Brook and Karrer.[10] **1,2,6-Trimethyl-3,5-dicarboethoxy-1,4-dihydropyridine (4)** was prepared by sodium dithionite reduction of the perchlorate salt.[3]

Acetonitrile (Baker Analyzed reagent) was dried over calcium hydride for 24 h and distilled from phosphorus pentoxide according to the procedure described by Adams.[11] **Tetraethylammonium perchlorate** (TEAP) was prepared by precipitation of the salt from a solution of tetraethylammonium bromide with sodium perchlorate and purified by recrystallization from ethanol and water seven times.

Cyclic Voltammetry. The cyclic voltammetric experiments were performed with a controlled potential operational amplifier polarograph in a conventional three-electron cell consisting of a platinum working electrode, a platinum gauze auxilary electrode, and a saturated calomel reference electrode. All cyclic voltammograms were recorded on a Moseley Model 7030A X-Y recorder.

The platinum electrodes were cleaned before each cyclic voltammogram by immersion in a dilute nitric acid solution rendering each anodic for 10 s then cathodic for 15 s and finally rinsed with distilled water. All cyclic voltammograms were performed in a solution of TEAP (0.1 M) in acetonitrile. The solution was sparged with nitrogen (dried by passing through Drierite) for about 15 min to eliminate any background current due to oxygen. Sufficient sample was dissolved in the acetonitrile to give a solution approximately 2×10^{-3} M in the substrate, and sweeps were made at scan rates of 15 V/min. Sweeps were initiated in both the anodic and cathodic directions to assure the assignments of the current peaks suspected as products of electrode reactions and not species present in the original sample of the substrate undergoing examination.

Coulometric Measurements. Exhaustive coulometric procedures were utilized for determination of the number of faradays required for the anodic and cathodic processes listed in Table I. Solutions containing accurately weighed amounts of the substrate (TEAP used as the carrier) were subjected to the desired reaction at a platinum gauze electrode. A platinum wire inside of a tube fitted with a fritted disk and containing only acetonitrile and TEAP served as the auxiliary electrode. Potentials were adjusted at or slightly beyond the peak potential of the desired reaction. The current flow was monitored and measured with a Wenking Electronischer potentiostat equipped with a digital readout. The solution resulting from the coulometric determinations was concentrated and the products of the electrode reactions identified both by comparisons of their electronic spectra and thin layer chromatographic retention times with those of authentic samples of the compounds.

Sodium Amalgam Reduction of 1. Ten grams of 2,6-dimethyl-3,5-dicarboethoxypyridine was heated for 2 h at 100 °C with 9 ml of freshly distilled methyl sulfate, 0.1 g of copper powder, and 0.25 g of anhydrous potassium carbonate. After cooling, 30 ml of water was added and the mixture extracted three times with 30 ml of ether. The aqueous fraction was cooled in an ice bath and 80 g of 3% sodium amalgam[12] and 3 ml of acetic acid were added with stirring over a 75-min period. The precipitated "primary ester" was filtered out and recrystallized from methanol (mp 162–165 °C). The yield of isolated "primary ester" was 57%.

Electrochemical Reduction of 1. Ten grams of 1,2,6-trimethyl-3,5-dicarboethoxypyridinium perchlorate was dissolved in 100 ml of anhydrous acetonitrile (distilled from phosphorus pentoxide after 2 weeks of storing over calcium hydride). About 2 g of tetraethylammonium perchlorate was dissolved in the solution to serve as the supporting electrolyte. The solution was stirred with a magnetic stirrer, cooled in an ice bath, and sparged with argon gas. The controlled potential electrolysis was performed with a three-electrode potentiostat using a calomel electrode for reference, 8 in.^{2} of platinum gauze as the working electrode, and a carbon rod contained in a glass fritted cell divider as the auxiliary electrode. The pyridinium cation was reduced at −1.1 V (vs. the calomel electrode) until no further current flow was observed (2–3 h). The "primary ester" mixture precipitated from the solution and was obtained in 52% yield (mp 163–166 °C).

1,1′,2,2′,6,6′-Hexamethyl-3,3′,5,5′-tetracarboethoxy-1,1′,-4,4′-tetrahydro-4,4′-bipyridine (4,4′ Dimer 3). Two grams of the "primary ester" mixture was dissolved in 100 ml of toluene and refluxed for 24 h. The toluene was removed under reduced pressure and the residue recrystallized from absolute ethanol, yielding 1.82 g (91% of theory) of the 4,4′ dimer **3**, mp 193 °C (reported 193 °C).[2] The mass

spectrum showed a parent peak at *m/e* 532 (calcd mol wt 532) and a base peak at *m/e* 266, corresponding to the monomeric unit of the dimer. The NMR spectra of this compound in $DCCl_3$ is shown in Figure 3.

Heating the "primary ester" for 10 min at 180 °C followed by recrystallization of the resulting material resulted in a 40% yield of 3.

1,1',2,2',6,6'-Hexamethyl-3,3',5,5'-tetracarboethoxy-1,1',-2,4'-tetrahydro-2,4'-bipyridine (2,4' Dimer 8). A Solution of the "primary ester" in methanol was allowed to cool slowly to room temperature. After a few days at room temperature, small amounts of crystalline material were formed. More rapid cooling or at temperatures below room temperature resulted in precipitation of the "primary ester" as a powder. The crystalline material (mp 176.5–177 °C) showed the same parent and base peaks in its mass spectrum as observed for the 4,4 dimer **3**. The NMR spectrum in $DCCl_3$ is shown in Figure 4.

Kinetic Measurements. Solutions (0.01 M) of the "primary ester" mixture in chlorobenzene were placed in a three-neck flask equipped with a large coil condenser. The remaining necks were stoppered and the flask immersed in an oil temperature bath. At appropriate time intervals, a 25-ml portion of the solution was removed and evaporated to dryness on a rotatory evaporator. The resulting residue was dissolved in about 5 ml of 1,1,2,2-tetrachloroethane. Four or five NMR sample tubes from each sample were removed from the reaction mixture.

The NMR analyses were obtained as soon as possible after the tetrachloroethane solutions of the reaction mixtures were prepared to avoid any reaction of the reactants or products of the rearrangement with the solvent. The NMR integrations of the *N*-methyl signals of **3** and **8** in the region of 3.0 ppm were obtained using the field sweep mode with a sweep width of 250 Hz and sweep times of 100 s per sweep. The signals were integrated 14–16 times, and, employing the methodology of Kassler,[13] the best 10–12 integrations used to determine the ratios of the 2,4' dimer **8** and the 4,4' dimer **3**. The extent of reaction of the 2,4' dimer **8** at each time interval was determined from the ratio obtained and from the initial amount of the "primary ester". The first-order rate constants and their standard deviations in Table II were calculated from least-squares treatment of the data obtained in this manner.

Registry No.—**1**, 59348-50-4; **1** perchlorate, 59348-51-5; **3**, 61024-92-8; **4**, 14258-07-2; **6**, 1149-23-1; **8**, 61024-93-9; 2,6-dimethyl-3,5-dicarboethoxypyridine, 1149-24-2; methyl sulfate, 77-78-1.

References and Notes

(1) This work was supported by a grant (GM AM 18191) from the Department of Health, Education and Welfare.
(2) (a) O. Mumm and W. Beth, *Ber.*, **54**, 1591 (1921); (b) O. Mumm and H. Ludwig, *ibid.*, **59**, 1605 (1926); (c) O. Mumm and J. Diedricksen, *Justus Liebigs Ann. Chem.*, **538**, 195 (1939).
(3) E. S. Huyser, J. A. K. Harmony, and F. L. McMillian, *J. Am. Chem. Soc.*, **94**, 3176 (1972).
(4) Cf. W. J. Blaedel and R. G. Haas, *Anal. Chem.*, **42**, 918 (1970); W. J. Blaedel and R. A. Jenkins, *ibid.*, **47**, 1337 (1975); R. D. Braun, K. S. V. Santhanam, and P. J. Elring, *J. Am. Chem. Soc.*, **97**, 259 (1975); J. Kuthan, V. Simonek, V. Volkovi, and J. Volke, *Z. Chem.*, **11**, 111 (1971).
(5) For discussion and other examples of nonequivalence of methylene protons arising from chirality introduced by restricted rotation see J. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Vol. 5, 2d ed, Pergamon Press, Oxford, 1969, pp 378–379.
(6) See A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", 2d ed, Wiley, New York, N.Y., 1961, pp 109–115.
(7) A. T. Nielser, D. W. Moore, J. H. Mazur, and K. H. Berry, Jr., *J. Org. Chem.*, **29**, 2898 (1964); P. M. Atlani, J. F. Biellman, and J. Moron, *Tetrahedron*, **29**, 391 (1973); P. Atlani, J. F. Bielman, R. Briere, and A. Rassat, *ibid.*, **28**, 5805 (1972); P. Atlani, J. F. Biellman, R. Briere, H. Lemaire, and A. Rassat, *Ind. Chim. Belg.*, **36**, 1066 (1971); P. Atlani, J. F. Biellman, R. Briere, J. Lemaire, and A. Rassat, *Tetrahedron*, **28**, 2827 (1972).
(8) A. Singer and S. M. McElvain, "Organic Syntheses", Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N.Y., 1943, p 214.
(9) B. Loev and K. M. Snader, *J. Org. Chem.*, **30**, 1914 (1965).
(10) P. R. Brook and P. Karrer, *Justus Liebigs Ann. Chem.*, **605**, 1 (1957).
(11) R. N. Adams, "Electrochemistry at Solid Electrodes", Marcel Dekker, New York, N.Y., 1969, p 30.
(12) R. N. McDonald and C. E. Reineke, *Org. Synth.*, **50**, 50 (1970).
(13) F. Kasler "Quantitative Analysis by NMR Spectroscopy", Academic Press, New York, N.Y., 1973, p 79.

Pyridopyrimidines. 6. Nucleophilic Substitutions in the Pyrido[2,3-*d*]pyrimidine Series[1]

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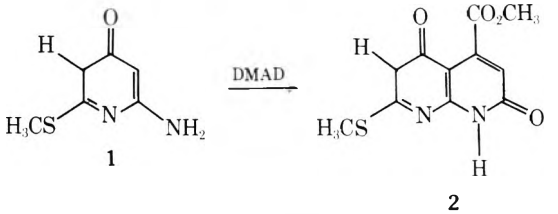
The scope of the reaction between 6-aminopyrimidines and dimethyl acetylenedicarboxylate to give 5-carbomethoxy-7-oxopyrido[2,3-*d*]pyrimidines was found to be limited primarily to 6-aminouracil derivatives. The preparation of a key synthetic intermediate, 2,4,7-trichloropyrido[2,3-*d*]pyrimidine, is reported. A study of nucleophilic displacement on this intermediate revealed that the reactivity was in the order 4 > 7 > 2 except in the case of aqueous sodium hydroxide, which gave 5-carboxy-7-chloro-2,4-dioxopyrido[2,3-*d*]pyrimidine. The observed selectivity enabled the preparation of a number of otherwise inaccessible pyridopyrimidines.

Unsubstituted 6-aminouracil and a variety of its *N*-alkyl derivatives have recently been found to react with dimethyl acetylenedicarboxylate (DMAD) in protic media (water or methanol) to give 5-carboxamido-7-oxopyrido[2,3-*d*]pyrimidines.[2,3] Our interest in pyrido[2,3-*d*]pyrimidines and nucleosides derived from them prompted us to continue the study of the utility of this reaction in providing candidate antitumor pyridopyrimidines. The present paper describes the synthesis of such heterocycles and their characterization; a companion paper[4] will describe the synthesis of ribonucleoside analogues from these bases.

It has been firmly established[2,3] that the reaction of DMAD with 6-aminouracils gave the 7-oxo rather than the 5-oxopyridopyrimidine isomer and the probable mechanism of this reaction has been described.[2] Since the procedure is a very

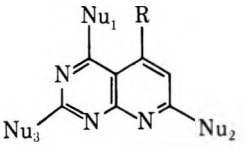


1 2

simple one, it was of interest to assess the scope of the reaction with a variety of pyrimidines. It was found that 6-amino-2-methylthio-4-oxopyrimidine (**1**) could be converted to 5-carbomethoxy-4,7-dioxo-2-methylthiopyrido[2,3-*d*]pyrimidine (**2**) in low yield. Of a number of other 6-aminopyrimidines studied, including 4,6-diamino-2-methylthio-, 4,6-diamino-2-oxo-, 4-amino-6-methylthio-2-oxo-, and 2,4-diamino-6-

oxopyrimidines, none gave isolable amounts of pyrido[2,3-*d*]pyrimidine products in the complex reaction mixtures. Thus the reaction of 6-aminouracils appears to be rather unique in forming pyrido[2,3-*d*]pyrimidines with DMAD in significant yield, probably because the relative isolation of the C-5, C-6 double bond enhances the reactivity of C-5 toward electrophilic attack.

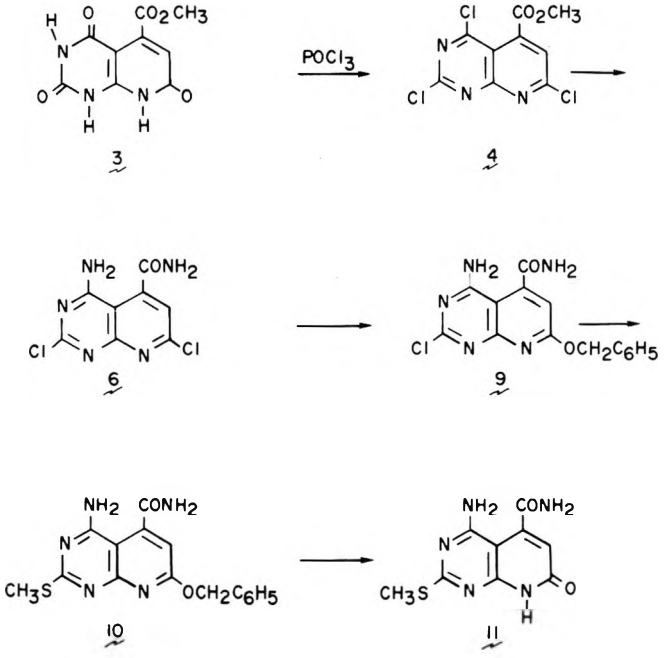
In view of the limited scope of the reaction of DMAD with 6-aminopyrimidines, an alternative procedure for obtaining pyrido[2,3-*d*]pyrimidines of potential biological interest was sought. The selective displacement of the 4-chloro group in 2,4-dichloropyrido[2,3-*d*]pyrimidine as demonstrated by Robins and Hitchings[5] suggested that conversion of 5-carbomethoxy 2,4,7-trioxopyrido[2,3-*d*]pyrimidine (**3**) to the trichloropyrido[2,3-*d*]pyrimidine (**4**) would give a compound which might be expected to undergo nucleophilic displacement of the chloro groups in the order of reactivity of 4 > 7 > 2.[6] If indeed this reactivity order were observed, the synthesis of the desired pyrido[2,3-*d*]pyrimidines would be as outlined in Scheme I. If selective displacement of the chloro groups of **4** were possible, the synthesis of pyrido[2,3-*d*]pyrimidines of general structure **5** can be envisioned by reaction with different nucleophiles in the order of Nu_1, Nu_2, and Nu_3.



5

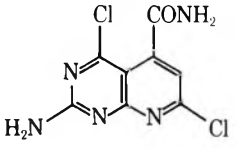
When **3** was refluxed in phosphorus oxychloride no reaction occurred, which contrasts with the ease of chlorodehydroxylation of 2,4-dioxopyrido[2,3-*d*]pyrimidine to give 2,4-dichloropyrido[2,3-*d*]pyrimidine.[5] When *N,N*-diethylaniline was added to the reaction mixture, an excellent yield was obtained of a single compound. This was determined to be structure **4** on the basis of elemental analysis, ^{1}H NMR, and mass spectrometry. The presence of three chlorine atoms was

Scheme I



confirmed by the appearance of peaks at *m/e* 291, 293, and 295 in the ratio of 3:3:1 for M^+, due to the isotope abundance of chlorine. Peaks were also present for the loss of $-OCH_3$ (M − 31) and $-CO_2CH_3$ (M − 59) which confirmed that the ester was present. ^{1}H NMR spectroscopy confirmed the presence of an *O*-methyl group and a single aromatic proton resonating at δ 4.05 and 7.58, respectively.

The reaction of **4** with methanolic ammonia at room temperature for 24 h gave a single new compound, which was tentatively assigned structure **6**. The ^{1}H NMR spectrum of **6** showed the loss of the signal due to the *O*-methyl of **4**, which was replaced by a broad two-proton doublet at δ 8.53 and 8.73 corresponding to one proton each for the amide protons. These signals disappeared on addition of D_2O. The mass spectrum revealed the presence of two chlorines as well as a loss of 17 mass units from the molecular ion of 257 corresponding to loss of NH_3. However, it was not possible to unequivocally eliminate the alternate structures, **7** and **8**.



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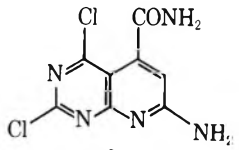
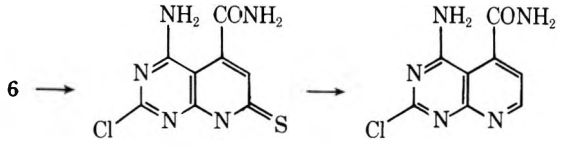


8

Nucleophilic displacement of the 7-chloro group of **6** was achieved by reaction with sodium benzylate in dimethyl sulfoxide. A signal centered at δ 7.45 which represents the phenyl ring and a singlet at δ 5.50 for the methylene group appeared in the ^{1}H NMR spectrum of **9**. Mass spectral data confirmed that one chlorine remained on the product. The final chlorine was displaced with sodium methylmercaptide in dimethyl sulfoxide to give compound **10**. The benzyloxy group of **10** was easily converted to the oxo group by reaction with 48% HBr to give compound **11**.

It was necessary to eliminate the other five isomers which would be obtained if the order of nucleophilic displacement were not in the sequence 4, 7, and 2. The unequivocal determination that the isomer was indeed **11** was made by performing two sets of reactions. The first set showed that, after amination, the second reaction occurred in the 7 position. This indicated that initial amination was in the pyrimidine ring, either the 2 or 4 position. The second set of reactions confirmed that the final nucleophilic displacement with methylmercaptide occurred at the 2 position. Thus the initial amination had occurred only at the 4 position, followed by substitution at the 7 position with sodium benzylate and finally at the 2 position to give ultimately **10**.

The replacement of the 7 substituent in these pyrido[2,3-*d*]pyrimidines with a hydrogen would give rise to a pair of doublets in the ^{1}H NMR spectrum for the 6 and 7 protons. The same displacement at the 2 or 4 position would give rise to a new singlet in addition to the singlet for C-6 H. The conversion of **6** into the pyrido[2,3-*d*]pyrimidine-7-thione **12** was

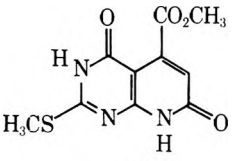


12 **13**

accomplished with sodium hydrosulfide in DMF. The use of 1 equiv of sodium hydrosulfide, when added slowly, allowed selective displacement of only the 7-chloro group. Confirmation was achieved by mass spectrometry which again showed the isotope effect of the single chloride present; peaks at *m/e* 255 and 257 in ratio of 3:1 were in complete accord with the proposed empirical formula. The shift in the long wavelength absorption band in the ultraviolet spectrum of **12** to 385 nm as compared with 314 nm of **6** was supportive of a 7-thione substitution.[7] Unequivocal evidence for the position of the thione group was provided by the conversion of **12** to

13 with Raney nickel. That the product of this reaction was **13** was determined by ^{1}H NMR and mass spectrometry as well as elemental analysis. The ^{1}H NMR spectrum of **13** showed two doublets at δ 7.53 and 9.03 with a $J_{6,7}$ = 4.8 Hz, as well as D_2O exchangeable signals at δ 8.45 (two protons), 8.48 (one proton), and 8.70 (one proton) for the amino group and amide group. The mass spectrum again contained the isotope effect of the chlorine on the molecular ion. These results clearly demonstrated that the initial nucleophilic attack with ammonia occurred in the pyrimidine ring. However, it was not possible to determine from these results if this displacement was at the 4 or 2 position of the pyrido[2,3-*d*]pyrimidine ring.

The final displacement was shown to be at the 2 position by conversion of **11** to **14.** When **11** was treated with sodium

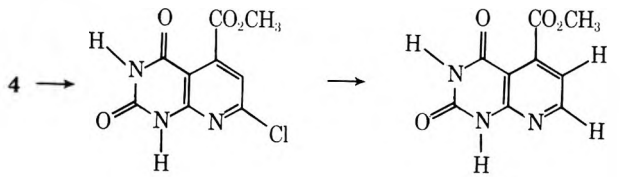


14

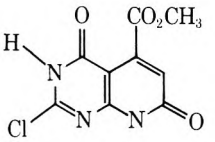
nitrite in dilute sulfuric acid, diazotization and subsequent hydrolysis of the 4-amino group occurred to give a mixture of two compounds as judged by thin layer chromatography. This mixture was hydrolyzed in aqueous sodium hydroxide to give 4,7-dioxo-2-methylthiopyrido[2,3-*d*]pyrimidine-6-carboxylic acid (**14**). The mass spectrum of **14** supported the structural assignment with the molecular ion at 253. A peak at M − 44 (209 amu) corresponding to loss of CO_2 further supported the presence of the carboxylic acid group. The ^{1}H NMR spectrum contained signal for C_6H and the methylthio at δ 6.95 and 2.47, respectively. Confirmation of the structure lay in the preparation of **14** by the basic hydrolysis of the ester **2.** The product of this hydrolysis proved to be identical by TLC, UV, ^{1}H NMR, and mass spectrometry with **14** obtained from compound **11.** Since the reaction of **1** with DMAD could only yield a pyrido[2,3-*d*]pyrimidine (**2**) with the methylthio group at position 2, compound **11** must have the methylthio group also at position 2. In addition, these reactions also confirmed that the product (**2**) of DMAD and **1** was the 7-oxo- and not the alternate 5-oxopyrido[2,3-*d*]pyrimidine. These results unequivocally established that the order of substitution with ammonia, sodium benzylate, and sodium mercaptide occurred at the 4, 7, and 2 positions, respectively, of the trichloropyrido[2,3-*d*]pyrimidine (**4**).

The ^{1}H NMR spectra of the above compounds which contain both the 4-amino and 5-carboxamido groups (**6, 9, 10, 11, 12, 13**) revealed an interesting pattern for the signals associated with these groups. In each case two broad singlets representing one proton each and one broad singlet representing two protons were present. These can be assigned tentatively to the carboxamide and amino group, respectively, by the following observations. The signals attributed to the carboxamido protons underwent collapse at ~85 °C to give a broad singlet. This observation was similar to that of acetamide and resulted from the slow rotation about the C–N bond in planar amides.[8] The signals of the amino group appeared as a broad singlet, because of rapid rotation on the ^{1}H NMR time scale. The signal attributed to the amino group varied considerably as substituents were changed at the 2 and 7 positions, whereas the signal attributed to the carboxamido group remained virtually constant. It would be expected that the group directly attached to the pyrido[2,3-*d*]pyrimidine ring system would be shifted by a change in the substituents on the ring.[8]

When **4** was reacted with hydroxide ion at room temperature a different pattern of displacement occurred. With 1.5 equiv of hydroxide ion, **4** gave a single compound in less than 50% yield. The mass spectrum of the product showed a molecular ion at 255 amu and the M + 2 peak indicated that only one chlorine remained, establishing that the product was a dioxopyrido[2,3-*d*]pyrimidine. This product was subjected to catalytic hydrogenolysis to give a compound which was established as **16** by virtue of the presence of a pair of doublets ($J_{6,7}$ = 4.8 Hz) in the ^{1}H NMR spectrum. Thus, dehalogenation had occurred from the 7 position of the ring, which confirms that the dioxopyrido[2,3-*d*]pyrimidine obtained from **4** was **15** and not **17.**



15 **16**



17

This study has established the order of reactivity of nucleophilic attack for substituents in positions 2, 4, and 7 of the pyrido[2,3-*d*]pyrimidine ring system. Through the intermediacy of the key intermediate **4** a very wide variety of hitherto unavailable pyridopyrimidine derivatives may be readily prepared.

Experimental Section

The ^{1}H NMR spectra were recorded on a Jeol C-60H spectrometer with tetramethylsilane or DSS as an internal standard. Chemical shifts are expressed as δ, parts per million, from the standard. Ultraviolet spectra were obtained on a Cary Model 15 spectrophotometer. Mass spectra were recorded on a LKB-GCMS Model 9000S, at 70 keV. Only the molecular ion and first major fragments are reported. Elemental analyses were performed by Het-Chem-Co, Harrisonville, Mo. Melting points were determined on a Thomas-Hoover Unimelt and are uncorrected. All analytical samples were dried in the presence of P_2O_5 in vacuo.

Thin layer chromatography was performed on 5 × 20 cm plates of Mallinckrodt SilicAR TLC-7GF (250-nm thickness). Solvent systems employed were (1) $CHCl_3$–MeOH (19:1), (2) EtOAc–*n*-PrOH–H_2O (4:1:2, upper layer), and (3) 1,2-dimethoxyethane–MeOH–NH_4OH (12:1:1).

5-Carbomethoxy-4,7-dioxo-2-methylthiopyrido[2,3-*d*]pyrimidine (2). To a solution of 4-amino-2-methylthio-6-oxopyrimidine (**1**, 0.80 g, 5.1 mmol) in water (25 ml) was added DMAD (0.90 g, 6.3 mmol). The solution was heated at reflux for 2 h, then cooled to room temperature. The precipitate was filtered and washed with methanol to give 50 mg of **2.** An additional 84 mg was obtained after refrigeration of the filtrate: yield 134 mg (10%); mp 313 °C dec; UV (pH 1) 292 nm (ϵ 10 800), 325 (16 000); (pH 7) 256 (12 400), 330 (15 800); (pH 11) 331 (14 400); ^{1}H NMR δ 2.53 (s, 3 H, SCH_3), 3.73 (s, 3 H, OCH_3), 6.13 (s, 1 H, C-6 H), 12.57 (br s, 1 H, N-8 H).

Anal. Calcd for $C_{10}H_9N_3O_4S$: C, 44.9; H, 3.37; N, 15.7. Found: C, 44.6; H, 3.67; N, 15.4.

5-Carbomethoxy-2,4,7-trichloropyrido[2,3-*d*]pyrimidine (4). Compound **3**[2] (8.0 g, 33.8 mmol) was refluxed in $POCl_3$ (125 ml) containing *N,N*-diethylaniline (8.0 ml) for 10 h. The volume was reduced to approximately 25 ml by distillation at reduced pressure. The black syrup was poured onto excess ice and stirred vigorously by hand for 15 min. The iced water suspension was extracted three times with CH_2Cl_2. The CH_2Cl_2 extracts were extracted four times with cold 1 N HCl (250 ml), then dried over Na_2SO_4 and filtered through charcoal. Evaporation gave 6.7 g (68%) of red powder, which was dissolved in hot CH_2Cl_2 (50 ml). Petroleum ether (bp 90–120 °C) was added slowly to cloud point. Cooling gave white needles of pure **4** (4.96 g, 53%): mp 109–110 °C; MS *m/e* 291 (M^+), 260 (M − OCH_3), 256 (M − Cl), 232

(M − CO_2CH_3); UV (MeOH) 313 nm (ε 10 500); ^{1}H NMR δ 4.05 (s, 3 H, OCH_3), 7.58 (s, 1 H, C-6 H).

Anal. Calcd for $C_9H_4N_3O_2Cl_3$: C, 36.95; H, 1.38; N, 14.37. Found: C, 36.65; H, 1.32; N, 14.17.

4-Amino-5-carboxamido-2,7-dichloropyrido[2,3-*d*]pyrimidine (6). Compound 4 (300 mg, 1.0 mmol) was treated with methanolic ammonia (25 ml), saturated at 0 °C, for 24 h at room temperature. The white solid was filtered and washed with MeOH to give 219 mg (83%) of **6**: mp >310 °C; MS *m/e* 257 (M^+), 240 (M − NH_3), 205 (M − NH_3 − Cl); UV (pH 1) 314 nm (ε 8200); (pH 7) 314 (8700); (pH 11) 333 (8200); ^{1}H NMR δ 8.53 (br s, 2 H, 4-NH_2), 8.53, 8.73 (br s, 2 H, $CONH_2$), 7.58 (s, 1 H, C-6 H).

Anal. Calcd for $C_8H_5N_5OCl_2$: C, 37.32; H, 1.95; N, 27.14. Found: C, 37.11; H, 1.91; N, 26.94.

For large-scale reactions, it was found that the following procedure gave high yields. Compound **3** (12 g) was refluxed for 12 h in $POCl_3$ (125 ml) containing *N,N*-diethylaniline (12 ml). Excess $POCl_3$ was removed and the syrup poured into ice (1 kg). Extraction with CH_2Cl_2 followed by extraction with 1 N HCl was as before. Drying the CH_2Cl_2 extract with Na_2SO_4 followed by evaporation afforded crude **4**. Treatment of this solid with methanolic ammonia for 12 h and filtration of the solid gave 9.9 g (76% overall yield) of **6**, identical by TLC, UV, and ^{1}H NMR with **6** obtained directly from **4**.

4-Amino-7-benzyloxy-5-carboxamido-2-chloropyrido[2,3-*d*]pyrimidine (9). Compound **6** (7.74 g, 30 mmol) was suspended in Me_2SO (60 ml). Benzyl alcohol (35 ml), in which Na (1.04 g, 45 mmol) was previously dissolved, was added dropwise over 2 h. After another 2 h, the yellow solution was poured into H_2O (300 ml) and the solid filtered. Recrystallization from DMF–H_2O gave 7.9 g (76%) of **9**: mp 225 °C dec; MS *m/e* 329 (M^+), 223 (M − C_6H_5CHO); UV (pH 1) 320 nm (ε 15 300); (pH 7) 318 (8700); (pH 11) 318 (9200); ^{1}H NMR δ 8.20 (br s, 2 H, NH_2), 8.43, 8.70 (br s, 2 H, $CONH_2$), 7.05 (s, 6 H, C-7 H + C_6H_5).

Anal. Calcd for $C_{15}H_{12}N_5O_2Cl·H_2O$: C, 51.76; H, 4.02; N, 20.14. Found: C, 51.97; H, 4.19; N, 19.83.

4-Amino-7-benzyloxy-5-carboxamido-2-methylthiopyrido-[2,3-*d*]pyrimidine (10). To a solution of CH_3SNa in Me_2SO, prepared by adding CH_3SH to Me_2SO (15 ml) containing Na (140 mg, 6.1 mmol), was added **9** (1.0 g, 2.9 mmol). After stirring at room temperature for 90 min, the yellow solution was cautiously poured into H_2O (100 ml). The yellow precipitate was filtered to give 820 mg (79%) of **10**. Recrystallization from DMF–H_2O afforded 709 mg (68%): mp 264–266 °C dec; MS *m/e* 341 (M^+), 323 (M − NH_3), 235 (M − $OCHC_6H_5$); UV (pH 1) 261 nm (ε 25 400), 332 (19 200); (pH 7) 262 (30 300), 330 (13 600); (pH 11) 260 (31 500), 330 (13 000); ^{1}H NMR δ 2.53 (s, 3 H, SCH_3), 7.70 (br s, 2 H, NH_2), 8.33, 8.62 (br s, 2 H, $CONH_2$), 6.87 (s, 1 H, C-6H), 7.43 (s, 5 H, C_6H_5), 5.47 (s, 2 H, $-CH_2$).

Anal. Calcd for $C_{16}H_{15}N_5O_2S·H_2O$: C, 53.47; H, 4.79; N, 19.49. Found: C, 53.22; H, 5.00; N, 19.89.

4-Amino-5-carboxamido-2-methylthio-7-oxopyrido[2,3-*d*]-pyrimidine (11). Compound **10** (1.7 g, 4.7 mmol) was stirred with 48% HBr (15 ml) for 3 min. The solution was adjusted to pH 3 with 1 N NaOH and the solid filtered. The solid was dissolved in hot DMF followed by addition of H_2O to cloud point. Filtration afforded 620 mg (52%) of **11**: mp >320 °C; MS *m/e* 251 (M^+), 234 (M − NH_3); UV (pH 1) 325 nm (ε 16 200); (pH 7) 263 (20 900), 330 (15 900); (pH 11) 335 (13 700); ^{1}H NMR δ 2.50 (s, 3 H, SCH_3), 7.45 (br s, 2 H, NH_2), 8.27, 8.57 (br s, 2 H, $CONH_2$), 6.27 (s, 1 H, C-6 H), 12.03 (br s, 1 H, N-8 H).

Anal. Calcd for $C_9H_9N_5O_2S$: C, 43.02; H, 3.61; N, 27.87. Found: C, 43.08; H, 3.93; N, 28.00.

4-Amino-5-carboxamido-2-chloro-7-thioxopyrido[2,3-*d*]pyrimidine (12). Compound **6** (1.59 g, 6.1 mmol) was dissolved in DMF (50 ml) by warming. To this solution was added NaSH (450 mg) in portions until all starting material had reacted (TLC). The solvent was removed in vacuo, and the solid triturated with MeOH (200 ml)–H_2O (50 ml). Filtration afforded 1.21 g (77%) of **12**. Recrystallization was carried out by dissolving in warm DMF and adding H_2O to cloud point. Cooling to room temperature gave 875 mg (56%) of **12** as yellow crystals: mp >220 °C (dec slowly); MS *m/e* 255 (M^+), 238 (M − NH_3); UV (pH 1) 266 nm (ε 12 500), 294 (9300), 385 (15 900); (pH 7) 270 (16 000), 373 (14 000); (pH 11) 272 (19 300), 368 (14 700); ^{1}H NMR δ 8.16 (br s, 2 H, NH_2), 8.33, 8.73 (br s, 2 H, $CONH_2$), 7.08 (s, 1 H, C-6H), 13.75 (br s, 1 H, N-8 H).

Anal. Calcd for $C_8H_6N_5OSCl$: C, 37.58; H, 2.37; N, 27.39. Found: C, 37.81; H, 2.47; N, 27.43.

4-Amino-5-carboxamido-2-chloropyrido[2,3-*d*]pyrimidine (13). Compound **12** (400 mg, 1.57 mmol) was dissolved in DMF (50 ml) and EtOH (10 ml). Raney nickel (2.5 g) was added, the mixture refluxed for 1 h and filtered through Celite, and the filtrate evaporated in vacuo. The solid was dissolved in hot DMF, water added to cloud point, and cooled. Filtration gave 196 mg (57%) of **13** as yellow crystals: mp >210 °C (dec slowly); MS *m/e* 223 (M^+), 206 (M − NH_3), 171 (M − NH_3 − Cl); UV (pH 1) 326 nm (ε 6 500); (pH 7) 326 (6400); (pH 11) 326 (6300); ^{1}H NMR δ 8.45 (br s, 2 H, NH_2), 8.48, 8.70 (br s, 2 H, $CONH_2$), 7.53 (d, 1 H, C-6 H), 9.03 (d, 1 H, C-7 H, $J_{6,7}$ = 4.8 Hz).

Anal. Calcd for $C_8H_6N_5OCl$: C, 42.97; H, 2.70; N, 31.32. Found: C, 43.09; H, 2.98; N, 31.12.

4,7-Dioxo-2-methylthiopyrido[2,3-*d*]pyrimidine-5-carboxylic Acid (14). Method A. To a solution of $NaNO_2$ in H_2O (12 ml)–H_2SO_4 (4 ml) was added **11** (251 mg, 1.0 mmol). After stirring for 4 h, the yellow precipitate was filtered. TLC showed two products. The solid was refluxed in 1 N NaOH (10 ml) for 1 h. After cooling, the pH was adjusted to ~3 with HCl. The white precipitate was filtered to give 169 mg (58%) of **14**: mp >320 °C (slowly dec >275 °C); MS: *m/e* 253 (M^+), 209 (M − CO); UV (pH 1) 292 nm (ε 10 500), 326 (15 600); (pH 7) 291 (9 000), 324 (15 900); (pH 11) 255 (16 000), 327 (16 300); ^{1}H NMR δ 2.47 (s, 3 H, SCH_3), 6.95 (s, 1 H, C-6 H).

Anal. Calcd for $C_9H_7N_3O_4S·2H_2O$: C, 37.37; H, 3.87; N, 14.52. Found: C, 36.99; H, 3.69; N, 14.48.

Method B. Compound **2** (300 mg, 1.1 mmol) was refluxed in 1 N NaOH (10 ml) for 30 min. After cooling, the pH was adjusted to ~3 with HCl. The white precipitate was filtered to give 223 mg (69%) of **14**. One recrystallization from H_2O gave a sample which was identical by TLC, UV, mass spectrum, and ^{1}H NMR with **14** obtained by method A.

5-Carbomethoxy-7-chloro-2,4-dioxopyrido[2,3-*d*]pyrimidine (15). To **4** (585 mg, 2.0 mmol), dissolved in MeOH (50 ml), was added 1 N NaOH (3 ml, 3 mmol). The solution was stirred for 2 h at 30 °C. Evaporation to about 5 ml followed by addition of H_2O (20 ml) gave a white precipitate. This was filtered to give 248 mg (49%) of **15**: mp 310–313 °C dec; MS *m/e* 255 (M^+), 224 (M − OCH_3), 197 (M − OCH_3 − HCNO); uv (pH 1) 311 nm (ε 6700); (pH 7) 312 (6500); (pH 11) 268 (10 500), 323 (4700); ^{1}H NMR δ 3.87 (s, 3 H, OCH_3), 7.42 (s, 1 H, C-6 H).

Anal. Calcd for $C_9H_6N_3O_4Cl$: C, 42.29; H, 2.37; N, 16.44. Found: C, 41.98; H, 2.58; N, 16.34.

5-Carbomethoxy-2,4-dioxopyrido[2,3-*d*]pyrimidine (16). Compound **15** (155 mg, 0.61 mmol), NaOAc (92 mg), and 10% Pd/C (100 mg) were placed in a hydrogenator in MeOH (100 ml) and shaken over H_2 (42 psi) for 60 h. The mixture was filtered through Celite and washed with MeOH. The filtrate was evaporated to dryness and triturated with H_2O. Filtration of the solid gave 89 mg (67%) of **16**. For analysis 50 mg was recrystallized from MeOH–H_2O to give 37 mg: mp 265 °C dec; UV (pH 1) 315 nm (9 600); (pH 7) 3.6 (8700); (pH 11) 273 (14 400), 340 (6300); ^{1}H NMR δ 3.88 (s, 3 H, OCH_3), 7.25 (d, 1 H, C-6H), 8.70 (d, 1 H, C-7H), 8.70 (d, 1 H, C-7 H, $J_{6,7}$ = 4.8 Hz).

Anal. Calcd for $C_9H_7N_3O_4$: C, 48.88; H, 3.19; N, 19.00. Found: C, 48.68; H, 3.38; N, 18.64.

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Registry No.—**1**, 1074-41-5; **2**, 61129-14-4; **3**, 57821-16-6; **4**, 61129-15-5; **6**, 61129-16-6; **9**, 61129-17-7; **10**, 61129-18-8; **11**, 61129-19-9; **12**, 61129-20-2; **13**, 61129-21-3; **14**, 61129-22-4; **15**, 61129-23-5; **16**, 61129-24-6; DMAD, 762-42-5; *N,N*-diethylaniline, 91-66-7; benzyl alcohol, 100-51-6.

References and Notes

(1) Part 5 in this series: A. D. Broom and D. G. Bartholomew, *J. Org. Chem.*, **41**, 3027 (1976).
(2) A. D. Broom, J. L. Shim, and G. L. Anderson, *J. Org. Chem.*, **41**, 1095 (1976).
(3) H. Orgura and M. Sakaguchi, *Chem. Pharm. Bull.*, **21**, 2014 (1973).
(4) G. L. Anderson and A. D. Broom, *J. Org. Chem.*, following paper in this issue.
(5) R. K. Robins and G. H. Hitchings, *J. Am. Chem. Soc.*, **77**, 2256 (1955).
(6) R. G. Shepherd and J. L. Fedrick, *Adv. Heterocycl. Chem.*, **4**, 146 (1964).
(7) B. S. Hurlbert, K. W. Ledig, P. Stenbuck, B. F. Valenti, and G. H. Hitchings, *J. Med. Chem.*, **11**, 703 (1968).
(8) L. M. Jackman and S. Sternhill, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, Oxford, 1969, p 361.
(9) T. Tsuji, S. Watanabe, Y. Nakadai, and S. Toyoshima, *Chem. Pharm. Bull.*, **10**, 9 (1962).

Pyridopyrimidines. 7. Ribonucleosides Structurally Related to the Antitumor Antibiotic Sangivamycin

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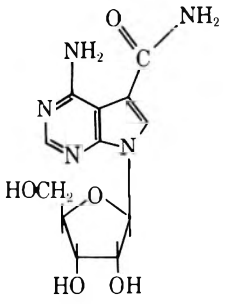
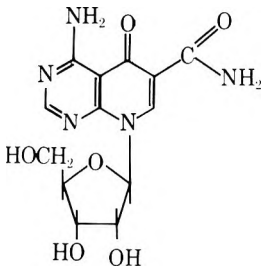
The synthesis and characterization of some new pyrido[2,3-*d*]pyrimidine ribonucleosides structurally related to the pyrrolo[2,3-*d*]pyrimidine antibiotic sangivamycin are reported. These include the N-8 ribonucleosides of 6-carboxamido-2,4-diamino-5-oxopyrido[2,3-*d*]pyrimidine, the isomeric 5-carboxamido-7-oxo derivative, and 4-amino-5-carboxamido-7-oxopyrido[2,3-*d*]pyrimidine.

The potent antileukemic activity[1] of the pyrrolo[2,3-*d*]-pyrimidine nucleoside antibiotic sangivamycin (**1**) prompted the synthesis of the pyrido[2,3-*d*]pyrimidine nucleoside **2**.[2]



1



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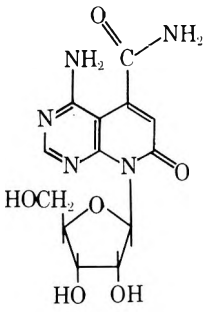
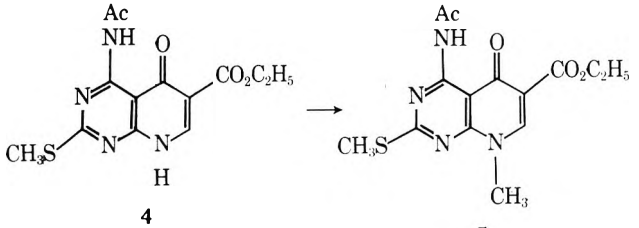


3

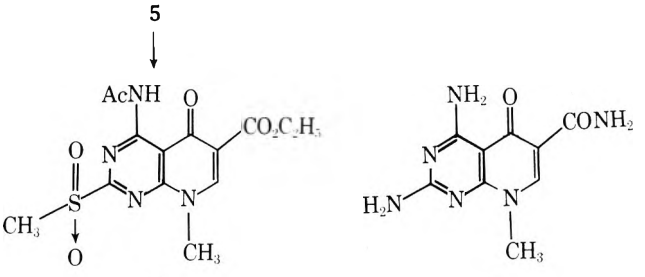
This compound, which may be regarded as a simple homologue of sangivamycin, was also found to have confirmed antileukemic activity.[3] These findings have led to a further investigation into the synthesis of ribonucleosides of pyrido[2,3-*d*]pyrimidines bearing the carboxamide group in either the 5 or 6 position. The present report describes the synthesis and characterization of a number of such nucleosides, the prototype molecule in this study being the 5-carboxamido-7-oxo isomer **3**.

The initial goal of this study was to extend the earlier work[2] to the synthesis of 6-carboxamido-2,4-diamino-5-oxo-8-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine. This reaction required a good leaving group in the 2 position of the pyridopyrimidine; it was decided that the initial exploration would be carried out using readily accessible bases by oxidation of the methylthio group followed by nucleophilic displacement. Alkylation of 4-acetamido-6-carbethoxy-2-methylthio-5-oxopyrido[2,3-*d*]pyrimidine (**4**)[2] with methyl iodide gave the 8-methyl derivative **5**. The position of alkylation is supported by the similarity of the UV spectrum of **5** to that of the previously reported[2] N-8 nucleoside of **4**. It has previously been shown that substitution of an alkyl group for hydrogen on the nitrogen of a potentially tautomeric heteroaromatic system results in a substantial downfield shift of the ^{1}H NMR signal for an adjacent proton.[4] A downfield shift of the C-7 H resonance of 0.35 ppm in **5** relative to that of **4** confirms N-8 alkylation.



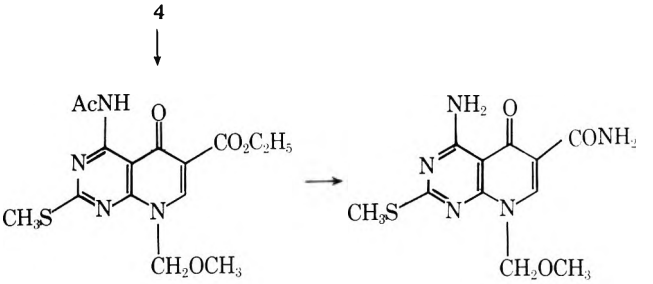
4 **5**

Oxidation of **5** with *m*-chloroperbenzoic acid yielded 4-acetamido-6-carbethoxy-8-methyl-2-methylsulfonyl-5-oxopyrido[2,3-*d*]pyrimidine (**6**). It has been shown that the methyl group will be shifted about 0.5 ppm downfield when a methylthio is oxidized to the methylsulfinyl and about 1.0 ppm when oxidized to the methylsulfonyl[5] in the pyridazine series. The shift of over 1 ppm from the methylthio of **5** is indicative of oxidation to the methylsulfonyl of (**6**). Treatment of **6** with liquid ammonia did not give the desired diamino carboxamide compound **7** as judged by the ^{1}H NMR spectrum of the product, which still had signals attributed to the ethyl ester. This was somewhat surprising in view of the previous conversion of the ester to the amide in the nucleoside series under identical conditions.[2]



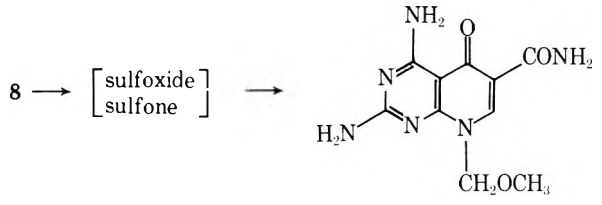
6 **7**

The replacement of the N-8 methyl with an N-8 methoxymethyl group did lead to the desired reaction. Compound **4** was alkylated with α-chloromethyl ether to give 4-acetamido-6-carbethoxy-8-methoxymethyl-2-methylthio-5-oxopyrido[2,3-*d*]pyrimidine (**8**).



8 **9**

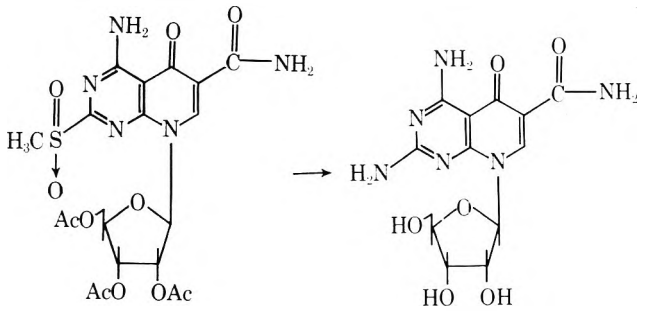
Alkylation at N-8 was supported by the similarity of the UV spectra and the downfield shift of C-7 H (0.63 ppm) as described previously. Upon treatment of **8** with liquid ammonia a good yield of 4-amino-6-carboxamido-8-methoxymethyl-2-methylthio-5-oxopyrido[2,3-*d*]pyrimidine (**9**) was obtained. Oxidation of **8** with *m*-chloroperbenzoic acid gave a mixture of two compounds, which by ^{1}H NMR spectroscopy appeared to be the corresponding sulfoxide and sulfone. This mixture was obtained even when the oxidizing agent was used in excess. The mixture was treated with liquid ammonia to give a good yield of 6-carboxamido-2,4-diamino-8-methoxymethyl-5-oxopyrido[2,3-*d*]pyrimidine (**10**). The difference



10

in reactivity of the esters of **6** and the oxidation products of **8** toward liquid ammonia may be explained by the electron-withdrawing effect of the methoxymethyl group which decreases electron density at the carbonyl carbon atom resulting in enhancement of reactivity, as compared to the electron-donating effect of the methyl group.[6] The ^{1}H NMR spectra of **9** and **10** were similar except that the methylthio signal at δ 2.53 of **9** was replaced by a broad singlet at δ 6.80 for the 2-amino group of **10.** These reactions demonstrated that the methylthio group in the 2 position could be easily converted to a group which would undergo nucleophilic displacement under conditions which would not disrupt the nucleoside.

This procedure was extended to the ribonucleoside series using 4-amino-6-carboxamido-2-methylthio-5-oxo-8-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine.[2] Acetylation gave the tri-*O*-acetyl derivative **11** which underwent *m*-chloroperbenzoic acid oxidation smoothly to give the tri-*O*-acetyl-2-methylsulfonyl derivative **12.** The ^{1}H NMR signal for the methylsulfonyl group appeared at δ 3.29, 0.66 ppm downfield from the methylthio group of **11;** this value is intermediate between the 0.5 and 1.0 ppm downfield shifts predicted for methylsulfinyl and methylsulfonyl, respectively.[5] The presence of the methylsulfonyl group was confirmed by the observation of a molecular ion at *m/e* 541 in the mass spectrum of **12.** Nucleophilic displacement of the methylsulfonyl group and deblocking of the sugar of **12** was accomplished with liquid ammonia to give compound **13.** The amino group at the 2

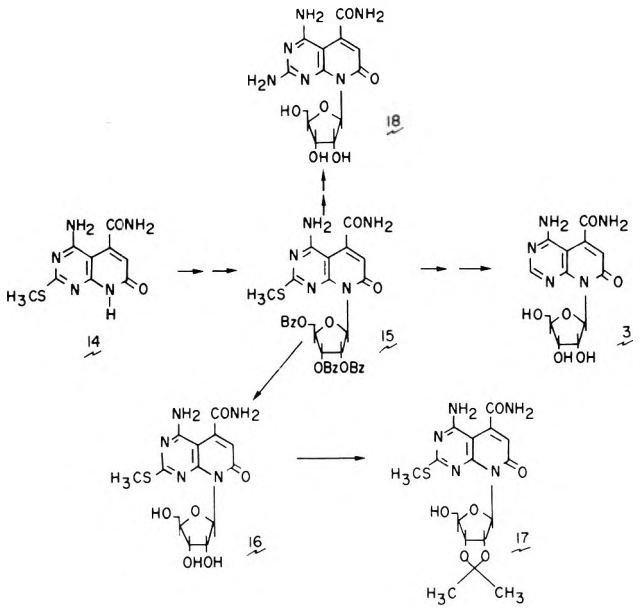


12 **13**

position was confirmed by the signal in the ^{1}H NMR spectrum at δ 6.78.

The synthesis of the sangivamycin homologue **3** required attachment of a β-D-ribofuranosyl moiety to the **8** position of 4-amino-5-carboxamido-2-methylthio-7-oxopyrido[2,3-*d*]-pyrimidine (**14**). The use of trimethylsilyl derivatives of nitrogen heterocycles circumvented difficulties associated with the low solubility and high melting point of **14.** Reaction (Scheme I) of **14** with hexamethyldisilazane gave the tris-

Scheme I



(trimethylsilyl) derivative which, when treated with freshly prepared 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in dry toluene in the presence of a mercuric bromide–mercuric oxide catalyst,[7] gave a complex mixture from which 4-amino-5-carboxamido-2-methylthio-7-oxo-8-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (**15**) was isolated by a chromatographic procedure. Treatment of **15** with methanolic sodium methoxide gave 4-amino-5-carboxamido-2-methylthio-7-oxo-8-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (**16**). Assignment of the β configuration was made by conversion of **16** to the 2′,3′-*O*-isopropylidene derivative **17.** The small coupling constant for the anomeric proton ($J_{1,2}$ < 1.0 Hz) permits assignment of β configuration.[8] Further support lies in the difference in the chemical shifts; $\Delta\delta$ of the methyl groups on the isopropylidene is 0.20, within the accepted range for β nucleosides of $0.18 \leq \Delta\delta \leq 0.23$.[9] The mass spectrum of **17** exhibited a signal at 423 amu corresponding to the molecular ion. The site of alkylation was established as N-8 by UV and ^{1}H NMR spectroscopy. The UV spectra of the nucleoside **16** and the starting pyridopyrimidine **14** were very similar at pH 1 and 7. The ^{1}H NMR spectra of **14** and **16** revealed almost identical chemical shifts for all the base protons. In contrast, the spectrum of 4-amino-7-benzyloxy-5-carboxamido-2-methylthiopyrido[2,3-*d*]pyrimidine,[10] an example of the lactim tautomer which would have resulted from O-7 alkylation, shows a signal for C-6 H at δ 6.87, 0.60 ppm downfield for C-6 H of **14** and **16.**

The blocked nucleoside **15** was treated (Scheme I) with Raney nickel followed by treatment with methanolic sodium methoxide to give the sangivamycin analogue, 4-amino-5-carboxamido-7-oxo-8-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (**3**). The ^{1}H NMR spectrum of **3** revealed the loss of the signal due to the protons of the 2-methylthio function and the presence of two one-proton singlets corresponding to C-2 H (δ 8.33) and C-6 H (δ 6.45).

Finally, oxidation of the blocked nucleoside **15** with *m*-chloroperbenzoic acid followed by treatment with liquid ammonia and deblocking with methanolic methoxide afforded (Scheme I) the 5-carboxamido-2,4-diamino-7-oxo-8-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (**18**).

Experimental Section

The ^1H NMR spectra were recorded on a Jeol C-60H spectrometer with tetramethylsilane or DSS as an internal standard. Chemical shifts are expressed as δ, parts per million, from the standard. Ultraviolet spectra were obtained on a Cary Model 15 spectrophotometer. Mass spectra were recorded on a LKB-GC MS Model 9000S at 70 keV. Only the molecular ion and first major fragments are reported. Elemental analyses were performed by Het-Chem-Co, Harrisonville, Mo. Melting points were determined on a Thomas-Hoover Unimelt and are uncorrected. All analytical samples were dried in the presence of P_2O_5 in vacuo.

Thin layer chromatography was performed on 5 × 20 cm plates of Mallinckrodt SilicAR TLC-7GF (250-nm thickness). Solvent systems employed were (1) $CHCl_3$–MeOH (19:1), (2) EtOAc–*n*-PrOH–H_2O (4:1:2, upper layer), and (3) 1,2-dimethoxyethane–MeOH–NH_4OH (12:1:1).

4-Acetamido-6-carbethoxy-8-methyl-2-methylthio-5-oxopyrido[2,3-*d*]pyrimidine (5). 4-Acetamido-6-carbethoxy-2-methylthio-5-oxopyrido[2,3-*d*]pyrimidine (**4**,[2] 1.49 g, 4.64 mmol) was dissolved in DMF (50 ml). Anhydrous potassium carbonate (700 mg) and methyl iodide (720 mg, 5 mmol) were added. The suspension was stirred at 25 °C for 3 h, then filtered. The filtrate was evaporated in vacuo and coevaporated with toluene and ethanol to yield a yellow solid. This was dissolved in boiling ethanol, filtered through charcoal–Celite, and cooled to 5 °C. Filtration afforded 1.31 g (84%) of **5**: mp 191 °C; UV (pH 1) 281 nm (ε 44 600); (pH 7) 281 (45 000); (pH 11) 279 (42 800); ^1H NMR δ 2.55 (s, 3 H, SCH_3), 2.50 (s, 3 H, CH_3CO), 3.73 (s, 3 H, NCH_3), 8.65 (s, 1 H, C-7 H).

Anal. Calcd for $C_{14}H_{16}N_4O_4S$: C, 49.99; H, 4.79; N, 16.66. Found: C, 49.80; H, 4.85; N, 16.76.

4-Acetamido-6-carbethoxy-8-methyl-2-methylsulfonyl-5-oxopyrido[2,3-*d*]pyrimidine (6). To a suspension of **5** (336 mg, 1 mmol) in EtOAc (50 ml) was added a solution of *m*-chloroperbenzoic acid (600 mg, 3 mmol) in EtOAc (10 ml). The solvent was evaporated in vacuo after 4 h. The solid was dissolved in chloroform (100 ml) and extracted twice with 10% aqueous sodium bicarbonate (40 ml). The chloroform layer was dried over sodium sulfate and evaporated to yield a white solid. Recrystallization twice from ethanol–water afforded 106 mg (28%) of **6**: mp 171–173 °C; UV (pH 1) 269 nm (ε 41 600), 311 (14 000); (pH 7) 268 (43 100), 311 (14 200); (pH 11) 266 (60 000), 307 (12 900); ^1H NMR δ 3.80 (s, 3 H, SO_2CH_3), 2.47 (s, 3 H, CH_3CO), 3.90 (s, 3 H, NCH_3), 8.80 (s, 1 H, C-7 H).

Anal. Calcd for $C_{14}H_{15}N_4O_6S·0.5H_2O$: C, 44.56; H, 4.54; N, 14.85. Found: C, 44.59; H, 4.68; N, 14.83.

4-Acetamido-6-carbethoxy-8-methoxymethyl-2-methylthio-5-oxopyrido[2,3-*d*]pyrimidine (8). To a suspension of compound **4** (645 mg, 2 mmol) and K_2CO_3 (800 mg) in DMF (10 ml) was added methyl α-chloromethyl ether[11] (0.17 ml, 2.22 mmol). After stirring for 1 h at room temperature, the mixture was filtered and washed with DMF. The filtrate was evaporated in vacuo to give a white solid. This was recrystallized from EtOH to yield 530 mg (72%) of **8**: mp 154–156 °C; UV (pH 1) 275 nm (ε 45 100); (pH 7) 276 (44 700), 274 (42 800); ^1H NMR δ 2.65 (s, 3 H, SCH_3), 2.57 (s, 3 H, CH_3CO), 3.40 (s, 3 H, CH_3O), 5.80 (s, 2 H, OCH_2), 8.93 (s, 1 H, C-7 H).

Anal. Calcd for $C_{15}H_{18}N_4O_5S·0.5H_2O$: C, 48.04; H, 5.10; N, 14.92. Found: C, 47.81; H, 4.94; N, 15.15.

4-Amino-6-carboxamido-8-methoxymethyl-2-methylthio-5-oxopyrido[2,3-*d*]pyrimidine (9). Compound **8** (3.75 g, 10 mmol) was treated with liquid ammonia (60 ml) in a glass-lined bomb for 48 h at room temperature. Evaporation of the ammonia gave a solid which was recrystallized from DMF to yield 2.35 g (77%) of **9**. Dissolution in hot DMF, then addition of H_2O to the cloud point and cooling afforded an analytical sample: mp 286–288 °C; UV (pH 1) 275 nm (ε 40 000); (pH 7) 274 (43 400); (pH 11) 274 (43400); ^1H NMR δ 2.53 (s, 3 H, SCH_3), 7.63, 8.92 (br s, 2 H, NH_2, $J_{HNH} \sim 4$ Hz), 8.42, 9.42 (br s, 2 H, $CONH_2$, $J_{HNH} \sim 4$ Hz), 3.37 (s, 3 H, CH_3O), 5.70 (s, 2 H, OCH_2), 8.80 (s, 1 H, C-7 H).

Anal. Calcd for $C_{11}H_{13}N_5O_3S·0.5H_2O$: C, 43.38; H, 4.64; N, 23.01. Found: C, 43.61; H, 4.68; N, 23.27.

6-Carboxamido-2,4-diamino-8-methoxymethyl-5-oxopyrido-[2,3-*d*]pyrimidine (10). To compound **8** (2.75 g, 7.33 mmol) in $CHCl_3$ (150 ml) at 5 °C was added *m*-chloroperbenzoic acid (3.75 g, 18.7 mmol) and the solution was stirred for 3 h. The solvent was removed in vacuo and the residue triturated with Et_2O (50 ml), then filtered to give a white solid. This solid was treated with liquid ammonia (70 ml) in a glass-lined bomb at room temperature for 72 h. After evaporation of the ammonia, the solid was recrystallized from DMF–H_2O to give 1.35 g (68%) of **10**. One further recrystallization from DMF–H_2O afforded an analytical sample: mp 290–291 °C; UV (pH 1) 265 nm (ε 45 000); (pH 7) 265 (35 500); (pH 11) 265 (36 900); ^1H NMR δ 6.80 (br s, 2 H, 2-NH_2), 7.60, 9.03 (br d, 2 H, 4-NH_2, $J_{HNH} \sim 4$ Hz), 8.59, 9.22 (br d, 2 H, $CONH_2$, $J_{HNH} \sim 4$ Hz), 3.32 (s, 3 H, CH_3O), 5.70 (s, 2 H, OCH_2), 8.59 (s, 1 H, C-7 H).

Anal. Calcd for $C_{10}H_{12}N_6O_3·0.5H_2O$: C, 43.95; H, 4.79; N, 30.76. Found C, 44.29; H, 4.71; N, 30.55.

4-Amino-6-carboxamido-2-methylthio-5-oxo-8-(2,3,5-tri-*O*-acetylribofuranosyl)pyrido[2,3-*d*]pyrimidine (11). 4-Amino-6-carboxamido-2-methylthio-5-oxo-8-(β-D-ribofuranosyl)-pyrido[2,3-*d*]pyrimidine (2.5 g, 6.2 mmol)[2] was stirred in pyridine (35 ml)–acetic anhydride (60 ml) for 48 h at 40 °C. The solution was evaporated in vacuo and coevaporated three times each with toluene and ethanol. The residue was dissolved in hot ethanol (300 ml)–chloroform (100 ml), and treated with charcoal. Filtration and evaporation to ≈250 ml gave a white precipitate which was filtered to give 3.03 g (93%) of **11**: mp 229–232 °C dec; MS *m/e* 509 (M^+); UV (pH 1) 275 nm (ε 40 000); (pH 7) 275 (40 000); (pH 11) 275 (41 000); ^1H NMR δ 8.77 (s, 1 H, C-7 H), 6.57 (d, 1 H, C-1′H, $J_{1'2'}$ = 3.0 Hz), 2.43 (s, 3 H, SCH_3).

Anal. Calcd for $C_{20}H_{23}N_5O_9S·H_2O$: C, 45.54; H, 4.78; N, 13.28. Found: C, 45.19; H, 4.79; N, 12.96.

4-Amino-6-carboxamido-2-methylsulfonyl-5-oxo-8-(2,3,5-tri-*O*-acetylribofuranosyl)pyrido[2,3-*d*]pyrimidine (12). To a suspension of **11** (527 mg, 1 mmol) in 1,2-dimethoxyethane (50 ml) was added *m*-chloroperbenzoic acid (500 mg, 2.5 mmol). After 15 min a clear solution resulted. After 8 h the solvent was removed in vacuo to give a white powder which was recrystallized from ethanol to yield 475 mg (88%) of **12**. One further recrystallization from ethanol afforded **12** as white needles: mp 225–226 °C dec; MS *m/e* 541 (M^+); UV (pH 1) 275 nm (ε 18 400); (pH 7) 275 (18 100); (pH 11) 268 (36 900); ^1H NMR (s, 1 H, C-7 H), 6.51 (d, 1 H, C-1′H, $J_{1'2'}$ = 2.3 Hz), 3.29 (s, 3 H, SO_2CH_3).

Anal. Calcd for $C_{20}H_{23}N_5O_{11}S$: C, 44.36; H, 4.28; N, 12.93. Found: C, 44.41; H, 4.57; N, 12.76.

6-Carboxamido-2,4-diamino-5-oxo-8-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (13). Compound **12** (5.47 g, 10 mmol) was treated with liquid ammonia (90 ml) in a glass-lined bomb for 36 h at room temperature. The ammonia was evaporated to give a white solid. The solid was dissolved in boiling H_2O, filtered through a charcoal pad, and cooled to 5 °C. The white, gelatinous precipitate was filtered to give 2.4 g (68%) of **13**. One further recrystallization from H_2O afforded an analytical sample: mp 265 °C dec; UV (pH 1) 266 nm (ε 45 000); (pH 7) 252 (27 700), 267 (35 800); (pH 11) 252 (27 400), 267 (35 800); ^1H NMR δ 8.66 (s, 1 H, C-7 H), 6.46 (d, 1 H, C-1′ H, $J_{1'2'}$ = 4.2 Hz).

Anal. Calcd for $C_{13}H_{16}N_6O_6$: C, 44.32; H, 4.58; N, 23.85. Found: C, 44.51; H, 4.78; N, 23.68.

4-Amino-5-carboxamido-2-methylthio-7-oxo-8-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (15). Compound **14** (6.02 g, 24 mmol) was refluxed in toluene (250 ml) with hexamethyldisilazane (15 ml) and a few crystals of ammonium sulfate for 18 h. The clear solution was filtered through a sintered-glass funnel using a vacuum pump equipped with a manostat to prevent foaming of filtrate. The solvent was removed in vacuo to a yellow solid (hygroscopic!). Mass spectrum indicates that three trimethylsilyl groups are present [*m/e* 467 (M^+)]. This was dissolved in anhydrous benzene (150 ml) containing $HgBr_2$ (7.5 g) and HgO (7.5 g). To this suspension was added 2,3,5-tri-*O*-benzoylribofuranosyl bromide [prepared from 1-acetyl-2,3,5-tri-*O*-benzoylribofuranose (15.2 g, 30 mmol)][12] in benzene. The mixture was refluxed for 10 h, cooled, and filtered. The filtrate was evaporated to give an oily solid. This was dissolved in $CHCl_3$ (300 ml) and extracted with 15% aqueous KI (3 × 200 ml), H_2O (200 ml), then saturated $NaHCO_3$ (200 ml) and dried over $MgSO_4$. Evaporation of the solvent gave a red oil which was dissolved in $CHCl_3$ (20 ml) and applied to a silica gel column (460 g). Elution was with $CHCl_3$ (1000 ml), then MeOH in $CHCl_3$, 0.5% (820 ml), 1% (800 ml), 2% (800 ml), 3% (1000 ml), and 4.5% (1000 ml). Fractions of 20 ml were collected. Fractions 251–286 were evaporated to dryness to give 6.57 g (39%) of **15**. Preceding this compound off the column was a complex mixture of compounds which was not investigated.

4-Amino-5-carboxamido-2-methylthio-7-oxo-8-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (16). To MeOH (40 ml), in which Na (300 mg) was previously dissolved, was added **15** (850 mg, 1.22 mmol). The solution was stirred at room temperature for 4 h. After neutralization with HOAc, the solvent was removed in vacuo. The residue was coevaporated with H_2O–EtOH (1:1) (20 ml) three times to give a solid. This recrystallized from H_2O to give 347 mg (74%) of **16**: mp 248 °C (effervescence); MS *m/e* 743 (M^+) for penta-Me_3Si derivative; UV (pH 1) 258 nm (ε 15 300), 331 (14 400); (pH 7) 264 (16 600), 336 (14 600); (pH 11) 264 (16 600), 336 (14 600); ^1H NMR

δ 6.31 (s, 1 H, C-6 H), 6.82 (d, 1 H, C-1′ H, $J_{1'2'}$ = 3.5 Hz), 2.53 (s, 3 H, SCH_3).

Anal. Calcd for $C_{14}H_{17}N_5O_6S$: C, 43.99; H, 4.45; N, 18.30. Found: C, 43.68; H, 4.63; N, 18.41.

4-Amino-5-carboxamido-2-methylthio-7-oxo-8-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (17). To DMF (4 ml) was added 1 drop of concentrated HCl and 0.6 ml of dimethoxypropane. After stirring for 1 h, **16** (60 mg) was added and the suspension stirred for 1 h. Ammonium hydroxide solution was added until pH 8 was obtained. The solution was evaporated in vacuo to give a white solid. The solid was dissolved in MeOH (3 ml)–H_2O (3 ml). Removal of MeOH in vacuo and filtration gave 44 mg (80%) of **17**: MS *m/e* 423 (M^+); ^1H NMR δ 6.35 (s, 1 H, C-6 H), 7.02 (s, 1 H, C-1′ H, $J_{1'2'}$ < 1.0 Hz), 1.32, 1.52 [2 s, 6 H, $C(CH_3)_2$], 2.50 (s, 3 H, SCH_3).

4-Amino-5-carboxamido-7-oxo-8-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (3). Compound **15** (1.0 g, 1.44 mmol) was refluxed in EtOH (100 ml) containing Raney nickel (3 g) for 12 h. Additional Raney nickel (3 g) was added and reflux continued for an additional 24 h. The reaction mixture was filtered while hot through Celite and the nickel washed with an additional 100 ml of hot EtOH. Evaporation of the filtrate to dryness gave 797 mg of oily solid which was dissolved in MeOH (100 ml). MEOH (10 ml), in which Na (100 mg) was previously dissolved, was added and the solution was stirred at room temperature overnight. H_2O (30 ml) was added, the pH was adjusted to 7 with Dowex 50-X8 (H^+), and the solution was filtered. Evaporation, followed by coevaporation with EtOH–H_2O three times, gave a white solid. Recrystallization from H_2O gave 209 mg (43%) of **3**: mp 240 °C dec; MS *m/e* 697 (M^+) for penta-Me_3Si derivative; UV (pH 1) 297 nm (ε 9500), 313 (sh, 7800; (pH 7) 250 (11 800), 322 (9000); (pH 11) 250 (11 100), 322 (8300); ^1H NMR δ 6.45 (s, 1 H, C-6 H), 8.33 (s, 1 H, C-24), 6.87 (d, 1 H, C-1′ H, $J_{1'2'}$ = 3.4 Hz), 7.50 (br s, 2 H, 4-NH_2), 8.30 8.60 (2 br s, 2 H, $CONH_2$).

Anal. Calcd for $C_{13}H_{15}N_5O_6$: C, 46.29; H, 4.48; N, 20.76. Found: C, 46.58; H, 4.78; N, 20.48.

5-Carboxamido-2,4-diamino-7-oxo-8-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine (18). Compound **15** (795 mg, 1.0 mmol) was dissolved in $CHCl_3$ (50 ml) containing m-chloroperbenzoic acid (400 mg, 2 mmol). After stirring for 3 h, the solvent was removed in vacuo. The solid was triturated with Et_2O and filtered. The white powder was treated with liquid NH_3 (30 ml) in a glass bomb for 18 h. Evaporation of the ammonia gave an oily solid which was dissolved in MeOH (50 ml) in which Na (23 mg) was previously dissolved. After stirring for 3 h at room temperature, the pH was adjusted to 7 with Dowex 50-X8 (H^+). The resin was removed by filtration and the filtrate evaporated in vacuo, then coevaporated three times with EtOH–H_2O. The residue was triturated with $CHCl_3$ (50 ml) and filtered. The solid was dissolved in H_2O–EtOH by heating. Cooling gave a precipitate, which was filtered and washed with EtOH and Et_2O to give 195 mg (55%) of **18**: mp 192 °C dec; UV (pH 1) 300 nm (ε 13 500), 327 (13 500); (pH 7) 342 (14 600); (pH 11) 342 (14 600); ^1H NMR δ 5.93 (s, 1 H, C-6 H), 6.77 (d, 1 H, C-1′ H, $J_{1'2'}$ = 3.0 Hz).

Anal. Calcd for $C_{13}H_{16}N_6O_6 \cdot 2H_2O$: C, 40.21; H, 5.19; N, 21.64. Found: C, 39.99; H, 5.31; N, 21.57.

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Registry No.—**3**, 61140-07-6; **4**, 36707-44-5; **5**, 61140-08-7; **6**, 61140-09-8; **8**, 61140-10-1; **8** sulfoxide, 61140-11-2; **8** sulfone, 61140-12-3; **9**, 61140-13-4; **10**, 61140-14-5; **11**, 61140-15-6; **12**, 61140-16-7; **13**, 61140-17-8; **14**, 61129-19-9; **15**, 61140-18-9; **16**, 61140-19-0; **17**, 61140-20-3; **18**, 61140-21-4; methyl α-chloromethyl ether, 107-30-2; 4-amino-6-carboxamido-2-methylthio-5-oxo-8-(β-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine, 36707-04-7; 2,3,5-tri-*O*-benzoylribofuranosyl bromide, 16205-60-0.

References and Notes

(1) J. A. Cairns et al., *Cancer Chemother. Rep.*, **51**, 197 (1967).
(2) B. H. Rizkalla and A. D. Broom, *J. Org. Chem.*, **37**, 3980 (1972).
(3) Antileukemic activity data (L1210 mouse tumor) are available from Drug Development Branch, National Cancer Institute, by citing NSC 177223.
(4) A. D. Broom and R. K. Robins, *J. Org. Chem.*, **34**, 1025 (1969).
(5) T. Sega, A. Pollack, B. Stanovnik, and M. Tisler, *J. Org. Chem.*, **38**, 3307 (1973).
(6) A. L. J. Beckwith in "The Chemistry of Amides", J. Zabicky, Ed., Wiley-Interscience, New York, N.Y., 1970, p 73.
(7) E. Wittenburg, *Chem. Ber.*, **101**, 1095 (1968).
(8) R. U. Lemieux and D. R. Lineback, *Annu. Rev. Biochem.*, **32**, 155 (1963).
(9) J. L. Imbach, J. L. Barascut, B. L. Kam, B. Rayner, C. Tamby, and C. Tapiero, *J. Heterocycl. Chem.*, **10**, 1069 (1973).
(10) G. L. Anderson, J. L. Shim, and A. D. Broom, *J. Org. Chem.*, preceding paper in this issue.
(11) Methyl α-chloromethyl ether has been reported to be carcinogenic and should be handled with extreme caution.
(12) J. D. Stevens, R. K. Ness, and H. G. Hetcher, Jr., *J. Org. Chem.*, **33**, 1806 (1968).

Synthesis and Stereochemistry of 3-Hydroxy-5-methylproline, a New Naturally Occurring Imino Acid

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3-Hydroxy-5-methylproline was synthesized via Dieckmann cyclization of methyl *N*-methoxycarbonyl-3-methoxycarbonylmethylaminobutyrate (**6**) to *N*,2-dimethoxycarbonyl-5-methylpyrrolid-3-one (**8**). Reduction of the latter to *N*,2-dimethoxycarbonyl-5-methylpyrrolidin-3-ol (**9**) and subsequent hydrolysis afforded a mixture (**10**) of the four diastereoisomers (**1**–**4**) of 3-hydroxy-5-methylproline, which were separated by ion-exchange chromatography. From ^1H NMR data and epimerization studies, the relative stereochemistry of these stereoisomers was established. The NMR study also revealed conformational differences between the various isomers. Isomer **1**, which was reported earlier to correspond with a component of the peptide antibiotic actinomycin Z_1, has 2,3-trans-2,5-cis stereochemistry and a C_3-exo, C_4-endo ("twist") conformation.

A preliminary communication[1] reported the identification of 3-hydroxy-5-methylproline as a component of the peptide antibiotic, actinomycin Z_1, and the same imino acid has also been identified in some members of an actinomycin complex from *Micromonospora floridensis* NRRL8020.[2] A synthesis of the four racemic diastereoisomers (racemates of **1**–**4**, Figure 1) and an investigation of their stereochemistry are described here.

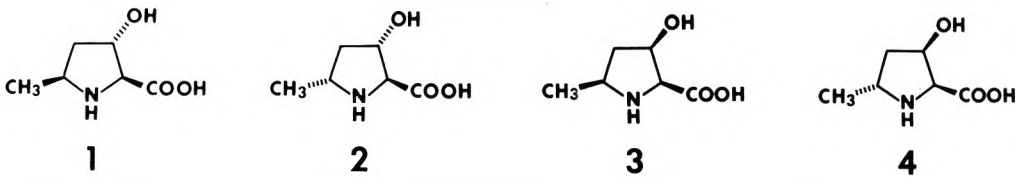


Figure 1. The four diastereoisomeric 3-hydroxy-5-methylprolines. The same numerals are used to denote the corresponding racemates.

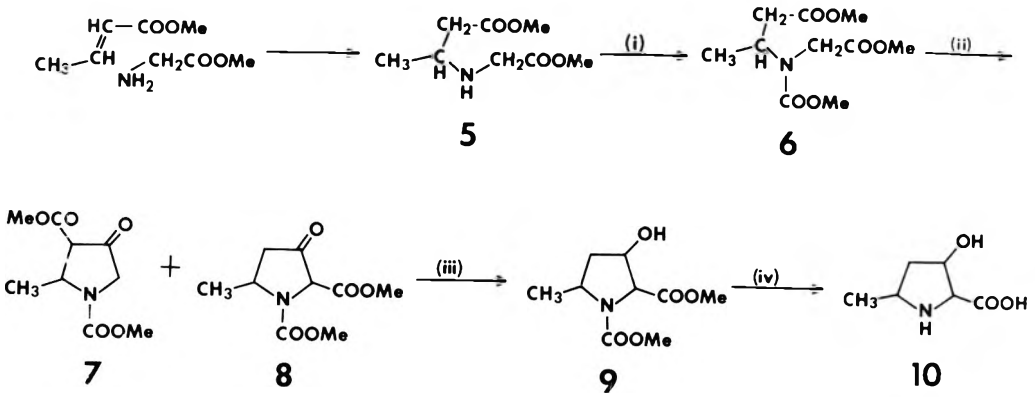


Figure 2. Synthesis of 3-hydroxy-5-methylproline. Reagents: (i) ClCOOMe; (ii) *t*-BuOK/PhMe; (iii) $NaBH_4$; (iv) $Ba(OH)_2/H_2O$.

Table I. Relative Intensities in the Mass Spectra of the Diastereoisomers of *N,O*-Ditrifluoroacetyl-3-hydroxy-5-methylproline Methyl Ester

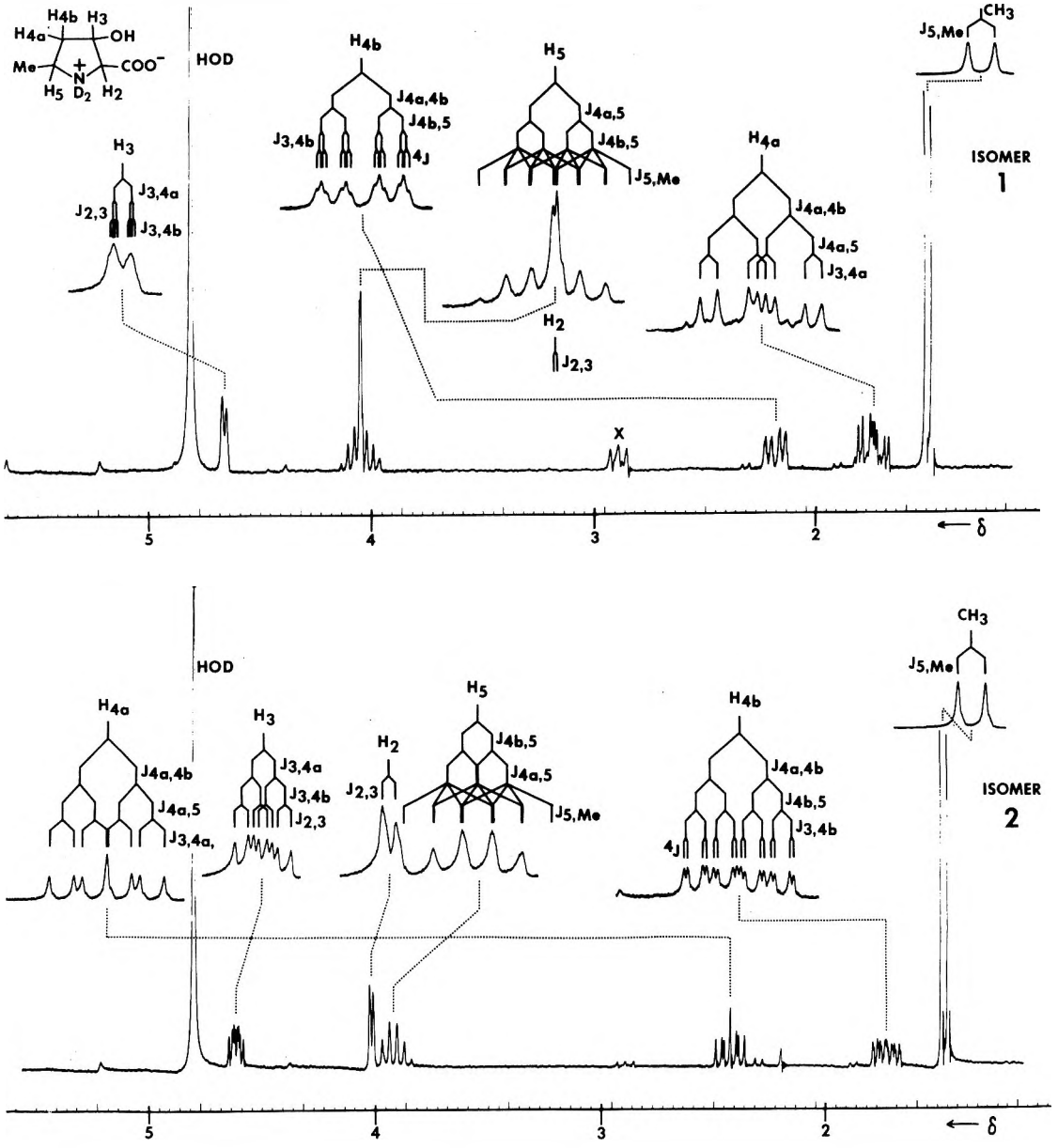
m/e	Natural (61218-64-2)[a]	Isomer 1 (61247-99-2)	Isomer 2 (61248-00-8)	Isomer 3 (61248-01-9)	Isomer 4 (61248-02-0)	Ion$^+$
351	0.002	0.002	0.033	0.023	0.028	M
292	1.00	1.00	1.00	1.00	1.00	M − COOMe
237	0.16	0.18	0.13	0.051	0.087	M − CF_3COOH
178	0.28	0.30	0.35	0.24	0.32	M − COOMe − CF_3COOH
153	0.04	0.05	0.14	0.043	0.22	
83	0.27	0.31	0.34	0.24	0.37	M − COOMe − CF_3COOH − CF_3CO
81	0.19	0.21	0.25	0.17	0.25	
69	0.76	0.65	0.75	0.54	0.78	CF_3
65	0.10	0.11	0.12	0.090	0.13	
59	0.32	0.35	0.43	0.31	0.36	$COOCH_3$
55	0.19	0.22	0.25	0.17	0.26	

[a] Registry no.

The synthetic route (Figure 2) parallels that reported for a synthesis of 3-hydroxyproline,[3] except that in the initial step the imino diester **5** was prepared by addition of methyl glycinate to methyl crotonate. Dieckmann cyclization of **6** gave a mixture of isomeric β-keto esters (**7** and **8**) and reduction of the latter provided a derivative (**9**) of 3-hydroxy-5-methylproline. Hydrolysis of **9** afforded 3-hydroxy-5-methylproline as an isomeric mixture (**10**) which was separated by ion-exchange chromatography into four crystalline diastereoisomeric racemates designated **1**–**4** according to their emergence from the column. The four diastereoisomers were distinguishable by paper electrophoresis, ion-exchange chromatography, and gas chromatography (GC) of their *N,O*-ditrifluoroacetyl methyl esters,[1] and by these criteria the natural imino acid was found to correspond in relative stereochemistry with **1**. In addition, these derivatives were subjected to combined GC–mass spectrometry and electron impact mass spectra were obtained (Table I). The derivative of **1** differed from those of **2**–**4** in producing a spectrum with a less intense molecular ion.

Stereochemical relationships between the various synthetic isomers were investigated by C_2-epimerization experiments. In aqueous alkali at 140 °C, **1** and **4** were each converted to an equilibrium mixture of these two isomers in the ratio of 2:1. Likewise, **2** and **3** each formed a 2:1 mixture of these isomers, and it follows that **1** and **4**, and also **2** and **3**, are pairs of C_2 epimers. Furthermore, since 3-hydroxyproline forms a 2:1 equilibrium mixture of trans and cis isomers in hot alkali,[3] it appears likely that **1** and **2** are the isomers which possess 2,3-trans stereochemistry. These observations permit an understanding of the relative yields of **1**–**4** during the synthesis. When **9** is hydrolyzed with alkali, the stereoisomeric composition of the resulting 3-hydroxy-5-methylproline is **1**, 16%; **2**, 50%; **3**, 27%; **4**, 7%, whereas acid hydrolysis gives **1**, 2%; **2**, 11%; **3**, 55%; **4**, 32%. The latter composition reflects the stereochemistry of **9**, whereas the former results from C_2-epimer equilibration. Since **9** is expected to be predominantly 2,3-cis, resulting from borohydride reduction of **8** (by analogy with studies on 3-hydroxyproline[4]), the results are consistent with 2,3-cis stereochemistry for **3** and **4**. ^1H NMR studies (discussed below) established 2,3-trans-2,5-cis stereochemistry for **1**, and it follows from the foregoing discussion that the relative stereochemistry is as shown for isomers **1**–**4**. The stereochemical composition resulting from the synthesis is explained by concluding that **8** is predominantly cis and **9** mainly cis,cis.

^1H NMR spectra of **1**–**4** were obtained in D_2O at 220 MHz. At this resolution all four spectra were first order (Figures



Figures 3 and 4. ^{1}H NMR spectra of 1 and 2. H_{4a} and H_{4b} are cis and trans, respectively, to the carboxyl group. "X" denotes signals caused by the internal standard (DSS).

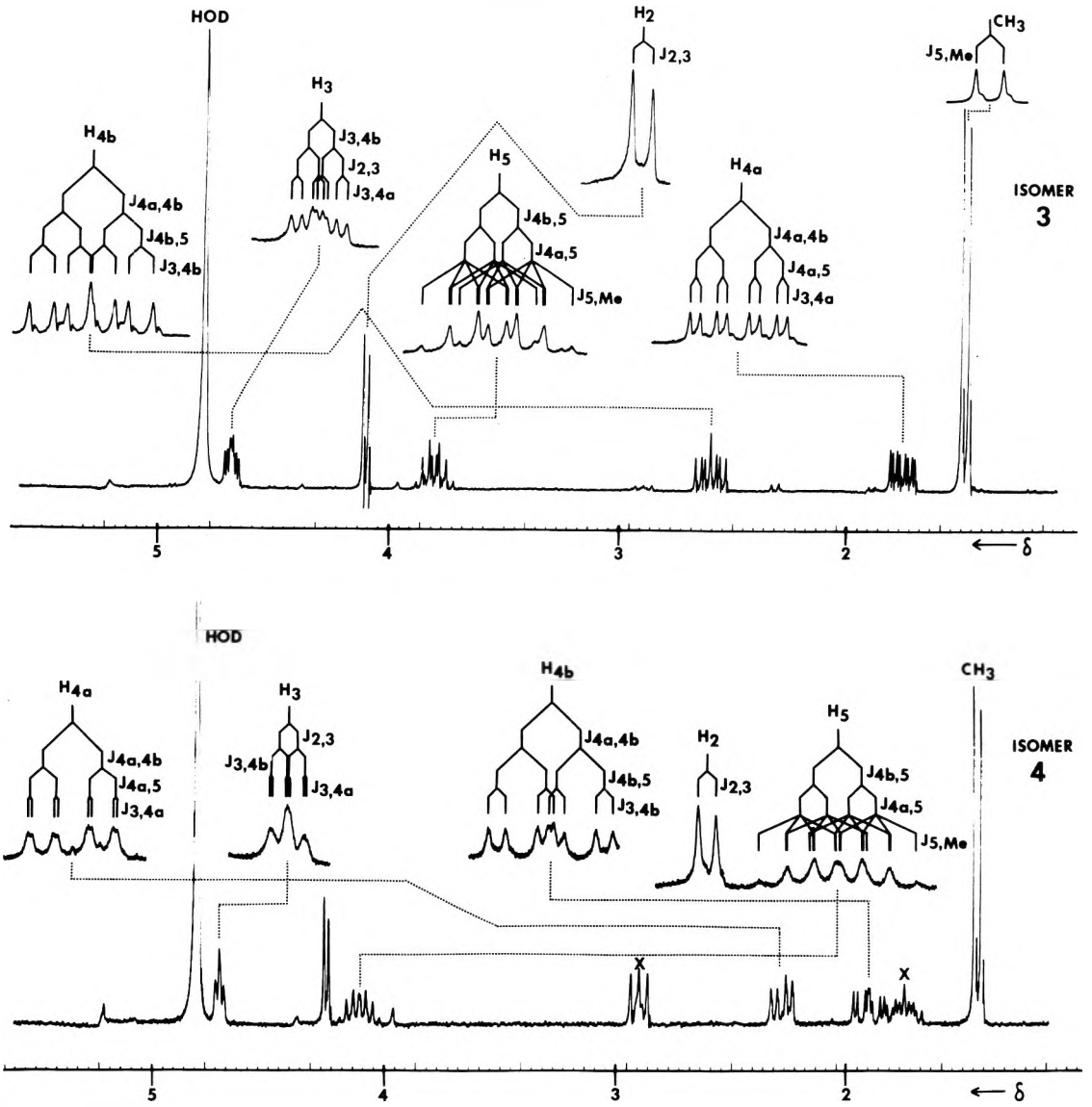
Table II. Coupling Constants[a] (Hz)

Isomer	$J_{2,3}$	$J_{3,4a}$	$J_{3,4b}$	$J_{4a,4b}$	$J_{4a,5}$	$J_{4b,5}$	$J_{5,Me}$	$^4J_{2,4}$
1	~0	4.4	1.0	14.3	11.8	6.1	6.7	~1
2	3.2	5.8	4.6	14.0	8.0	7.2	6.8	1.0
3	4.9	2.5	5.9	14.3	6.5	9.1	6.8	
4	4.2	1.0	4.0	14.1	6.0	11.4	6.9	

[a] H_{4a} and H_{4b} are cis and trans, respectively, to the carboxyl group.

3–6), permitting direct measurement of all the coupling constants (Table II). The striking chemical shift differences (Table III) between the geminal 4 protons cannot be attributed to the effects of the hydroxyl or carboxyl substituents, to judge by analogy with the 4 protons in proline[5,6] or the 3 protons in hydroxyproline and *allo*-hydroxyproline.[7,8] They can be explained by the known shielding effect of a methyl group upon the adjacent cis proton in five- or six-membered rings.[9] This effect produces a shift difference of δ 0.66 in the geminal 2 protons of methylcyclopentane[10] and δ 0.53 in the 5 protons of 2,3-*trans*-3,4-*cis*-3-hydroxy-4-methylproline[11] and can be used to assign the 4-proton signals in the isomers of 3-hydroxy-5-methylproline (Figures 3–6).

The stereochemistry of **1** and **4** can be deduced from their vicinal coupling constants as follows. The minimal value of $J_{2,3}$ in **1**, which implies a dihedral angle close to 90°, requires 2,3-trans stereochemistry and parallels the case of *trans*-3-hydroxyproline.[3,4] Likewise, the minimal $J_{3,4b}$ reveals that H_{4b} is trans to H_3 and hence to the carboxyl group. The value of 11.8 Hz for $J_{4a,5}$ must result from a trans dihedral angle close to 180°. It follows that H_5 is trans to the carboxyl group and hence the methyl is cis. These dihedral angles comprise a 3-



Figures 3 and 4. ^{1}H NMR spectra of **3** and **4**. H_{4a} and H_{4b} are cis and trans, respectively, to the carboxyl group. "X" denotes signals caused by the internal standard (DSS).

Table III. Chemical Shifts (δ)

Isomer	Me	H_{4a}	H_{4b}	H_5	H_2	H_3
1	1.49	1.76	2.20	4.05	4.05	4.67
2	1.47	2.43	1.75	3.92	4.01	4.61
3	1.49	1.76	2.59	3.80	4.10	4.69
4	1.43	2.28	1.91	4.09	4.23	4.70

exo-4-endo ("twist") conformation, which explains the long-range coupling (^4J) between H_2 and H_{4b}, since these protons are joined by a "W" bond conformation. In comparing the coupling constants of **4** with those of **1** (in Table II, note that for this purpose protons 4a and 4b are exchanged), these are seen to be almost identical except for $J_{2,3}$. It follows that their relative stereochemistry at C_3 and C_5 is the same, in accord with the observation that they are C_2 epimers. Furthermore, the ring conformation (3-endo,4-exo) of **4** is the same, relative to the hydroxyl and methyl substituents, as that of **1**. This conformation renders the hydroxyl group quasi-axial and the methyl quasi-equatorial, and the same conformation meets the same requirements in the case of 2,3-*trans*-3,4-*cis*-3-hydroxy-4-methylproline.[11,12] The latter imino acid has three coupling constants (0, 4, and 11 Hz for $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$, respectively) very similar to corresponding vicinal couplings in **1**. It is also noteworthy that the conformations established for hydroxyproline[7,13] and *allo*-hydroxyproline[7] compel the hydroxyl group to adopt a quasi-axial configuration.

Interpretation of the coupling constant data for **2** and **3** in terms of stereochemistry and conformation presents a more difficult task than for **1** and **4**. Attempts to establish mutually compatible dihedral angles using various forms of the Karplus relationship are still under study. There is a possibility that rapid interconversion of different conformational populations prevails, as in the case of proline.[5] The relative stereochemistry at C_2 and C_3 cannot be deduced with certainty from the $J_{2,3}$ values for **2** and **3**, but these parameters, in the case of their *N,O*-di-*p*-toluenesulfonyl methyl esters ($J_{2,3}$ = 0 and 6.9 Hz, respectively), revealed that **2** undoubtedly possesses 2,3-trans stereochemistry and that its derivative has a ring conformation more similar to that of **1** than does the free imino acid. Conformational alteration in the conversion of substituted prolines to their *N*-*p*-toluenesulfonyl derivatives has been reported previously.[14] Isomer **2** also shares with **1** the presence of a long-range coupling between H_2 and H_{4b}, which was confirmed when irradiation at the frequency of the latter produced sharpening of the H_2 doublet. The ^4J value (1.0 Hz)

requires a cis arrangement of these protons in order to approximate a "W" four-bond conformation, and this serves to confirm the assignment of H_{4b} based upon the shielding effect of the methyl group. Although four-bond couplings have been observed with other bond conformations, the resulting ^4J values are generally smaller (0.4–0.8 Hz) than that observed here.[15]

The possibility that relative lanthanide-induced shifts could be utilized to confirm the stereochemistry and the assignments of H_{4a} and H_{4b} in **2** and **3** was investigated using europium(III) nitrate. In the case of hydroxyproline it was reported that the 3 and 5 protons cis to the carboxyl group were shifted more than those which were trans, in accord with the expected geometry of the 1:1 complex in which the europium is bound to the carboxylate anion.[16] The observed upfield shifts of the various protons in **2** and **3** were expressed relative to the shift of H_2, and as such varied little during eight incremental additions of reagent up to a reagent/substrate molar ratio of 0.8. The mean relative shifts (Hz) were as follows: for **2**, H_2, 1.00; H_3, 1.87; H_{4a}, 0.59; H_{4b}, 0.55; H_5, 0.77; Me, 0.32. For **3**, H_2, 1.00; H_3, 1.31; H_{4a}, 0.65; H_{4b}, 0.45; H_5, 0.52; Me, 0.16. The markedly greater shift of H_3 in **2** than in **3** confirms the 2,3 stereochemistry proposed for these isomers, and the greater shift of H_5 in **2** than **3** is in accord with their postulated 2,5 stereochemistry. Comparison of the induced shifts in H_{4a} and H_{4b}, while in accord with the assignments in the case of **3**, is invalid in the case of **2** because the difference is too small to be significant. Ambiguity occurs because an induced shift depends not only upon the distance of the proton from the lanthanide ion, but also upon the angle this vector makes with the magnetic axis, and is therefore strongly dependent upon conformation.[16] It is concluded that the comparisons discussed here, while valid for H_3, become increasingly unreliable as the proton–lanthanide distance increases. In considering the comparatively small methyl proton shifts, which appear to contradict the result for H_5, the latter must be considered a more dependable stereochemical criterion.

Evaluation of all the evidence confirms that structures **1–4** correctly depict the stereochemistry of the four diastereoisomers. That the naturally occurring imino acid corresponds with **1** is not unexpected. The ^{1}H NMR spectrum of actinomycin Z_1 was reported[17] to include a "singlet" in the region ($\sim\delta$ 6.0) occupied only by the α protons of proline and its congeners in the actinomycin series. The data presented here explain that observation, which is compatible only with the presence of a trans 3-substituted proline residue. *cis*-5-Methylproline occurs in actinomycin Z_5, another component of the same complex[18,19] and examination of space-filling (CPK) molecular models reveals that *trans*-5-methylproline, in contrast to the cis isomer, could not be accommodated without alteration of the peptide backbone conformation which is common to all the actinomycins which have been investigated.[20,21]

Experimental Section

For gas chromatography (GC) a Shimadzu Model 4BM, equipped with flame ionization detectors, was employed with argon (60 ml/min) as carrier gas. Glass columns (2.5 m × 3 mm) contained 3% OV225 (column A) or 3% OV17 (column B) on Gas-Chrom Q (100–120 mesh). The derivatization procedure for the *N,O*-ditrifluoroacetyl methyl esters of **1–4**, and their retention times, were reported previously.[1]

For combined GC–mass spectrometry, an LKB9000 instrument was used, with a 6-ft column of 1% OV17 on Gas-Chrom Q at 108 °C. Electron impact mass spectra (Table I) were obtained for the *N,O*-ditrifluoroacetyl methyl esters of each synthetic diastereoisomer and of the natural compound in an actinomycin Z_1 hydrolysate. The conditions for paper chromatography and high-voltage paper electrophoresis were described earlier.[1]

Infrared (IR) spectra were obtained on a Perkin-Elmer Model 337. ^{1}H NMR spectra were obtained on a Varian HR-220 in the cw mode. Solutions of **1–4** were in D_2O with DSS as internal standard. The temperature was 18 °C, pH 6.4, and the concentration was 0.2 M for **1–3** and 0.1 M for **4**. Eight additions of a 0.8 M solution of $Eu(NO_3)_3$ in D_2O were made to the sample solutions (0.8 ml) of **2** and **3** in increments of 25 μl, each representing a 1:10 molar ratio of reagent to imino acid. Chemical shifts were determined and the upfield induced shifts (Hz) expressed relative to H_2 = 1.00 at each reagent concentration.

Methyl 3-Methoxycarbonylmethylaminobutyrate (5). Methyl crotonate (15.21 g, 0.15 mol) and glycine methyl ester hydrochloride (40.8 g, 0.33 mol) were stirred in methanol (200 ml) during addition of triethylamine (35 g, 0.35 mol). After 2 days at 26 °C, the precipitate was filtered off and the filtrate evaporated. The residue, in ethyl acetate (500 ml), was washed with aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated. The residual oil was distilled at 0.28 Torr and the fraction bp 76–78 °C collected: yield 13.46 g (47%); IR ($CHCl_3$) 1730 cm^{-1} (ester C=O).

Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 50.52; H, 8.03; N, 7.82.

Methyl *N*-Methoxycarbonyl-3-methoxycarbonylmethylaminobutyrate (6). A solution of **5** (3.35 g, 71 mmol) in ethyl acetate (100 ml) was stirred vigorously with water (150 ml) and $NaHCO_3$ (10.0 g) during addition of methyl chloroformate (8.0 g, 85 mmol). After 2 h at room temperature, ethyl acetate (150 ml) was added and the layers separated. The organic phase was washed with water, dried (Na_2SO_4), and evaporated. The residual oil was distilled at 0.4 Torr and the fraction bp 107–110 °C collected: yield 16.39 g (94%); IR ($CHCl_3$) 1690 (urethane C=O) and 1740 cm^{-1} (ester C=O).

Anal. Calcd for $C_{10}H_{17}NO_6$: C, 48.57; H, 6.93; N, 5.67. Found: C, 48.65; H, 7.14; N, 5.60.

***N*,2-Dimethoxycarbonyl-5-methylpyrrolid-3-one (8).** To a solution of potassium *tert*-butoxide (88 mmol) in toluene (prepared using 3.45 g of potassium by the published method[22]) at 0 °C was added a solution of **6** (14.27 g, 58 mmol) in dry toluene (30 ml) with stirring during 15 min in a stream of nitrogen. After 90 min, acetic acid (6 ml) and chloroform (300 ml) were added and the solution was washed with 10% aqueous NaH_2PO_4 (300 ml). The chloroform extracts were washed with pH7 phosphate buffer, dried (Na_2SO_4), and evaporated. The resulting mixture of **7** and **8** was separated via partition between toluene (350 ml) and pH 9.5 carbonate buffer (3 × 200 ml) at 0 °C. The combined aqueous layers were reextracted with chloroform until complete separation of the two components was apparent from GC. The chloroform extracts were dried (Na_2SO_4) and evaporated. The residual **8** was distilled at 0.025 Torr and the fraction bp 97.5–99 °C collected: yield 3.57 g (29%); IR ($CHCl_3$) 1700 (urethane C=O), 1750 (ester C=O), and 1770 cm^{-1} (ketone C=O).

Anal. Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.10; H, 5.99; N, 6.68.

***N*,2-Dimethoxycarbonyl-5-methylpyrrolidin-3-ol (9).** Phosphate buffer, pH 7.2 (250 ml), was cooled to 0 °C and $NaBH_4$ (8.0 g) was gradually added with stirring, followed by **8** (3.50 g, 16 mmol) in methanol (165 ml). The pH was maintained at 8–9 by addition of NaH_2PO_4·H_2O, and after 1 min further $NaBH_4$ (4.0 g) was added. After 4 min the mixture was adjusted to pH 3 with aqueous H_2SO_4, then neutralized with NaOH and extracted with chloroform (3 × 500 ml). The chloroform extracts were dried (Na_2SO_4) and evaporated, and the residue chromatographed on a column (40 × 4.7 cm) of silica gel 60 (70–230 mesh) using 25% ethyl acetate in chloroform. Appropriate fractions were pooled and evaporated and the residual oil distilled (short path) at 150 °C (0.20 Torr): yield 2.18 g (62%); IR ($CHCl_3$) 1680 (urethane C=O) and 1760 cm^{-1} (ester C=O).

Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.56; H, 7.07; N, 6.26.

3-Hydroxy-5-methylproline (10). Aqueous 0.3 N $Ba(OH)_2$ (130 ml) was added to **9** (1.97 g, 9.1 mmol) and the mixture was heated under reflux in a stream of nitrogen for 60 h. The cooled solution was neutralized with H_2SO_4, filtered, washed with ethyl acetate (250 ml), and evaporated. The residue was dissolved in water and applied to a column (2.2 × 27 cm) of cation exchange resin AG50W-X2. After washing with water (600 ml) the product was eluted with 2 N NH_4OH, and evaporation gave a white solid (1.02 g, 77%) which gave four spots on paper electrophoresis (yellow with ninhydrin) and four peaks on the amino acid analyzer.[1]

Separation of the 3-Hydroxy-5-methylproline Diastereoisomers. The isomeric mixture **10** (1.02 g) was dissolved in 0.2 M ammonium acetate buffer (pH 3.8) containing 40% methanol (20 ml) and divided into four equal aliquots. Each aliquot was chromatographed on a column (61 × 3.6 cm) of cation exchange resin (Baker CGC-241, 8% cross-linked, 200–400 mesh) using the same solvent. Fractions (10 ml) were collected and aliquots examined by paper chromatography and high-voltage paper electrophoresis;[1] **1** was located in fractions

46–53, **2** in fractions 56–67, **3** in fractions 81–90, and **4** in fractions 94–100. Similar fractions from the four separations were pooled and evaporated, and each isomer was desalted on a column (26 × 2.0 cm) of Dowex 50W-X8 as described above (for **10**). After evaporation, each isomer was crystallized from water/acetone. **1** formed needles, mp 267–628 °C dec, yield 72 mg. Anal. Calcd for $C_6H_{11}NO_3$: C, 49.64; H, 7.64; N, 9.55. Found: C, 49.72; H, 7.89; N, 9.80. **2** formed plates, mp 242–243 °C dec, yield 369 mg. Found: C, 49.58; H, 7.79; N, 9.72. **3** formed plates, mp 204–205 °C dec, yield 253 mg. Found: C, 49.24; H, 7.84; N, 9.52. **4** formed plates, mp 259–260 °C dec, yield 15 mg.

Epimerization Studies. Each diastereoisomeric racemate **1–4** (0.1 mg) in 1 N NaOH (0.1 ml) was kept at 140 °C (sealed tube) for 22 h. HCl (1.5 N, 0.1 ml) was added and the solution was evaporated in vacuo. Each residue was derivatized as reported previously[1] (*N,O*-ditrifluoroacetyl methyl esters) and analyzed by GC[1] on column A at 130 °C. The following compositions were observed: **1** → 68% **1** + 32% **4**; **2** → 68% **2** + 32% **3**; **3** → 70% **2** + 30% **3**; **4** → 62% **1** + 28% **4** + 10% **3**.

Hydrolysis of 9 with Acid and Alkali. A. 9 (6 mg) in acetic acid (0.5 ml) was heated with concentrated HCl (0.5 ml) at 110 °C (sealed tube) for 16 h, then evaporated in vacuo. After derivatization as before,[1] GC on column B at 115 °C indicated the following isomeric composition: **1**, 2%; **2**, 11%; **3**, 55%; **4**, 32%.

B. Reverse Reaction. Each isomer **1–4** (0.1 mg) was converted to the *N*-methoxycarbonyl methyl ester by treatment with 5 N methanolic HCl (0.5 ml, 80 °C, 1 h) followed by evaporation and treatment with methyl chloroformate (10 mg) in ethyl acetate (0.2 ml) and $NaHCO_3$ (20 mg) in water (0.2 ml). GC on column B at 165 °C gave the following retention times (min): **1**, 8.3; **2**, 8.1; **3**, 7.5; **4**, 7.1. GC analysis of **9** indicated an isomeric composition of almost entirely **3** and **4** in approximately 2:1 ratio.

C. 9 (2 mg) in 0.3 N $Ba(OH)_2$ (1 ml) was heated at 110 °C (sealed tube) for 16 h, then neutralized with 1 N H_2SO_4, filtered, and evaporated. After derivatization and GC as above (A) the isomeric composition was **1**, 16%; **2**, 50%; **3**, 27%; **4**, 7%.

***N,O*-Di-*p*-toluenesulfonyl Methyl Ester of 3.** A solution of **3** (62 mg) in 5 N methanolic HCl (2 ml) was kept at 80 °C (sealed tube) for 1 h. After evaporation, the residue was treated with *p*-toluenesulfonyl chloride (260 mg) in pyridine (27 ml) containing triethylamine (0.06 ml) at 5 °C for 2.5 days. After evaporation in vacuo, the residue was partitioned between 0.1 N HCl (15 ml) and ethyl acetate (30 ml) and the ethyl acetate extract was washed with aqueous $NaHCO_3$ and water and dried (Na_2SO_4). After evaporation, the residue was chromatographed on a column (16 × 1.5 cm) of silica gel 60 (70–230 mesh) with chloroform and the product located by TLC on fluorescent silica gel. The product crystallized from ethyl acetate/petroleum ether as needles: mp 116–118 °C; yield 121 mg (61%); NMR ($CDCl_3$, internal Me_4Si) δ 1.35 (d, J = 7.5 Hz, 5-CH_3, 3), 2.01 (m, 4-H, 1), 2.05 (m, 4-H, 1), 2.44 (s, Tos CH_3, 3), 2.46 (s, Tos CH_3, 3), 3.63 (s, OCH_3, 3), 3.87 (m, 5-H, 1), 4.54 (d, J = 6.9 Hz, 2-H, 1), 4.85 (m, 3-H, 1), 7.31 (d, $J \sim 8$ Hz, ArH, 2), 7.35 (d, $J \sim 8$ Hz, ArH, 2), 7.70 (d, $J \sim 7$ Hz, ArH, 2), and 7.74 (d, $J \sim 7$ Hz, ArH, 2).

Anal. Calcd for $C_{21}H_{25}NO_7S_2$: C, 53.94; H, 5.39; N, 3.00; S, 13.72. Found: C, 54.03; H, 5.43; N, 2.92; S, 13.58.

***N,O*-Di-*p*-toluenesulfonyl methyl ester of 2** was prepared as described above using 2 (48 mg) with methanolic HCl (1.4 ml), then pyridine (1.6 ml), triethylamine (0.04 ml) and *p*-toluenesulfonyl chloride (140 mg), yield 44 mg (28%). The product could not be crystallized: NMR ($CDCl_3$, internal Me_4Si) δ 1.22 (d, J = 6.7 Hz, 5-CH_3, 3), 2.42 (s, Tos CH_3, 3), 2.47 (s, Tos CH_3, 3), 2.48 (m, 4-H, 2), 3.69 (s, OCH_3, 3), 4.19 (m, 5-H, 1), 4.50 (~s, 2-H, 1), 4.95 (d, J = 4.8 Hz, 3-H, 1), 7.26 (d, $J \sim 8$ Hz, ArH, 2), 7.36 (d, $J \sim 8$ Hz, ArH, 2), 7.67 (d, $J \sim 8$ Hz, ArH, 2), and 7.75 (d, $J \sim 8$ Hz, ArH, 2).

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Registry No.—**1**, 61248-03-1; **2**, 61248-04-2; **2** *N,O*-*p*-toluenesulfonyl methyl ester, 61218-65-3; **3**, 61248-05-3; **3** *N,O*-*p*-toluenesulfonyl methyl ester, 61248-06-4; **4**, 61248-07-5; **5**, 61218-66-4; **6**, 61218-67-5; **7**, 61218-68-6; **8**, 61218-69-7; **9**, 61218-70-0; methyl crotonate, 18707-60-3; glycine methyl ester HCl, 5680-79-5.

References and Notes

(1) E. Katz, K. T. Mason, and A. B. Mauger, *Biochem. Biophys. Res. Commun.*, **63**, 502 (1975).
(2) K. T. Mason, E. Katz, and A. B. Mauger, presented at the 15th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, D.C., 1975.
(3) J. Blake, C. D. Willson, and H. Rapoport, *J. Am. Chem. Soc.*, **86**, 5293 (1964).
(4) F. Irreverre, K. Morita, A. V. Robertson, and B. Witkop, *J. Am. Chem. Soc.*, **85**, 2824 (1963).
(5) M. Ellenberger, L. Pogliani, K. Hauser, and J. Valat, *Chem. Phys. Lett.*, **27**, 419 (1974).
(6) L. Pogliani, M. Ellenberger, and J. Valat, *Org. Magn. Reson.*, **7**, 61 (1975).
(7) R. J. Abraham and K. A. McLauchlan, *Mol. Phys.*, **5**, 195, 513 (1962).
(8) R. J. Abraham and W. A. Thomas, *J. Chem. Soc.*, 3739 (1964).
(9) L. M. Jackman and S. Sternhell, "Applications of NMR Spectroscopy in Organic Chemistry", Pergamon Press, Oxford, 1969, pp 236–237.
(10) R. L. Lipnick, *J. Am. Chem. Soc.*, **96**, 2941 (1974).
(11) F. Benz, F. Knüsel, J. Nüesch, H. Treichler, W. Voser, R. Nyfeler, and W. Keller-Schierlein, *Helv. Chim. Acta*, **57**, 2459 (1974).
(12) G. Koyama, *Helv. Chim. Acta*, **57**, 2477 (1974).
(13) L. Pogliani and M. Ellenberger, *Spectrosc. Lett.*, **6**, 261 (1973).
(14) R. H. Andreatta, V. Nair, and A. V. Robertson, *Aust. J. Chem.*, **20**, 2701 (1967).
(15) L. Pogliani, *Spectrosc. Lett.*, **8**, 37 (1975).
(16) F. Inagaki, M. Tasumi, and T. Miyazawa, *J. Chem. Soc., Perkin Trans. 2*, 167 (1976).
(17) H. Brockmann and E. A. Stähler, *Tetrahedron Lett.*, 3685 (1973).
(18) E. Katz, K. T. Mason, and A. B. Mauger, *Biochem. Biophys. Res. Commun.*, **52**, 819 (1973).
(19) H. Brockmann and E. A. Stähler, *Tetrahedron Lett.*, 2567 (1973).
(20) H. Lackner, *Angew. Chem., Int. Ed. Engl.*, **14**, 375 (1975).
(21) A. B. Mauger in "Peptides: Chemistry, Structure and Biology", R. Walter and J. Meienhofer, Ed., Ann Arbor Science Publishers, Ann Arbor, Mich., 1975, pp 181–186.
(22) H. Plieninger and S. Leonhauser, *Ber.*, **92**, 1579 (1959).

Absolute Configuration of Glycerol Derivatives. 3.[1] Synthesis and Cupra A Circular Dichroism Spectra of Some Chiral 3-Aryloxy-1,2-propanediols and 3-Aryloxy-1-amino-2-propanols

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Synthesis of the 2*R* and 2*S* isomers of several 3-aryloxypropane-1,2-diols, beginning from (2*R*)- and (2*S*)-3-tosyloxypropane-1,2-diol acetonide (**3** and **6**), is reported. Some of the diols were converted into the corresponding 3-aryloxy-1-amino-2-propanols. Determination of their Cupra A CD spectra showed that absolute configuration can be readily assigned based on the sign of the short wavelength transition (~280 nm). 2*S* enantiomers give positive Cotton effects in this region; 2*R* enantiomers give negative Cotton effects.

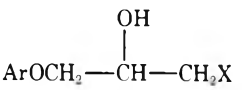
Effects related to absolute configuration are significant and fundamental factors contributing to the intensity and duration of the physiological and pharmacological responses of most neurotransmitters, hormones, and drugs, especially as related to the actions of these compounds at the molecular level on important biochemical processes.[2,3] In the case of drugs, enantiomers may demonstrate several hundredfold differences in pharmacological effects, potency at different receptors, as well as significant differences in their rates and pathways of metabolic disposition. All of these factors contribute to the observed enantiomeric differences in the pharmacological responses.[4,5] It logically developed that the study of the effects of absolute configuration on the pharmacological properties of drugs has received extensive investigation in many classes of compounds, and that development of methods for the determination of absolute configuration is an important area in the study of the configurational aspects of drug action.

Chiroptical (ORD and CD) techniques occupy a unique place in such method development studies because they may provide information concerning absolute configuration of compounds by simple and economical methods when compared to x-ray crystallographic techniques, and also offer the advantage over standard chemical degradative methods of being nondestructive. CD–ORD techniques may also provide information concerning solution behavior of important biomolecules useful to our understanding of the relationships between molecular structure and biological activity.

In spite of many advances, large gaps in our knowledge remain concerning the effects of absolute configuration on biological activity of many drug-related molecules. These deficiencies are, in part, a result of the lack of available facile chiroptical methods useful to readily establish absolute configuration of dissymmetric centers in these molecules.

In this report we present results of our initial attempts to use glycerol derivatives of known absolute configuration to synthesize the enantiomers of several drug-related systems. After obtaining the enantiomers of known absolute configuration, the chiroptical behavior of these isomers was studied, in order to obtain a suitable technique which could ultimately be applied to more diverse systems, to determine chirality of isomers of unknown absolute configuration.

A large number of drugs are 3-aryloxy-1,2-propanediols of general structure **1** (X = OH), or related amines (X = NH_2 or



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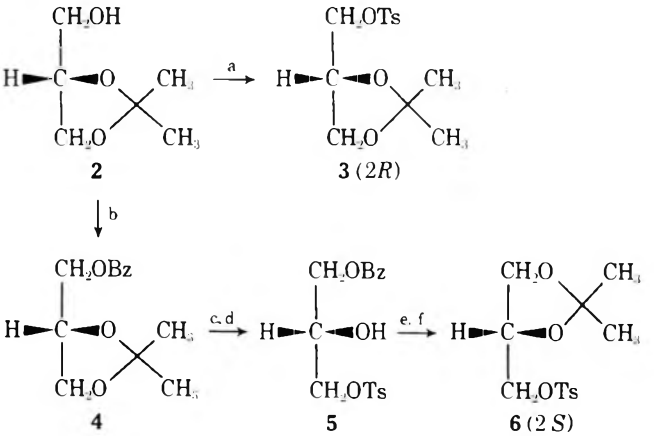
NHR), all of which may be considered derivatives of glycerol. These include centrally acting muscle relaxants (diols, 1-carbamate esters of these diols, amino alcohol derivatives, e.g., oxazolidinones such as the 5-aryloxymethyl-2-oxazolidinones), the β-adrenergic blocking agents, e.g., propranolol, Ar = α-naphthyl, X = NHiPr, and the competitive α-adrenergic blocking agents, e.g., the 2-alkylaminoethylbenzodioxanes,[1] X = NR_2, and secondary alcohol is an ether of the aromatic ring.

In this communication we report the establishment of a facile method for obtaining the enantiomers of known absolute configuration of many of these compounds, beginning from chiral glycerol derivatives, and the results of Cupra A CD spectra determinations with these compounds.

Synthesis. In the successful synthesis of the 2*R* and 2*S* isomers of 1-tosyloxy-2,3-propanediol acetonide (**3** and **6**) from a single chiral starting material of known absolute configuration, compound **2** is the cornerstone of this synthetic scheme. (2*S*)-Glycerol 1,2-acetonide (**2**) is readily available from (2*R*,3*S*,4*S*,5*R*)-mannitol 1,2,5,6-diacetonide by the method of Baer[6] (lead tetracetate oxidation followed by catalytic reduction of the intermediate glyceraldehyde 2,3-acetonide). In Scheme I is the synthesis of **3** and **6**, which is based

Scheme I



a, TsCl/pyridine; b, BzCl, KOH (DMF); c, H_3O^+; d, TsCl/pyridine; e, H_2(Pd/C); f, acetone ($ZnCl_2$).

on the method of Fischer[7,8] with some modifications. Conversion of **2** to **4** was most readily accomplished in DMF as solvent, rather than in excess benzyl chloride as reported by Belleau.[9,10] Catalytic reductions were also performed at low pressure. It is noteworthy that this scheme allows for preparation of *both* isomers with no reactions involving the chiral center. Subsequent processes also require no inversion steps.

Synthesis of the diols (**7**–**18**) was accomplished by allowing

Table I. Cupra A CD Spectra of Chiral 3-Aryloxy-1,2-propanediols and 3-Aryloxy-1-amino-2-propanols

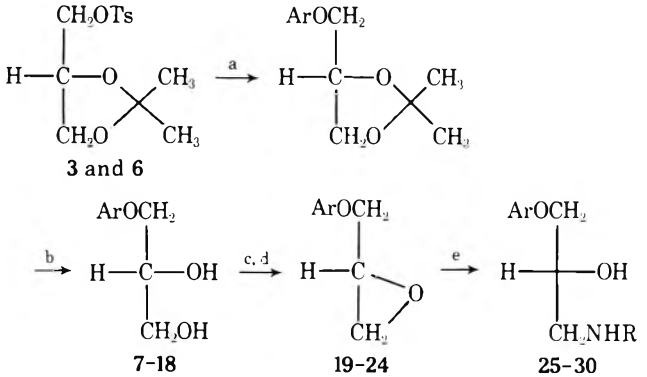
$$ArOCH_2—CH(OH)—CH_2X$$

Registry no.	1,2-Propanediols X = OH	Stereochemistry	Ar	Relative $[\theta]_\lambda$ max	
52153-43-2	**7**	2*R*	*o*-CH_3Ph	$[\theta]_{550}$ +27	$[\theta]_{270}$ −570
52153-44-3	**8**	2*S*	*o*-CH_3Ph	$[\theta]_{550}$ −34	$[\theta]_{270}$ +560
61248-73-5	**9**	2*R*	3,5-di-MePh	$[\theta]_{580}$ +28	$[\theta]_{275}$ −575
61248-74-6	**10**	2*S*	3,5-di-MePh	$[\theta]_{580}$ −32	$[\theta]_{275}$ +570
61248-75-7	**11**	2*R*	2-OCH_3Ph	$[\theta]_{580}$ +23	$[\theta]_{285}$ −500
61248-76-8	**12**	2*S*	2-OCH_3Ph	$[\theta]_{580}$ −40	$[\theta]_{285}$ +545
61248-77-9	**13**	2*R*	3-CF_3Ph	$[\theta]_{560}$ +33	$[\theta]_{270}$ −725
	14	2*S*	3-CF_3Ph		
41432-48-8	**15**	2*R*	4-NHAcPh	$[\theta]_{560}$ +28	$[\theta]_{270}$ −980
56715-20-9	**16**	2*S*	4-NHAcPh	$[\theta]_{560}$ −34	$[\theta]_{270}$ +1100
61248-78-0	**17**	2*R*	1-Naphthyl	$[\theta]_{540}$ +31	$[\theta]_{320}$ −435
56715-19-6	**18**	2*S*	1-Naphthyl	$[\theta]_{540}$ −50	$[\theta]_{320}$ +370
	1-Amino-2-propanols X = NH_2				
61248-79-1	**25**	2*R*	3,5-di-MePh	$[\theta]_{660}$ +99	$[\theta]_{280}$ −690
61248-80-4	**26**	2*S*	3,5-di-MePh	$[\theta]_{660}$ −70	$[\theta]_{280}$ +710
61248-81-5	**27**	2*R*	2-OCH_3Ph	$[\theta]_{620}$ +220	$[\theta]_{280}$ −3530
61248-82-6	**28**	2*S*	2-OCH_3Ph	$[\theta]_{620}$ −215	$[\theta]_{280}$ +3300
13071-11-9	**29**	2*R*	1-Naphthyl	$[\theta]_{640}$ +54	$[\theta]_{290}$ −745
4199-10-4	**30**	2*S*	1-Naphthyl	$[\theta]_{640}$ −40	$[\theta]_{290}$ +785

3 or **6** to react with an excess of the appropriate phenol in the presence of 1 equiv of NaOH. The intermediate acetonides were readily converted into the corresponding diols by acidic hydrolysis (HCl, aqueous acetone). Yields and conditions are given in the Experimental Section.

Conversion of the diols to corresponding amino alcohols (**25–30**) depended upon conversion of the diol to the corresponding epoxide, accomplished by tosylation of the primary alcohol and intramolecular displacement. Subsequently, the epoxides were opened using ammonia (or other amine, e.g., isopropylamine).

Scheme II



a, ArOH/NaOH; b, H_3O^+; c, TsCl/pyridine; d, NaOH; e, RNH_2.

Diols
Ar = 2-MePh **7** (2*R*), **8** (2*S*)
Ar = 3′,5′-di-MePh **9** (2*R*), **10** (2*S*)
Ar = 2-MeOPh **11** (2*R*), **12** (2*S*)
Ar = 3-CF_3Ph **13** (2*R*), **14** (2*S*)
Ar = 4-NHAcPh **15** (2*R*), **16** (2*S*)
Ar = α-naphthyl **17** (2*R*), **18** (2*S*)

Epoxides
Ar = 3,5-di-MePh **19** (2*R*), **20** (2*S*)
Ar = 2-MeOPh **21** (2*R*), **22** (2*S*)
Ar = α-naphthyl **23** (2*R*), **24** (2*S*)

Amines
Ar = 3,5-di-MePh; R = H **25** (2*R*), **26** (2*S*)
Ar = 2-MeOPh; R = H **27** (2*R*), **28** (2*S*)
Ar = α-naphthyl; R = *i*-Pr **29** (2*R*), **30** (2*S*)

Circular Dichroism Studies. The use of rotational measurements of cuprammonium solutions of glycols is a well-known method for the assignment of absolute configuration. The technique, widely applicable to carbohydrates in the visible region,[11] has more recently been extended to CD measurements on several glycols and 1,2-amino alcohols,[12-22] and a few 1,3-glycols, e.g., the chloramphenicol diastereoisomers,[23] and to certain mandelic acids.[24] Related metal ligands, e.g., Ni and Pr, have also been used extensively in the determination of chirality of diols and 1,2-amino alcohols.[12,25-30] Other related CD configurational methods include the benzoate chirality method,[31-33] and the use of osmate[20,34] and thionocarbonate esters.[35]

Because we had earlier used the Cupra A technique successfully for determination of absolute configuration of the mephenesin isomers (**7** and **8**),[36] we sought to extend the method. Diols **7–18** and amino alcohols **25–30** show two Cotton effects in Cupra A solution (Table I and Figure). A weak, long-wavelength band is observed, maximum at ca. 560–580 nm in the diols (ε 20–50), and 620–660 nm (ε 50–220) in the amino alcohols. A stronger, shorter wavelength Cotton effect, maximum near 280 nm, is observed in all diols and amino alcohols (ε 500–3000) except in **17** and **18**, where the maximum is near 320 nm. Both bands are related to d → d* transitions of Cu(II)–diol complexes, since they are not observed in the diols or in Cupra A solutions alone. Mitscher has demonstrated that while a bidentate ligand is necessary (diol or amino alcohol), ammonia probably occupies two additional positions in the Cu complex.[22]

Based on the model studies of Bukhari,[12-16] the *S*-diol–Cupra A complexes are assigned the λ conformation (− chirality according to Dillon and Nakanishi[29,30]), and the *R*-diol–Cupra A complexes then have the δ conformation (+ chirality), assuming that the aryloxyalkyl substituent occupies the equatorial position, as would be expected.[37]

Although the absolute configuration of the diols seems readily assignable on the basis of either of the observed bands, the short-wavelength one, λ_{max} ~280 nm, is considered to be

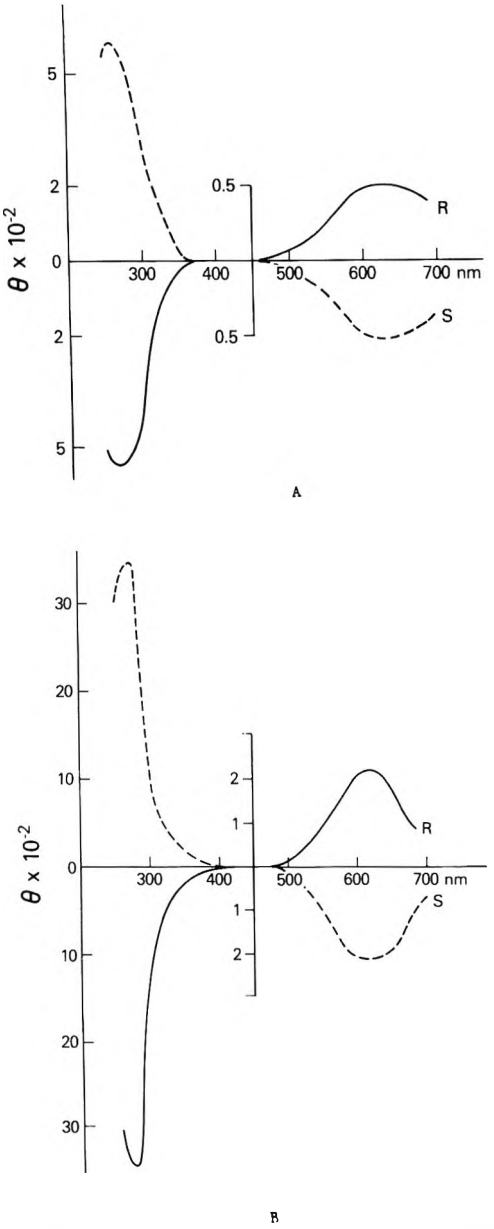
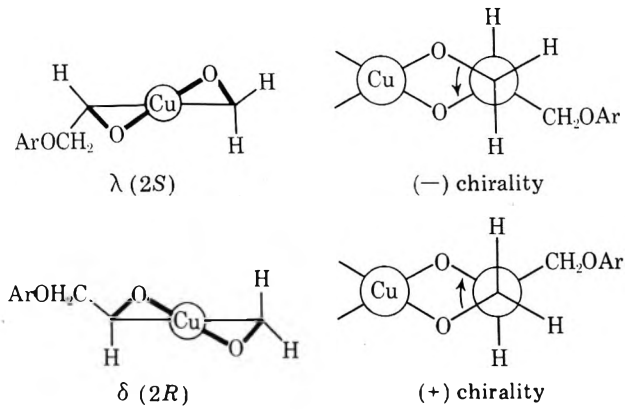
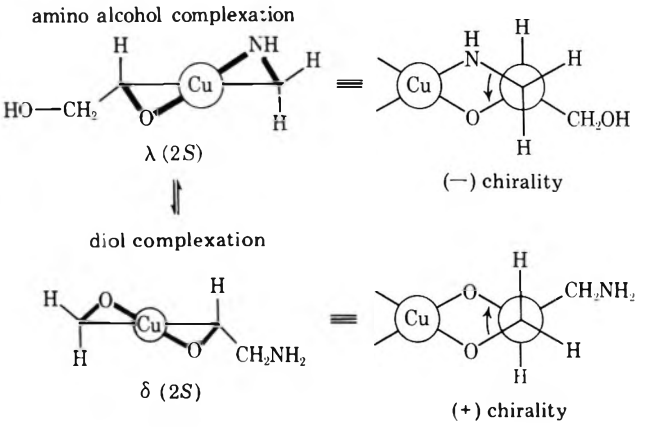


Figure 1. (A) Cupra A CD spectrum of diols 11 and 12; (B) Cupra A CD spectra of amino alcohols 27 and 28.



more reliable primarily because of its greater intensity. The transition in the ultraviolet region was also considered more reliable in 1-phenyl-2-alkylaminoethanols by Mitscher.[22] The assignments are in agreement with results of his study[22] of the effect of various N substituents on CD spectra of these amino alcohols. In 1-phenyl-2-alkylaminoethanols, *R* isomers showed λ complexes, because the Cahn–Ingold–Prelog sequence rules[38] place the substituents in the order O > CH_2N > Ar whereas in our case O > CH_2OAr > CH_2N (or CH_2OH).

Since several of the intermediates from the synthetic schemes were available, some of these were also subjected to Cupra A CD spectra (Table II). The isomeric (2*R*)- and (2*S*)-glycerol 1-tosylates (**31** and **32**), available from hydrolysis of **3** and from **6**, respectively, showed inverted Cupra A CD spectra. Compound **5**, also a tosylate with only one hydroxyl group, showed a Cupra A spectrum similar to that of the diols and amino alcohols. These results were interpreted to indicate that in Cupra A solution, amino alcohols are formed from the tosylates (by direct displacement or through the intermediate epoxide) and that the observed spectra result primarily from amino alcohol–Cupra A complexes formed in situ. The signs of the Cotton effects observed are consistent with such behavior, since the amino glycol **33** (2*S* stereochemistry) would result from 2*R* tosylate **31** and amino glycol **34** (2*R* stereochemistry) would arise from 2*S* tosylate **5**. Supporting this interpretation is the Cupra A spectrum of **33** (2*S*) which was prepared from **31** (2*R*) by the method of Sowden and Fischer.[8]



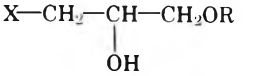
The results (Tables I and II) indicate the general applicability of the Cupra A technique to the study of absolute stereochemistry of a large number of 1,2-diols and 1,2-amino alcohols. With the absolute configurations established, it is now possible to study effects of stereochemistry on aspects of biological activity of several of these compounds, to further explore applicability of this CD technique to other related compounds, and to investigate the use of related chiroptical techniques on these compounds of known absolute configurations. These aspects are presently under investigation.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. NMR spectra were recorded on a Varian T-60 spectrometer using Me_4Si as internal standard. Notations used in the NMR descriptions are s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. NMR and IR data are provided for only one enantiomer in each set of two. Circular dichroism spectra were recorded on a Cary Model 60 ORD instrument with a 6001 CD attachment. Intensities are not absolute since the reaction between glycols or amino alcohols and Cupra A is an equilibrium process. Microanalyses were performed by Dr. F. B. Strauss, Oxford, England.

(2*R*)-3-Tosyloxy-1,2-propanediol Acetonide (3). To a cold (0 °C) solution of 4.0 g (0.003 mol) of (2*S*)-propanediol 1,2-acetonide (**2**), prepared by the method of Baer,[6] in 6 ml of anhydrous pyridine was added 7.0 g (0.037 mol) of *p*-TsCl. After stirring for 24 h, ether (200 ml) was added, the solution was washed with aqueous 1 N HCl (2 × 100 ml) and H_2O (5 × 100 ml), dried ($MgSO_4$), and filtered, and ether was evaporated to yield 6.5 g (75%) of a clear oil: α_D −4.5° (*c* 1.0, EtOH); IR (neat) 3.29, 5.70, 6.21, 6.84, 7.29, 7.91, 8.18, 8.37, 8.45, 9.10, 9.44, 10.19, 12.10, and 15.01 μ; NMR ($CDCl_3$) δ 7.86 and 7.40 (2 d, 4,

Table II. Circular Dichroism Spectra of Certain Diol Tosylates and Amino Glycols in the Presence of Cupra A Solution



Registry no.	Compd	Stereochemistry	$[\theta]_\lambda$ max	
41274-09-3	**31**, X = OTs; R = H	2*R*	$[\theta]_{580}$ −81	$[\theta]_{270}$ +1860
50765-70-3	**32**, X = OTs; R = H	2*S*	$[\theta]_{580}$ +59	$[\theta]_{270}$ −1420
16495-04-8	**5**, X = OTs; R = Bz	2*S*	$[\theta]_{620}$ +49	$[\theta]_{270}$ −920
61273-21-5	**33**, X = NH_2; R = H	2*S*	$[\theta]_{600}$ −65	$[\theta]_{270}$ +1650
61248-83-7	**34**, X = NH_2; R = Bz	2*R*	$[\theta]_{580}$ +150	$[\theta]_{270}$ −2760

ArH, J = 8 Hz), 4.60–3.60 (m, 5, H_1, H_2, and H_3), 2.50 (s, 3, $ArCH_3$), 1.40 (s, 6, 2 CH_3).

(2*S*)-3-Benzyloxy-1,2-propanediol Acetonide (4). To 26.4 g (0.20 mol) of (2*S*)-propanediol 1,2-acetonide (**2**)[6] in 100 ml of DMF was added 13.4 g (0.24 mol) of finely powdered KOH with stirring and cooling. Benzyl chloride (31.6 g, 0.25 mol) was added and the solution allowed to warm to room temperature and then heated at 70 °C for 6 h and cooled. H_2O was added and the mixture extracted with $CHCl_3$ (4 × 100 ml). The $CHCl_3$ extracts were washed with H_2O (3 × 100 ml), dried ($MgSO_4$), and evaporated to yield a yellow oil. Vacuum distillation afforded 30.8 g (70%) of **4**: bp 100 °C (0.05 mm); α_D +18.7° (neat); IR (neat) 3.32, 3.28, 3.46, 6.69, 6.89, 7.24, 7.31, 7.98, 8.25, 9.15, 9.50, 11.87, 13.60, and 14.36 μ; NMR ($CDCl_3$) δ 7.33 (s, 5, ArH), 4.60 (s, 2, CH_2Ar), 4.50–3.36 (m, 5, H_1, H_2 and H_3), 1.45 and 1.40 (2 s, 6, 2 CH_3).

(2*S*)-1-Benzyloxy-1,2-propanediol 3-Tosylate (5). (2*S*)-3-Benzyloxy-1,2-propanediol acetonide (**4**, 22.2 g, 0.1 mol) in a mixture of 20 ml of 2 N HCl and enough acetone to effect solution was refluxed for 1.5 h. The mixture was cooled, absolute EtOH (150 ml) added, and the mixture concentrated by rotary evaporation. The residual oil was dissolved in $CHCl_3$ (400 ml), washed with H_2O (3 × 50 ml), and dried (Na_2SO_4) and the solvent evaporated to yield 15.4 g (85%) of (2*R*)-3-benzyloxy-1,2-propanediol as a clear oil, which was used without further purification: IR (neat) 2.95, 3.45, 6.92, 9.23, 13.60, and 14.40 μ; NMR ($CDCl_3$) δ 7.40 (s, 5, ArH), 4.63 (s, 2, CH_2Ar), 4.16–3.50 (m, 5, H_1, H_2, and H_3), 2.53 (broad s, 2, 2 OH).

To a cold (0 °C) solution of 16.21 g (0.089 mol) of (2*R*)-3-benzyloxy-1-2-propanediol in 30 ml of anhydrous pyridine was added dropwise a solutionw of 17.1 g (0.09 mol) of *p*-TsCl in 200 ml of anhydrous benzene. The mixture was stirred for 48 h, diluted with 200 ml of benzene, washed with 2 N HCl (3 × 100 ml) and H_2O (4 × 100 ml), dried ($MgSO_4$), and evaporated to yield an oil. Crystallization from ether–hexane gave 15.0 g (50%) of **5**: mp 50–52 °C; α_D +7.0° (*c* 0.5, EtOH); IR (KBr) 3.00, 3.40, 7.40, 8.49, 9.12, 10.60, 12.01, 12.37, 13.45, 14.47, and 14.84 μ; NMR ($CDCl_3$) δ 7.80 (d, 2, H_2 and H_6 of Ts group, J = 8 Hz), 7.33 (m, 7, Ph and H_3 and H_5 of Ts group), 4.51 (s, 2, CH_2Ar), 4.10 (m, 3, H_2 and H_3), 3.53 (d, 2, H_1, J = 5 Hz), 2.63 (s, 1, OH), 2.46 (s, 3, $ArCH_3$); CD (c 0.15, Cupra A) $[\theta]_{660}$ +39, $[\theta]_{620}$ +49, $[\theta]_{530}$ 0, $[\theta]_{360}$ 0, $[\theta]_{300}$ −200, $[\theta]_{270}$ −920.

Anal. Calcd for $C_{17}H_{20}SO_5$: C, 60.73; H, 5.94. Found: C, 60.64; H, 5.88.

(2*S*)-3-Tosyloxy-1,2-propanediol Acetonide (6). A solution of 3.36 g (0.01 mol) of **5** in 50 ml of MeOH with 1.6 g of 10% Pd/C was shaken under 40 psig H_2 until uptake ceased (3 h). The catalyst was filtered, solvent evaporated, and the resulting oil crystallized from ether to yield 1.2 g (50%) of (2*S*)-3-tosyloxy-1,2-propanediol (**32**): mp 60–61 °C; α_D +7.2° (*c* 0.1, EtOH); IR (KBr) 2.95, 3.40, 6.25, 7.40, 8.45, 8.98, 9.45, 10.15, 10.76, 12.05, and 12.35 μ; NMR ($CDCl_3$) δ 7.83 and 7.36 (2 d, 4, ArH, J = 8 Hz) 5.20 (s, 2, 2 OH), 4.33–3.50 (m, 5, H_1, H_2, and H_3), 2.53 (s, 3, $ArCH_3$); CD (c 0.18, Cupra A) $[\theta]_{660}$ +27, $[\theta]_{580}$ +59, $[\theta]_{500}$ 0, $[\theta]_{300}$ −810, $[\theta]_{270}$ −1420.

Anal. Calcd for $C_{10}H_{14}SO_5$: C, 48.79; H, 5.68. Found: C, 48.94; H, 5.67.

A solution was prepared by dissolving $ZnCl_2$ (13.6 g, 0.1 mol) in 20 ml of dry acetone (tightly stoppered flask). After 1 h the solution was decanted into a flask containing 2.46 g (0.01 mol) of diol **32**. The resulting mixture was stirred for 8 h, then added to a vigorously stirring solution of 21 g (0.15 mol) of K_2CO_3, 20 ml of H_2O, and 30 ml of ether, stirred for 1 h, and filtered and the filtrate was dried (K_2CO_3). The solvent was removed to yield 1.85 g (65%) of **6** as an oil, α_D +4.7° (*c* 1.0, EtOH).

(2*R*)-3-*o*-Tolyloxy-1,2-propanediol (7). To a solution of 21.6 g (0.20 mol) of *o*-cresol in 30 ml of 2-methoxyethanol was added 8.0 g (0.20 mol) of powdered NaOH in 10 ml of H_2O. The mixture was refluxed for 24 h with 14.3 g (0.05 mol) of (2*R*)-tosylate **3**, cooled, added to 300 ml of 10% NaOH, and extracted with ether (3 × 200 ml). The ether extracts were washed with H_2O (3 × 100 ml) and dried ($MgSO_4$) and the solvent removed to yield 8.7 g (78%) of a light yellow liquid. Vacuum distillation afforded the acetonide of **7**: bp 100–104 °C (0.2 mm); α_D +33° (c 1.0, absolute EtOH); IR (neat) 3.32, 6.26, 6.69, 6.86, 7.28, 8.05, 8.62, 8.91, 9.25, 9.49, 11.80, 12.00, 13.35, and 14.08 μ; NMR ($CDCl_3$) δ 7.33–6.69 (m, 4, ArH), 4.67–3.67 (m, 5, H_1, H_2, and H_3), 2.23 (s, 3, $ArCH_3$), 1.45 and 1.38 (2 d, 6, 2 CH_3).

(2*S*)-3-o-Tolyloxy-1,2-propanediol acetonide (5.25 g, 0.023 mol) was heated with 50 ml of 1 N HCl at 70 °C for 1 h. Cooling afforded 3.0 g (72%) of **7** as white needles: mp 89–90 °C (lit. mp 89–90 °C);[36] IR (KBr) 3.00, 3.38, 6.24, 6.69, 6.85, 8.00, 8.89, 9.20, 9.41, 9.56, 10.10, 13.30, and 13.42 μ; NMR ($CDCl_3$) δ 7.40–6.67 (m, 4, ArH), 4.33–3.60 (m, 5, H_1, H_2, and H_3), 3.06 (broad s, 1, OH), 2.86 (broad s, 1, OH), 2.30 (s, 3, $ArCH_3$); CD (c 0.216, Cupra A) $[\theta]_{610}$ 0, $[\theta]_{560}$ +27, $[\theta]_{380}$ 0, $[\theta]_{350}$ −39, $[\theta]_{270}$ −570.

(2*S*)-3-o-Tolyloxy-1,2-propanediol (8). Compound **8** was prepared by a route analogous to **7** using o-cresol and (2*S*)-tosylate **6** affording (2*R*)-3-o-tolyloxy-1,2-propanediol acetonide in 50% yield after distillation: α_D −240 (*c* 0.5, absolute EtOH). The acetonide was converted to **8** by hydrolysis (1 N HCl in acetone) in 85% yield: mp 89–90 °C (lit. mp 89–90 °C);[36] CD (c 0.176, Cupra A) $[\theta]_{610}$ 0, $[\theta]_{560}$ −34, $[\theta]_{470}$ 0, $[\theta]_{350}$ +35, $[\theta]_{270}$ +560.

(2*R*)-3-(3′,5′-Dimethylphenoxy)-1,2-propanediol (9). A solution of 24.4 g (0.2 mol) of 3,5-dimethylphenol and 8.0 g (0.2 mol) of powdered NaOH in 60 ml of ethanol was added to 28.6 g (0.10 mol) of (2*R*)-tosylate **3** and the mixture refluxed for 24 h. The solvent was evaporated and the residue partitioned between 400 ml of 10% NaOH and 500 ml of ether. The ether was washed with 10% NaOH (3 × 200 ml) and H_2O (3 × 100 ml), dried ($MgSO_4$), and evaporated to give 19.29 g (81%) of a yellow oil: IR (neat) 3.30, 6.18, 6.25, 6.78, 7.25, 7.52, 7.68, 7.95, 8.18, 8.48, 8.53, 9.30, 11.85, 12.05, and 14.55 μ; NMR ($CDCl_3$) δ 6.58 (s, 3, ArH), 4.60–3.67 (m, 5, H_1, H_2, and H_3), 2.25 (s, 6, $ArCH_3$), 1.45 and 1.37 (2 s, 6, 2 CH_3).

Ten milliliters of 1 N HCl was added to a solution of 19.29 g (0.082 mol) of the acetonide of **9** in 50 ml of acetone and heated at 70 °C for 2 h. Absolute ethanol (200 ml) was added and the solution evaporated, affording an oil which solidified. Crystallization from ether–hexane gave 5.0 g (31%) of **9**: mp 74.5–75.5 °C; IR (neat) 2.90, 3.40, 6.22, 6.26, 6.90, 7.58, 7.72, 8.53, 8.66, 9.35, 12.08, and 14.60 μ; NMR ($CDCl_3$) δ 6.50 (s, 3, ArH), 4.33–3.40 (m, 7, H_1, H_2, H_3, and 2 OH), 2.23 (s, 3, $ArCH_3$); CD (c 0.168, Cupra A) $[\theta]_{650}$ +15, $[\theta]_{580}$ +28, $[\theta]_{470}$ 0, $[\theta]_{370}$ 0, $[\theta]_{340}$ −55, $[\theta]_{275}$ −575.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.37; H, 8.16. Found: C, 67.48; H, 8.16.

(2*S*)-3-(3′,5′-Dimethylphenoxy)-1,2-propanediol (10). Compound **10** was prepared by a route analogous to **9** using 3,5-dimethylphenol and (2*S*)-tosylate **6** affording (2*R*)-(3′,5′-dimethylphenoxy)-1,2-propanediol acetonide in 80% yield as a yellow oil. The acetonide was converted to **10** by hydrolysis (1 N HCl in acetone) in 56% yield: mp 74–75 °C; CD (c 0.168, Cupra A) $[\theta]_{650}$ −24, $[\theta]_{560}$ −32, $[\theta]_{470}$ 0, $[\theta]_{380}$ 0, $[\theta]_{340}$ +65, $[\theta]_{275}$ +575.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.37; H, 8.16. Found: C, 67.41; H, 8.08.

(2*R*)-3-(2′-Methoxyphenoxy)-1,2-propanediol (11). A solution of 16.2 g (0.13 mol) of 2-methoxyphenol and 7.0 g (0.13 mol) of $NaOCH_3$ in 40 ml of ethanol was added to 18.5 g (0.065 mol) of (2*R*)-tosylate **3**. The reaction mixture was refluxed for 24 h and cooled and solvent evaporated. The residue was suspended in 300 ml of ether, washed with 10% NaOH (3 × 80 ml) and H_2O (3 × 80 ml), dried ($MgSO_4$), and evaporated to yield 11.5 g (75%) of oil: IR (neat) 3.34, 6.28, 6.65, 6.75, 7.25, 7.55, 7.95, 8.25, 8.48, 9.14, 9.65, 10.25, 11.55, 11.84, 12.85, 13.45, 14.03, 14.34, and 15.14 μ; NMR ($CDCl_3$) δ 6.87 (s, 4, ArH), 4.60–3.80 (m, 5, H_1, H_2, and H_3), 3.77 (s, 3, OCH_3), 1.43 and 1.35 (2 s, 6, 2 CH_3).

Ten milliliters of 1 N HCl was added to a solution of 11.5 g (0.048 mol) of the acetonide of **11** in 50 ml of acetone and the mixture refluxed for 2 h. After cooling, the resulting solid was crystallized from CCl_4 to yield 6.0 g (63%) of **11**: mp 96–97 °C; IR (KBr) 3.00, 3.35, 6.25, 6.61, 6.82, 7.24, 7.51, 7.71, 7.94, 8.12, 8.45, 8.84, 9.03, 9.35, 9.56, 9.77, 10.04, 10.72, 11.00, 11.95, 13.04, and 13.45 μ; NMR ($CDCl_3$) δ 6.96 (s, 4, ArH), 4.30–3.70 (m, 8, H_1, H_2, H_3, and OCH_3), 3.60 (broad s, 1, secondary OH), 2.86 (t, 1, primary OH, J = 6 Hz); CD (*c* 0.166, Cupra A) $[\theta]_{650}$ +20, $[\theta]_{580}$ +23, $[\theta]_{380}$ 0, $[\theta]_{340}$ −81, $[\theta]_{285}$ −500.

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.63; H, 7.06. Found: C, 60.62; H, 7.18.

(2*S*)-3-(2′-Methoxyphenoxy)-1,2-propanediol (12). Compound **12** was prepared by a procedure analogous to **11** using 2-methoxyphenol and (2*S*)-tosylate **6** affording (2*R*)-3-(2′-methoxyphenoxy)-1,2-propanediol acetonide as a yellow oil in 85% yield. The acetonide was hydrolyzed (1 N HCl in acetone) to afford **12** in 58% yield: mp 94–95 °C (CCl_4); CD (*c* 0.162, Cupra A) $[\theta]_{650}$ −48, $[\theta]_{580}$ −40, $[\theta]_{460}$ 0, $[\theta]_{c}380$ 0, $[\theta]_{340}$ + 78, $[\theta]_{285}$ +545.

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.63; H, 7.06. Found: C, 60.85; H, 7.08.

(2*R*)-3-(3′-Trifluoromethylphenoxy)-1,2-propanediol (13). To 12.15 g (0.075 mol) of 3-trifluoromethylphenol in 20 ml of ethanol was added a solution of 3.0 g (0.075 mol) of NaOH in 5 ml of H_2O and 14.3 g (0.05 mol) of (2*R*)-tosylate **3**. After refluxing for 20 h, the solvent was evaporated and the residue treated with 30 ml 10% NaOH and extracted with ether (3 × 100 ml). The ether was washed with H_2O (3 × 100 ml), dried ($MgSO_4$), and evaporated to yield 13.2 g (95%) of yellow oil. Distillation afforded the acetonide of **13**: bp 80–94 °C (0.2 mm); α_D +11° (*c* 0.5, absolute EtOH); IR (neat) 3.31, 6.26, 6.70, 6.89, 7.28, 7.50, 8.13, 8.55, 8.85, 9.45, 11.08, 11.32, 11.87, 12.61, 13.31, 14.39, and 15.28 μ; NMR ($CDCl_3$) δ 7.66–7.00 (m, 4, ArH), 4.80–3.70 (m, 5, H_1, H_2, and H_3), 1.55 and 1.48 (2 s, 6, 2 CH_3).

To 3.58 g (0.013 mol) of the acetonide of **13** was added 60 ml of 1 N HCl and enough reagent acetone to effect solution. The mixture was heated at 70 °C for 1 h and cooled and the resulting oil extracted with $CHCl_3$ (3 × 100 ml). The $CHCl_3$ was washed with H_2O (3 × 80 ml), dried (Na_2SO_4), and evaporated to yield 2.6 g (85%) of **13** as an oil which solidified: mp 68–69 °C; IR (KBr) 2.93, 3.38, 6.26, 6.69, 6.89, 7.50, 7.70, 8.05, 8.55, 8.88, 9.36, 9.55, 11.13, 11.33, 12.75, 13.35, and 14.36 μ; NMR ($CDCl_3$) δ 7.60–7.00 (m, 4, ArH), 4.10 (m, 3, H_2 and H_3), 3.80 (d, 2, H_1, J = 4 Hz), 3.00 (s, 2, 2 OH); CD (*c* 0.13, Cupra A) $[\theta]_{640}$ +23, $[\theta]_{560}$ +33, $[\theta]_{460}$ 0, $[\theta]_{340}$ −90, $[\theta]_{300}$ −325, $[\theta]_{270}$ −725.

Anal. Calcd for $C_{10}H_{11}O_3F$: C, 50.88; H, 4.66. Found: C, 51.02; H, 4.69.

(2*S*)-3-(3-Trifluoromethylphenoxy)-1,2-propanediol (14). Compound **14** was prepared by a method analogous to **13** using 3-trifluoromethylphenol and (2*S*)-tosylate **6** affording (2*R*)-3-(3′-trifluoromethylphenoxy)-1,2-propanediol acetonide (93%) as a yellow oil. The acetonide was hydrolyzed (1 N HCl in acetone) to **14** (100% yield), mp 60–63 °C.

(2*R*)-3-(4-Acetamidophenoxy)-1,2-propanediol (15). A solution of 2.8 g (0.07 mol) of powdered NaOH and 10.57 g (0.07 mol) of 4-acetamidophenol in 30 ml of ethanol was added to 10.5 g (0.036 mol) of (2*R*)-tosylate **3** and the mixture refluxed for 16 h. The solution was cooled and solvent evaporated to yield a dark brown sludge. Aqueous 5% NaOH (30 ml) was added and the precipitate collected and washed with H_2O (2 × 20 ml), affording 7.6 g (72%) of (2*S*)-3-(4-acetamidophenoxy)-1,2-propanediol acetonide as a yellow solid: mp 145–146 °C (lit. mp 142–143.5 °C);[19] IR (KBr) 2.90, 3.01, 3.33, 6.02, 6.24, 6.48, 6.63, 7.09, 7.30, 7.65, 8.05, 8.50, 8.62, 9.30, 9.52. 11.92, and 12.20 μ; NMR (Me_2SO-d_6) δ 9.90 (s, 1, NH), 7.60 (d, 2, H_3 and H_5 of Ar ring, J = 9 Hz), 6.96 (d, 2, H_2 and H_6 of Ar ring, J = 9 Hz), 4.80–3.67 (m, 5, H_1, H_2, and H_3), 2.13 (s, 3, CH_3CO), 1.48 and 1.43 (2 s, 6, 2 CH_3).

A mixture of 4.0 g (0.015 mol) of the acetonide of **15** was heated in 50 ml of 80% aqueous HOAc at 70 °C for 1 h. The solution was added to 500 ml of ether and the precipitate collected. Crystallization from isopropyl alcohol–ether (charcoal) afforded 2.6 g (77%) of **15**: mp 153–155 °C (lit. mp 153–155 °C);[19] IR 3.06, 3.32, 3.38, 6.02, 6.23, 6.45, 6.61, 6.80, 7.07, 7.28, 7.58, 7.67, 7.79, 7.98, 8.48, 8.98, 9.08, 9.40, 9.53, 9.84, 10.15, 10.34, 10.56, 12.01, and 14.38 μ; NMR (Me_2SO-d_6) δ 9.83 (s, 1, NH), 7.53 and 6.90 (2 d, 4, ArH, J = 9 Hz), 4.88 (d, 1, secondary OH, J = 4 Hz), 4.65 (t, 1, primary OH, J = 6 Hz), 4.20–3.30 (m, 5, H_1, H_2, and H_3), 2.06 (s, 3, CH_3CO); CD (*c* 0.146, Cupra A) $[\theta]_{680}$ +16, $[\theta]_{570}$ +28, $[\theta]_{480}$ 0, $[\theta]_{370}$ 0, $[\theta]_{330}$ −125, $[\theta]_{270}$ −980.

Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.69; H, 6.66; N, 6.22. Found: C, 58.63; H, 6.68, N, 6.20.

(2*S*)-3-(4-Acetamidophenoxy)-1,2-propanediol (16). Compound **16** was prepared in a procedure analogous to **15** using 4-acetamidophenol and (2*S*)-tosylate **6** affording crude (2*R*)-3-(4-acetamidophenoxy)-1,2-propanediol acetonide in 73% yield, mp 135–140 °C. The acetonide was hydrolyzed (80% aqueous HOAc, 80 °C, 1 h) to afford **16**, as a white solid: mp 152–153 °C (lit. mp 153–155 °C);[19] CD (*c* 0.156, Cupra A) $[\theta]_{680}$ −20, $[\theta]_{560}$ −34, $[\theta]_{480}$ 0, $[\theta]_{370}$ 0, $[\theta]_{330}$ +125, $[\theta]_{270}$ +1100.

Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.69; H, 6.66; N, 6.22. Found: C, 58.80; H, 6.83; N, 6.32.

(2*R*)-3-(1-Naphthyloxy)-1,2-propanediol (17). A solution of 7.2 g (0.05 mol) of 1-naphthol in 20 ml of ethanol and 2.0 g (0.05 mol) of NaOH in 5 ml of H_2O was added to 9.8 g (0.034 mol) of (2*R*)-tosylate **3** and the mixture refluxed for 18 h. The ethanol was evaporated and the residue treated with 50 ml 5% NaOH and extracted with 500 ml of ether. The ether was washed with H_2O (3 × 200 ml), dried ($MgSO_4$), and evaporated to yield an oil. Vacuum distillation gave 6.5 g (74%) of pure (2*S*)-3-(1-naphthyloxy)-1,2-propanediol acetonide: bp 130–141 °C (0.2 mm); α_D +33° (*c* 0.5, absolute EtOH); IR (neat) 3.24, 3.30, 3.36, 3.44, 6.30, 6.61, 6.83, 7.15, 7.23, 7.28, 7.85, 8.05, 8.21, 8.60, 9.04, 9.34, 9.78, 11.85, 12.61, and 12.95 μ; NMR ($CDCl_3$) δ 8.46–6.70 (m, 7, ArH), 4.80–3.80 (m, 5, H_1, H_2, and H_3), 1.51 and 1.45 (2 s, 6, 2 CH_3).

To 6.5 g (0.025 mol) of the acetonide of **17** was added 50 ml of 1 N HCl and enough acetone to effect solution. The mixture was heated at 75 °C for 2 h and cooled and the solid collected. Recrystallization from benzene afforded 4.7 g (87%) of **17**: mp 109–111 °C; IR (KBr) 3.05, 3.39, 6.34, 6.90, 7.15, 7.86, 8.06, 9.08, 9.35, 9.80, 10.13, 10.72, 12.72, 13.05, and 13.68 μ; NMR (Me_2SO-d_6) δ 8.60–6.80 (m, 7, ArH), 5.06 (d, 1, secondary OH, J = 4 Hz), 4.70 (t, 1, primary OH, J = 6 Hz), 4.40–3.40 (m, 5, H_1, H_2, and H_3); CD (*c* 0.15, Cupra A/MeOH, 4:1) $[\theta]_{650}$ 0, $[\theta]_{540}$ +31, $[\theta]_{490}$ 0, $[\theta]_{370}$ 0, $[\theta]_{320}$ −435, $[\theta]_{310}$ −365.

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.58; H, 6.42. Found: C, 71.49; H, 6.44.

(2*S*)-3-(1-Naphthyloxy)-1,2-propanediol (18). Compound **18** was prepared by a procedure analogous to **17** using 1-naphthol and (2*S*)-tosylate **6** affording (2*R*)-3-(1-naphthyloxy)-1,2-propanediol acetonide in 50% yield, α_D −30° (*c* 0.5, absolute EtOH). The acetonide was hydrolyzed (1 N HCl in acetone) affording **18** in 92% yield: mp 108–110 °C (benzene); CD (*c* 0.154, Cupra A) $[\theta]_{650}$ −34, $[\theta]_{540}$ −50, $[\theta]_{490}$ 0, $[\theta]_{370}$ 0, $[\theta]_{340}$ +90, $[\theta]_{320}$ +370, $[\theta]_{310}$ +330.

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.58; H, 6.42. Found: C, 71.45; H, 6.42.

(2*R*)-3-(3′,5′-Dimethylphenoxy)-1,2-epoxypropane (19). A solution of 3.86 g (0.02 mol) of *p*-TsCl in 50 ml of anhydrous benzene was added dropwise to an ice-cold solution of 4.0 g (0.02 mol) of 2*R* diol **9** in 12 ml of anhydrous pyridine. After stirring for 24 h at room temperature, the reaction mixture was diluted with 150 ml of benzene, washed with 1 N HCl (3 × 75 ml) and H_2O (3 × 100 ml), dried ($MgSO_4$), and evaporated to yield an oil. Purification by column chromatography gave 2.98 g (42%) of (2*S*)-1-tosyloxy-3-(3′,5′-dimethylphenoxy)-2-propanol. IR (neat) 2.82, 3.40, 6.22, 6.28, 6.78, 7.35, 7.55, 7.71, 8.40, 8.50, 8.65, 9.10, 9.28, 10.20, 10.70, 12.05, 12.30, 13.20, 14.60, and 15.00 μ; NMR ($CDCl_3$) δ 7.73 and 7.21 (2 d, 4, TsArH, J = 8 Hz), 6.47 (m, 3, ArH), 4.20–3.80 (m, 5, H_1, H_2, and H_3), 2.36 (s, 3, $TsCH_3$), 2.26 (s, 6, $ArCH_3$).

A solution of 1.29 g (0.024 mol) of $NaOCH_3$ in 5 ml of H_2O was added to 8.4 g (0.024 mol) of the tosylate in MeOH. The solution was refluxed for 1 h, cooled, and solvent removed. Ether (300 ml) was added, NaOTs removed by filtration, and the solution washed with H_2O (3 × 80 ml), dried ($MgSO_4$), and evaporated to yield an oil. Vacuum distillation gave 0.90 g (25%) of epoxide **19**: bp 85–95 °C (0.5 mm); α_D −8.4° (*c* 0.5, EtOH); IR (neat) 3.39, 6.25, 6.85, 7.56, 7.71, 8.51, 8.65, 9.36, 11.03, 12.04, 13.00, and 14.08 μ; NMR ($CDCl_3$) δ 6.58 (s, 3, ArH), 4.06 (m, 2, H_3), 3.36 (m, 1, H_2), 2.83 (m, 2, H_1), 2.33 (s, 6, $ArCH_3$).

(2*S*)-3-(3′,5′-Dimethylphenoxy)-1,2-epoxypropane (20). Compound **20** was prepared in a procedure analogous to **19** from diol **10** and TsCl affording a crude tosylate (82% yield) as a yellow oil. Epoxide formation using NaOH afforded epoxide **20** in quantitative yield obtained as a yellow oil, used without further purification.

(2*R*)-3-(2-Methoxyphenoxy)-1,2-epoxypropane (21). To a cold solution of 4.66 g (0.0235 mol) of 2*R* diol **11** in pyridine was added dropwise a solution of 4.48 g (0.0235 mol) of *p*-TsCl in 75 ml of anhydrous benzene. The solution was stirred for 4 days at room temperature, then diluted with 300 ml of ether, washed with 1 N HCl (3 × 100 ml) and H_2O (3 × 100 ml), dried ($MgSO_4$), and evaporated to yield 7.34 g (89%) of crude tosylate: IR (neat) 2.84, 3.38, 6.24, 6.65, 6.86, 7.34, 7.94. 8.15, 8.42, 8.51, 8.88, 9.13, 9.80, 10.18, 10.65, 12.30, 13.44, and 15.05 μ; NMR ($CDCl_3$) δ 7.83 and 7.33 (2 d, 4, TsArH, J = 8 Hz), 6.93 (s, 4. ArH), 4.40–3.70 (m, 6, H_1, H_2, H_3, and OH), 3.93 (s, 3, OCH_3), 2.45 (s, 3, $ArCH_3$).

To a solution of 9.17 g (0.026 mol) of the tosylate in 20 ml of MeOH was added 1.4 g (0.026 mol) of $NaOCH_3$ in H_2O and the mixture re-

fluxed for 2 h. The solvent was evaporated and the residue suspended in 200 ml of ether. The NaOTS was removed by filtration and the ether evaporated to give an oil which crystallized from ether. Recrystallization from isopropyl alcohol gave 1.35 g (29%) of **21** as needles: mp 55–57 °C; IR (KBr) 3.37, 6.26, 6.63, 6.87, 7.50, 7.96, 8.12, 8.41, 8.88, 9.75, 10.96, 11.63, 12.10, 12.88, 13.42, and 14.33 μ; NMR ($CDCl_3$) δ 7.00 (s, 4, ArH), 4.10 (m, 2, H_3), 3.93 (s, 3, OCH_3), 3.43 (m, 1, H_2), 2.83 (m, 2, H_1).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.69; H, 6.66. Found: 66.64; H, 6.76.

(2*S*)-3-(2′-Methoxyphenoxy)-1,2-epoxypropane (22). Compound **22** was prepared by a method analogous to **21** from diol **12** and TsCl, affording a crude tosylate (80% yield) as a yellow oil. Epoxide formation, using $NaOCH_3$, afforded epoxide **22** in 45% yield, isolated as needles, mp 56–57 °C (isopropyl alcohol).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.69; H, 6.66. Found: C, 66.72; H, 6.64.

(2*R*)-1-Amino-3-(3′,5′-dimethylphenoxy)-2-propanol (25). Excess ammonia was condensed (dry ice cold finger) into a solution of 0.70 g (0.004 mol) of (2*R*)-epoxide **19** in 100 ml of isopropyl alcohol and allowed to stand for 3 days. The solvent was removed to yield 0.70 g (90%) of **25** as a viscous yellow oil: IR (neat) 2.84, 3.39, 6.25, 6.85, 7.55, 7.70, 8.52, 8.64, 9.33, 12.04, and 14.58 μ; NMR ($CDCl_3$) δ 6.58 (s, 3, ArH), 3.98 (m, 3, H_2 and H_3), 3.10–2.56 (m, 5, H_1, NH_2, and OH), 2.33 (s, 6, $ArCH_3$); CD (*c* 0.100, Cupra A) $[\theta]_{660}$ +99, $[\theta]_{600}$ +75, $[\theta]_{520}$ 0, $[\theta]_{350}$ 0, $[\theta]_{320}$ −135, $[\theta]_{280}$ −690.

(2*S*)-1-Amino-3-(3′,5′-dimethylphenoxy)-2-propanol (26). (2*S*)-Epoxide **20** (0.89 g, 0.005 mol) was dissolved in 20 ml of NH_3-saturated isopropyl alcohol and allowed to stand for 4 days at room temperature. The solvent was removed to yield 0.9 g (92%) of **26** as a viscous yellow oil: CD (*c* 0.10, Cupra A) $[\theta]_{660}$ −70, $[\theta]_{600}$ −37, $[\theta]_{520}$ 0, $[\theta]_{350}$ 0, $[\theta]_{320}$ +155, $[\theta]_{280}$ +710.

(2*R*)-1-Amino-3-(2′-methoxyphenoxy)-2-propanol (27). (2*R*)-Epoxide **21** (0.90 g, 0.005 mol) was dissolved in 100 ml of NH_3-saturated isopropyl alcohol and allowed to stand at room temperature for 3 days. The solvent was removed to yield a solid which crystallized from ethyl acetate to yield 0.40 g (41%) of **27**: mp 91–93 °C; IR (KBr) 2.95, 3.22, 3.38, 3.47, 3.66, 6.28, 6.65, 6.85, 7.52, 7.95, 8.17, 8.48, 8.90, 9.21, 9.40, 9.55, 9.73, 10.23, 10.50, 10.80, 12.16, 12.95, 13.35, and 13.60 μ; NMR ($CDCl_3$) δ 6.95 (s, 4, ArH), 4.33–3.66 (m, 7, H_2, H_3, OH, and OCH_3), 3.33–2.50 (m, 4, H_1 and NH_2); CD (*c* 0.148, Cupra A) $[\theta]_{680}$ +135, $[\theta]_{600}$ +220, $[\theta]_{510}$ 0, $[\theta]_{360}$ 0, $[\theta]_{280}$ −3530.

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.91; H, 7.61; N, 7.10. Found: C, 60.84; H, 7.57; N, 7.00.

(2*S*)-1-Amino-3-(2′-methoxyphenoxy)-2-propanol (28). (2*S*)-Epoxide **22** (0.90 g, 0.005 mol) was dissolved in 100 ml of NH_3-saturated isopropyl alcohol and allowed to stand at room temperature for 3 days. The solvent was removed to give a solid which crystallized from ethyl acetate to yield 0.45 g (50%) of **28**: mp 91–93 °C; CD (*c* 0.148, Cupra A) $[\theta]_{680}$ −150, $[\theta]_{600}$ −200, $[\theta]_{500}$ 0, $[\theta]_{360}$ 0, $[\theta]_{280}$ +3300.

(2*R*)-1-(Isopropylamino)-3-(1-naphthyloxy)-2-propanol Hydrochloride (29). Tosyl chloride (0.95 g, 0.005 mol) in 20 ml of anhydrous pyridine was added dropwise over 1 h to a solution of 1.09 g (0.005 mol) of 2*R* diol **17** in 2.0 ml of anhydrous pyridine at 25 °C. After stirring for 24 h, ether (300 ml) was added and the solution washed with 2 N HCl (5 × 100 ml) and H_2O (5 × 100 ml), dried ($MgSO_4$), and evaporated. The crude tosylate (1.25 g, 0.003 mol) was heated for 30 min at 60 °C with 0.162 g (0.003 mol) of $NaOCH_3$ in 10 ml of methanol. The solution was concentrated by rotary evaporation, diluted with 300 ml of ether, and filtered to remove the NaOTs. Oily epoxide **23**, obtained after evaporation of solvent, was allowed to stand in 25.0 g (0.42 mol) of isopropylamine for 3 days. The isopropylamine was evaporated, the residual oil dissolved in ether, and the HCl salt precipitated by addition of ether saturated with gaseous HCl. The resulting salt was crystallized from 1-propanol to yield 0.44 g (30%) of **29** HCl: mp 188–189 °C; IR (KBr) 2.94, 3.34, 3.55, 6.33, 6.63, 6.85, 7.18, 7.28, 7.86, 8.05, 8.65, 9.04, 9.29, 9.71, 9.82, 10.07, 10.43, 10.99, 12.59, 12.90, 13.58, and 14.36 μ; NMR (D_2O) δ 8.50–6.60 (m, 7, ArH), 4.60–3.80 (m, 3, H_2 and H_3), 3.50–2.83 (m, 3, H_1 and CH), 1.32 and 1.22 (2 d, 6, 2 CH_3, J = 6 Hz); CD (*c* 0.120, Cupra A) $[\theta]_{700}$ 0, $[\theta]_{660}$ +54, $[\theta]_{530}$ 0, $[\theta]_{360}$ 0, $[\theta]_{325}$ −140, $[\theta]_{290}$ −745.

Anal. Calcd for $C_{16}H_{22}NO_2Cl$: C, 65.00; H, 7.44; N, 4.73. Found: C, 65.07; H, 7.48; N, 4.86.

(2*S*)-1-Isopropylamino)-3-(1-naphthyloxy)-2-propanol Hydrochloride (30). Compound **30** was prepared by a method analogous to **29** from diol **18** and TsCl affordng a crude tosylate (97% yield) as an oil). Epoxide formation using $NaOCH_3$ afforded crude epoxide **24**, which was allowed to react with isopropylamine. Formation of the HCl salt afforded **30** HCl (27% yield), mp 188–190 °C (isopropyl alcohol).

(2*R*)-3-Tosyloxy-1,2-propanediol (31). To 11.4 g (0.04 mol) of (2*R*)-tosylate **3** was added 10 ml of 2 N HCl and enough acetone to effect solution. The mixture was refluxed for 2 h and cooled, absolute ethanol (200 ml) added, and the solvent removed to yield an oil. Crystallization from ether afforded 6.9 g (70%) of **31**: mp 60–61 °C; α_D −7.2° (*c* 0.1, EtOH); IR (KBr) 2.95, 3.40, 6.25, 7.40, 8.45, 8.98, 9.45, 10.15, 10.76, 12.05, and 12.35 μ; NMR ($CDCl_3$) δ 7.83 and 7.36 (2 d, 4, ArH, J = 8 Hz), 5.20 (s, 2, 2 OH), 4.33–3.50 (m, 5, H_1, H_2, and H_3), 2.53 (s, 3, $ArCH_3$); CD (*c* 0.154, Cupra A) $[\theta]_{660}$ −52, $[\theta]_{580}$ −81, $[\theta]_{500}$ 0, $[\theta]_{300}$ + 1090, $[\theta]_{270}$ +1860.

(2*S*)-1-Amino-2,3-propanediol (33). Sodium methoxide (0.74 g, 0.0137 mol) was carefully added to a stirring 0 °C solution of 3.38 g (0.0137 mol) of **31** in 15 ml of absolute MeOH. After stirring overnight, ether (75 ml) was added and the precipitated NaOTs removed by filtration. The filtrate was concentrated by rotary evaporation to yield 1.0 g (100%) of the epoxide as a yellow oil: IR (neat) 2.90, 3.36, 7.35, 8.39, 8.49, 9.09, 9.60, 11.04, 11.70, and 12.08 μ; NMR ($CDCl_3$) δ 4.06 and 3.60 (2 dd, 2, H_1, J_{gem} = 12, J_{cis} = 2, J_{trans} = 4 Hz), 3.11 (m, 2, H_2 and OH), 2.85 (m, 2, H_3).

The crude epoxide (0.057 g, 0.78 mmol) was dissolved in 15 ml of NH_3-saturated isopropyl alcohol and allowed to stand for 3 days. Removal of the solvent gave 0.065 g (93%) of **33** as a viscous oil: IR (neat) 2.95, 3.38, 8.21, 8.40, 8.90, and 9.65 μ; NMR (CD_3OD) δ 4.40 (s, 4, OH and NH_2), 3.23 (m, 3, H_2, H_3), 2.36 (broad m, 2, H_1); CD (*c* 0.166, Cupra A) $[\theta]_{700}$ 0, $[\theta]_{600}$ −65, $[\theta]_{500}$ 0, $[\theta]_{350}$ 0, $[\theta]_{300}$ +535, $[\theta]_{270}$ +1650.

(2*R*)-3-Benzyloxy-1-amino-2-propanol (34). To a solution of 0.335 g (0.001 mol) of **5** in 5 ml of absolute MeOH was added 0.054 g (0.001 mol) of $NaOCH_3$ in 1.0 ml of H_2O and the mixture refluxed for 1 h. The solvent was evaporated, anhydrous ether (100 ml) added, and the precipitated NaOTs removed by filtration. The ether was evaporated to yield 0.130 g (80%) of (2*S*)-1-benzyloxy-2,3-epoxypropane as an oil: IR (neat) 3.30, 3.48, 6.70, 6.89, 7.31, 7.98, 8.49, 9.15, 11.05, 11.85, 13.50, and 14.33 μ; NMR ($CDCl_3$) δ 7.36 (s, 5, ArH), 4.60 (s, 2, CH_2Ar), 3.77 and 3.38 (2 dd, 2, H_1, J_{gem} = 12, J_{cis} = 3, J_{trans} = 6 Hz), 3.20 (m, 1, H_2), 2.70 (m, 2, H_3).

The crude epoxide (0.164 g, 0.001 mol) was dissolved in 15 ml of NH_3-saturated isopropyl alcohol and allowed to stand for 3 days. Evaporation of the solvent afforded 0.18 g (100%) of **34** as a viscous oil: IR (neat) 2.91, 3.39, 3.45, 6.88, 7.31, 8.48, 9.07, 13.45, and 14.35 μ; NMR ($CDCl_3$) δ 7.36 (s, 5, ArH), 4.56 (s, 2, CH_2Ar), 3.50 (broad m, 3, H_2 and H_3), 2.73 (broad m, 5, H_1, NH_2, and OH); CD (*c* 0.22, Cupra A) $[\theta]_{700}$ 0, $[\theta]_{580}$ +150, $[\theta]_{500}$ 0, $[\theta]_{350}$ 0, $[\theta]_{300}$ −1400, $[\theta]_{275}$ −2760.

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Registry No.—**2**, 22323-82-6; **3**, 23788-74-1; **4**, 16495-03-7; **6**, 23735-43-5; **7** acetonide, 52094-01-6; **8** acetonide, 52094-00-5; **9** acetonide, 61248-84-8; **9** tosylate, 61248-85-9; **10** acetonide, 61248-86-0; **11** acetonide, 61267-51-4; **11** tosylate, 61248-87-1; **12** acetonide, 61248-88-2; **12** tosylate, 61248-89-3; **13** acetonide, 61248-90-6; **14**, 61248-91-7; **14** acetonide, 61248-92-8; **15** acetonide, 39219-47-1; **16** acetonide, 61248-93-9; **17** acetonide, 61248-94-0; **18** acetonide, 61248-95-1; **18** tosylate, 56715-24-3; **19**, 61248-96-2; **20**, 61248-97-3; **21**, 61248-98-4; **22**, 61248-99-5; **23**, 56715-28-7; **24**, 61249-00-1; **31** epoxide, 57044-25-4; *p*-TsCl, 98-59-9; benzyl chloride, 100-44-7; (2*R*)-3-benzyloxy-1,2-propanediol, 56552-80-8; *o*-cresol, 95-48-7; 3,5-dimethylphenol, 108-68-9; 2-methoxyphenol, 90-05-1; 3-trifluormethylphenol, 98-17-9; 4-acetamidophenol, 103-90-2; 1-naphthol, 90-15-3; (2*R*)-1-benzyloxy-2,3-epoxypropane, 14618-80-5.

References and Notes

(1) Part 2 of this series: W. L. Nelson and J. E. Wennerstrom, *J. Chem. Soc., Chem. Commun.*, 921 (1976).
(2) Review: A. J. Casy in "Medicinal Chemistry", 3d ed, A. Burger, Ed., Wiley, New York, N.Y., 1970, Chapter 7, pp 81–107.
(3) W. L. Alworth, "Stereochemistry and Its Application in Biochemistry. The Relations between Substrate Symmetry and Biological Stereospecificity", Wiley-Interscience, New York, N.Y., 1972.
(4) R. Bentley, "Molecular Asymmetry in Biology", Vol. 1 and 2, Academic Press, New York, N.Y., 1969.
(5) E. J. Ariens in "Modern Concepts in the Relationships between Structure and Pharmacological Activity", K. J. Brunings, Ed., Macmillan, New York, N.Y., p 247.

(6) E. Baer, *Biochem. Prep.*, **2**, 31 (1952).
(7) E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, **128**, 453 (1969).
(8) J. C. Sowden and H. O. L. Fischer, *J. Am. Chem. Soc.*, **64**, 1291 (1942).
(9) B. Belleau and J. Puranen, *J. Med. Chem.*, **6**, 325 (1963).
(10) D. Triggle and B. Belleau, *Can. J. Chem.*, **40**, 120 (1962).
(11) R. E. Reeves, *Adv. Carbohydr. Chem.*, **6**, 107 (1951).
(12) S. T. K. Bukhari, R. D. Gutherie, A. I. Scott, and A. D. Wrixon, *Chem. Commun.*, 1580 (1968).
(13) S. T. K. Bukhari, R. D. Gutherie, A. I. Scott, and A. D. Wrixon, *Tetrahedron*, **26**, 3653 (1970).
(14) S. T. K. Bukhari and R. D. Gutherie, *Carbohydr. Res.*, **12**, 469 (1970).
(15) S. T. K. Bukhari and R. D. Gutherie, *J. Chem. Soc. C*, 1073 (1969).
(16) R. S. Downing and F. L. Urbach, *J. Am. Chem. Soc.*, **90**, 5344 (1968).
(17) A. K. Ganguly, O. Z. Sarre, and J. Morton, *Chem. Commun.*, 1488 (1969).
(18) A. K. Mallams, *J. Am. Chem. Soc.*, **91**, 4505 (1969).
(19) R. W. Gillard and R. Wootton, *J. Chem. Soc. B*, 921 (1968).
(20) A. I. Scott and A. D. Wrixon, *Chem. Commun.*, 1184 (1969).
(21) A. Harner and C. S. P. Jenkins, *Chem. Commun.*, 350 (1969).
(22) L. A. Mitscher, M. S. Bathala, and G. W. Clark, in preparation.
(23) L. A. Mitscher, P. W. Howison, and T. D. Sokowlowski, *J. Med. Chem.*, **16**, 98 (1973).
(24) L. A. Mitscher, M. S. Bathala, G. W. Clark, P. W. Howison, and T. D. Sokowlowski, in preparation.
(25) J. Dillon and K. Nakanishi, *J. Am. Chem. Soc.*, **96**, 4057 (1974).
(26) K. Nakanishi and J. Dillon, *J. Am. Chem. Soc.*, **93**, 4098 (1971).
(27) K. Nakanishi, D. A. Schoolery, M. Koreeda, and J. Dillon, *Chem. Commun.*, 235 (1971).
(28) J. Dillon and K. Nakanishi, *J. Am. Chem. Soc.*, **96**, 5059 (1974).
(29) J. Dillon and K. Nakanishi, *J. Am. Chem. Soc.*, **97**, 5409 (1975).
(30) J. Dillon and K. Nakanishi, *J. Am. Chem. Soc.*, **97**, 5417 (1975).
(31) N. Harada and K. Nakanishi, *Acc. Chem. Res.*, **5**, 257 (1972).
(32) N. Harada and K. Nakanishi, *J. Am. Chem. Soc.*, **91**, 3989 (1969).
(33) S. L. Chen, N. Harada, and K. Nakanishi, *J. Am. Chem. Soc.*, **96**, 7352 (1974).
(34) E. Bunnenberg and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 5953 (1960).
(35) A. H. Haines and C. S. P. Jenkins, *Chem. Commun.*, 350 (1969).
(36) W. L. Nelson and C. E. Wood, Jr., *J. Chem. Soc., Chem. Commun.*, 896 (1973).
(37) R. D. Gillard and H. M. Irving, *Chem. Rev.*, **65**, 603 (1965).
(38) (a) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experentia*, **12**, 81 (1956); (b) *Angew. Chem., Int. Ed. Engl.*, **5**, 385 (1966).
(39) J. C. Danilewicz and J. E. G. Kemp, *J. Med. Chem.*, **16**, 168 (1973).

Synthesis and Reactions of 7-Hydrazonocephalosporanates

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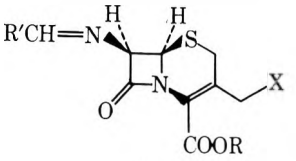
p-Nitrobenzyl 7-hydrazonocephalosporanates **3** (R_1 = *p*-NO_2PhCH_2; R_2 = H) were synthesized and identified as isomers. Thienylacetylation and reduction gave the hydrazino compound **5**. Compounds **3** react with NBS in aqueous acetone to give ketones **6**. Reduction of **6** gives alcohol **7** (R_1 = CH_2Ph; R_2 = H) which was acylated and deblocked to give a series of cephalosporin oxygen analogues.

Many chemical modifications at C_7 of cephalosporins have been achieved through activation of the C_7 position in such structures as **1**. Another method of entry into this posi-

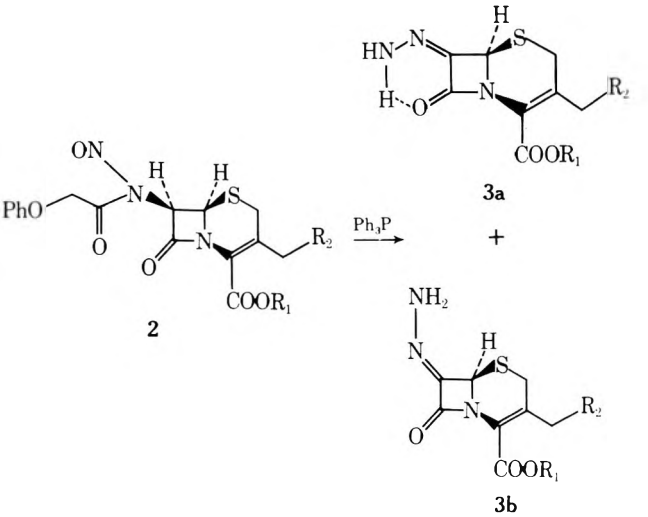


1

tion involves oxidation of C_7 to form the diazo compound followed by further reactions characteristic of this group.[1]

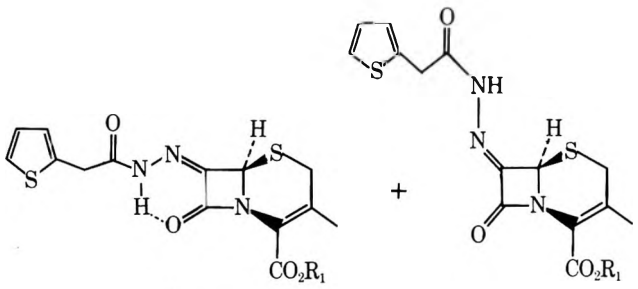
7-Diazocephalosporanates have been synthesized via diazotization of the amine,[2,3] and rearrangement of 6β-*N*-nitrosophenoxyacetamidocephalosporanates in the presence of base.[4] The latter reaction gives a poor yield since the *N*-nitroso amide is surprisingly resistant to rearrangement. Several new methods have been applied to this system and will be reported here.

The nitroso compound, *p*-nitrobenzyl 7β-*N*-nitrosophenoxyacetamidodeacetoxycephalosporanate **2** (R_1 = *p*-NO_2PhCH_2; R_2 = H), reacts with triphenylphosphine to give a mixture of *p*-nitrobenzyl 7-hydrazonocephalosporanates **3** (R_1 = *p*-NO_2PhCH_2; R_2 = H). It is postulated that the triphenylphosphine forces the *N*-nitroso–diazo rearrangement, giving the diazo derivative, which forms an adduct generating **3** on hydrolysis. Phenoxyacetic acid was isolated as a byproduct. The trichloroethyl ester of **3** (R_1 = CCl_3CH_2; R_2 = H) has been reported derived from the diazotization of 7-aminocephalosporanate with isoamyl nitrite in formic acid.[5] The analogous hydrazono compounds have also been synthesized in the penicillin series.[6] However, the existence of two isomers has not been reported in either series. The isomers are separable by chromatography and can be distinguished by

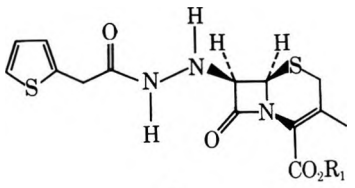


their physical properties. The intramolecular hydrogen bonding of structure **3a** is expected to produce a less polar and lower melting compound. In addition the infrared absorption of the β-lactam carbonyl should be lowered by this bonding effect by about 20 cm^{-1}.[7] These effects are observed and the structure assignments made accordingly. The isomers are interconvertible in the presence of base. Starting with either isomer, a mixture of both is obtained in the presence of pyridine.

Thienylacetylation of **3a** or **3b** (R_1 = *p*-NO_2PhCH_2; R_2 = H) gave a pair of isomers **4** (R_1 = *p*-NO_2PhCH_2). Stereospecific reduction of the hydrazones with potassium borohydride and removal of the blocking group gave one product from both isomers, the hydrazino analogue of deacetoxycephalothin **5** (R_1 = H). The phenoxyacetyl, acetyl, and free hydrazino an-



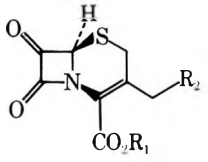
4a 4b



5

alogues have been reported[5] but without experimental details.

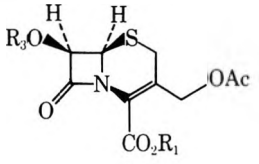
The hydrazono compound **3** (R_1 = p-NO_2PhCH_2 or Ph_2CH; R_2 = H or OAc) reacts with N-bromosuccinimide in aqueous acetone to give the ketone **6**. The same compound can be synthesized from 7-diazocephalosporanates[2] by treatment with N-bromosuccinimide or N-bromoacetamide in aqueous acetone. This method is applicable to cephalosporin C to produce esters of **6**. N,N-Phthaloylcephalosporin C di-



6

benzhydryl ester was treated with dinitrogen tetroxide and triphenylphosphine to give **3a** and **3b** (R_1 = Ph_2CH; R_2 = OAc), which react further with N-bromosuccinimide to give **6** (R_1 = Ph_2CH; R_2 = OAc).

Ketone **6** (R_1 = Ph_2CH; R_2 = OAc) was reduced with potassium borohydride to give the alcohol **7** (R_1 = Ph_2CH; R_3



7

= H). Spectral data indicate that only the cis isomer is formed. Removal of the protecting group gave the oxygen analogue of 7-ACA, **7** (R_1 = R_3 = H). Acylation prior to deblocking gave the oxygen analogues of cephalosporin **7** [R_1 = H; R_3 = $PhCH(NH_2)CO$, $PhCH_2SO_2$, $PhOCH_2CO$, $C_4H_3SCH_2CO$].

Compounds **7** (R_1 = H) were tested for bioactivity with the following (minimum inhibitory concentration, μg/ml against *Staph. aureus* A100): R_3 = $PhCH_2SO_2$, 12.5; $PhOCH_2CO$, 12.5; $C_4H_3SCH_2CO$, 12.5.

Experimental Section

General. Melting points were determined on a Fisher-Johns melting point apparatus. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. IR spectra were recorded on a Perkin-Elmer 237 spectrophotometer. NMR spectra were taken on a Varian T-60 spectrometer and are reported in parts per million downfield from Me_4Si. Baker-flex silica gel 1B-F was used for thin layer chromatography.

***p*-Nitrobenzyl 7β-*N*-Nitrosophenoxyacetamidodeacetoxycephalosporanate 2 (R_1 = p-NO_2PhCH_2; R_2 = H).** Dinitrogen tetroxide (7 g) was dissolved in 100 ml of methylene chloride. A solution of *p*-nitrobenzyl 7β-phenoxyacetamidodeacetoxycephalosporinate in methylene chloride (30 ml) was added in 20 min with stirring at 0 °C to a mixture of anhydrous sodium acetate (7 g), dinitrogen tetroxide (50 ml of above solution), and methylene chloride (50 ml). The mixture was stirred at 0 °C for 1 h. Additional portions of dinitrogen tetroxide (30 ml, 20 ml) were added immediately after and 30 min after addition of the cephalosporin derivative. Excess dinitrogen tetroxide was consumed by adding saturated sodium bicarbonate. The aqueous phase was extracted with methylene chloride. The combined organic extracts were washed with water, dried (Na_2SO_4), and evaporated to a yellow oil. Crystallization from acetone–petroleum ether gave 3.0 g of yellow solid, 81%: mp 120–121 °C dec; $[\alpha]^{25}D$ −25.2° (*c* 0.76, $CHCl_3$); IR (CH_2Cl_2) 1790, 1745, 1725, 1535, 1350, 1225 cm^{-1}; NMR ($CDCl_3$) δ 8.28–7.50 (q, 4 H), 7.35–6.83 (m, 5 H), 5.87 (d, J = 4.5 Hz, 1 H), 5.57 (s, 2 H), 5.33 (d, J = 4 Hz, 2 H), 5.00 (d, J = 4.5 Hz, 1 H), 3.62–2.75 (q, J = 16 Hz, 2 H), 2.36 (s, 3 H).

Anal. Calcd for $C_{23}H_{20}N_4SO_8$ (512.49): C, 53.90; H, 3.93; N, 10.93; S, 6.26. Found: C, 53.82; H, 3.86; N, 10.76; S, 6.40.

Benzhydryl 7β-(Benzhydryl-5-*N,N*-phthaloyl-5-aminoadipamido)cephalosporanate. N,N-Phthaloylcephalosporin C dibenzhydryl ester was prepared according to published procedures:[6] mp 165–167 °C (lit. 161–163 °C); IR ($CDCl_3$) 3410, 3330, 1780, 1740, 1730, 1685, 1510, 1385, 1230 cm^{-1}; NMR ($CDCl_3$) δ 7.80 (m, 4 H), 7.30 (m, 20 H), 6.95 (s, 1 H), 6.90 (s, 1 H), 6.45 and 6.30 (2 s, 1 H), 5.82 (q, 1 H), 5.20–4.62 (m, 4 H), 3.70–3.02 (q, J = 19 Hz, 2 H), 2.43–2.22 (m, 4 H), 2.05 (s, 3 H), 1.90–1.60 (m, 2 H).

Benzhydryl 7β-*N*-Nitrosobenzhydryl-5-*N,N*-phthaloyl-5-aminoadipamidocephalosporanate. The above compound (0.5 g) was treated with dinitrogen tetroxide in the same manner as **2**. A yellow oil was obtained: IR (film) 1780, 1730, 1720, 1525, 1385, 1240 cm^{-1}; NMR ($CDCl_3$) δ 7.80 (m, 4 H), 7.30 (m, 20 H), 6.95 (s, 1 H), 6.90 (s, 1 H), 5.79 (d, J = 4.5 Hz, 1 H), 5.30–4.70 (m, 4 H), 3.30 (s, br, 4 H), 2.40 (br, 2 H), 1.95 (s, 3 H), 1.90 (br, 2 H).

***N*-Nitrosoamide–Hydrazone Transformations.** N-Nitrosoamide **2** was refluxed with 1 equiv of triphenylphosphine in benzene for 45 min. The reaction mixture was cooled to room temperature and was stirred vigorously with excess water for 2 h. Methylene chloride was added and the organic layer was washed with 5% sodium bicarbonate solution and water, dried (Na_2SO_4), and evaporated to a brown oil. Separation of products (**3**) was effected by chromatography on silicic acid eluted by a mixture of methylene chloride and ethyl ether.

***p*-Nitrobenzyl 7-Hydrazonodeacetoxycephalosporanate 3a (R_1 = p-NO_2PhCH_2; R_2 = H).** R_f 0.45 (1:10 Et_2O–CH_2Cl_2). The product was crystallized from chloroform–petroleum ether, 28%: mp 115–116 °C; IR (CH_2Cl_2) 3435, 3300, 1760, 1730, 1610, 1525, 1350 cm^{-1}; NMR ($CDCl_3$) δ 8.25–7.50 (q, 4 H), 6.80 (s, 2 H), 5.38 (s, 2 H), 5.17 (s, 1 H), 3.73–3.00 (q, J = 19 Hz, 2 H), 2.19 (s, 3 H); MS M^+ *m/e* 362; high-resolution mass spectrum gave molecular formula $C_{15}H_{14}N_4SO_5$.

***p*-Nitrobenzyl 7-Hydrazonodeacetoxycephalosporanate 3b (R_1 = p-NO_2PhCH_2; R_2 = H).** R_f 0.20 (1:10 Et_2O–CH_2Cl_2). The product was crystallized from chloroform, 58%: mp 165–166 °C; IR (CH_2Cl_2) 3430, 3290, 1780, 1730, 1615, 1525, 1350 cm^{-1}; NMR ($CDCl_3$) δ 8.25–7.50 (q, 4 H), 6.10 (s, 2 H), 5.35 (s, 2 H), 5.30 (s, 1 H), 3.65–3.00 (q, J = 18 Hz, 2 H), 2.20 (s, 3 H); MS M^+ *m/e* 362; high-resolution mass spectrum gave molecular formula $C_{15}H_{14}N_4SO_5$.

Anal. Calcd for $C_{15}H_{14}N_4SO_5$ (362.36): C, 49.72; H, 3.89; N, 15.46; S, 8.85. Found: C, 49.54; H, 3.90; N, 15.32; S, 8.93.

Benzhydryl 7-Hydrazonocephalosporanate 3a (R_1 = Ph_2CH; R_2 = OAc). R_f 0.44 (1:10 Et_2O–CH_2Cl_2); oily product, yield 20%; IR ($CHCl_3$) 3455, 3320, 1760, 1730, 1620, 1375, 1220 cm^{-1}; NMR ($CDCl_3$) δ 7.38 (s, 10 H), 7.00 (s, 1 H), 6.85 (s, 2 H), 5.25 (s, 1 H), 5.23–4.55 (q, J = 14 Hz, 2 H), 3.75–3.10 (q, J = 19 Hz, 2 H), 2.02 (s, 3 H).

Benzhydryl 7-Hydrazonocephalosporanate 3b (R_1 = Ph_2CH; R_2 = OAc). R_f 0.24 (1:10 Et_2O–CH_2Cl_2). The product was crystallized from benzene: yield 45%; mp 152–154 °C; IR ($CDCl_3$) 3430, 3310, 1780, 1730, 1230 cm^{-1}; NMR ($CDCl_3$) δ 7.40 (s, 10 H), 6.98 (s, 1 H), 6.25 (s, 2 H), 5.28 (s, 1 H), 5.08–4.55 (q, J = 14 Hz, 2 H), 3.72–3.05 (q, J = 18 Hz, 2 H), 2.02 (s, 3 H).

Isomerizations of the Geometrical Isomers 3a and 3b. Starting with a pure isomer (either **3a** or **3b**, R_1 = p-NO_2PhCH_2; R_2 = H) in methylene chloride in the presence of 1.5 equiv of pyridine, after a month at room temperature, a mixture of both isomers (**3a** and **3b**) results. The isomers were separated by chromatography and their amounts were determined. Thus from 1 g of **3b**, 0.45 g of **3a** and 0.45 g of **3b** were isolated; from 76 mg of **3a**, 40 mg of **3a** and 25 mg of **3b** were isolated.

2-Thienylacetylation of 3b. p-Nitrobenzyl 7-hydrazonodeacetoxycephalosporanate **3b** (R_1 = p-NO_2PhCH_2; R_2 = H; 1 g, 2.76

mmol), pyridine (0.33 ml, 1.5 equiv), and 2-thienylacetyl chloride (0.72 g, 1.5 equiv) were dissolved in methylene chloride (60 ml) at 0 °C. The solution was stirred at room temperature for 18 h and then diluted with methylene chloride (100 ml). The organic phase was successively washed by cold, dilute (0.1 N) hydrochloric acid, cold 5% sodium bicarbonate solution, and ice water, dried (Na_2SO_4), and evaporated to a brown oil. Products **4a** (0.7 g, 52%) and **4b** (R_1 = *p*-NO_2PhCH_2; R_2 = H; 0.5 g, 37%) were isolated by column chromatography on silicic acid eluted with 1:10 Et_2O–CH_2Cl_2.

2-Thienylacetylation of 3a. *p*-Nitrobenzyl 7-hydrazonodeacetoxycephalosporanate **3a** (R_1 = *p*-NO_2PhCH_2; R_2 = H; 0.2 g) was treated with pyridine and 2-thienylacetyl chloride as in the case of **3b.** After column chromatography, the two products isolated were identical with those isolated in 2-thienylacetylation of **3b** based on IR, NMR, and TLC data. Yields of products isolated were **4a** (0.11 g, 41%); **4b** (0.07 g, 23%).

***p*-Nitrobenzyl 7-(2-Thienylacetyl)hydrazonodeacetoxycephalosporanate 4a.** R_f 0.45 (1:10 Et_2O–CH_2Cl_2); IR (CH_2Cl_2) 3290, 1770, 1720, 1680, 1520 cm^{-1}; NMR (acetone-d_6) δ 8.35–7.70 (q, 4 H), 7.35 (m, 1 H), 7.00 (m, 2 H), 5.58 (s, 1 H), 5.50 (s, 2 H), 4.20 (s, br, 2 H), 4.02–3.28 (q, J = 19 Hz, 2 H), 2.97 (s, br, 1 H), 2.24 (s, 3 H).

Anal. Calcd for $C_{21}H_{18}N_4S_2O_6$ (486.53): C, 51.84; H, 3.73; N, 11.52; S, 13.18. Found: C, 51.81; H, 3.70; N, 11.50; S, 13.17.

***p*-Nitrobenzyl 7-(2-Thienylacetyl)hydrazonodeacetoxycephalosporanate 4b.** R_f 0.19 (1:10 Et_2O–CH_2Cl_2); mp 178– 179 °C; IR (CH_2Cl_2) 3300, 1785, 1725, 1670, 1525 cm^{-1}; NMR (acetone-d_6) δ 8.38–7.72 (q, 4 H), 7.37 (m, 1 H), 7.00 (m, 2 H), 5.72 (s, 1 H), 5.50 (s, 2 H), 4.28 (s, br, 2 H), 3.84–3.21 (q, J = 18 Hz, 2 H), 2.90 (br, 1 H), 2.28 (s, 3 H).

Anal. Calcd for $C_{21}H_{18}N_4S_2O_6$ (486.53): C, 51.84; H, 3.73; N, 11.52; S, 13.18. Found: C, 51.56; H, 3.69; N, 11.26; S, 12.93.

Borohydride Reduction of 4a. To a cooled, stirred solution of *p*-nitrobenzyl 7-(2-thienylacetyl)hydrazonodeacetoxycephalosporanate (**4a,** R_1 = *p*-NO_2PhCH_2; R_2 = H; 0.65 g, 1.34 mmol) in tetrahydrofuran (20 ml) was added a cold solution of potassium borohydride (0.16 g, 2.2 molar equiv) in 50% aqueous THF (30 ml). After 3 min, 1 N hydrochloric acid was added to bring the pH of the solution to 2. The solution was diluted with water and extracted twice with methylene chloride. The combined extracts was washed once with 5% sodium bicarbonate solution and once with water, dried (Na_2SO_4), and evaporated to a yellow solid. Crystallization from chloroform gave white crystalline *p*-nitrobenzyl 7β-(2-thienylacetyl)hydrazinodeacetoxycephalosporanate **5** (R_1 = *p*-NO_2PhCH_2), 0.50 g, 72%: mp 183–184 °C dec; IR (CH_2Cl_2) 3390, 3280, 1775, 1725, 1680, 1520 cm^{-1}; NMR ($CDCl_3$) δ 8.20 (d, 2 H), 7.58 (d over br s, 3 H), 7.20 (m, 1 H), 6.95 (m, 2 H), 5.32 (s, 2 H), 5.27 (br, 1 H), 4.98 (d, J = 4.2 Hz, 1 H), 4.75 (m, 1 H), 3.78 (s, 2 H), 3.60–2.98 (q, J = 18 Hz, 2 H), 2.20 (s, 3 H).

Anal. Calcd for $C_{21}H_{20}N_4S_2O_6$ (488.54): C, 51.63; H, 4.13; N, 11.47; S, 13.13. Found: C, 51.44; H, 4.17; N, 11.25; S, 12.97.

Borohydride Reduction of 4b. *p*-Nitrobenzyl 7-(2-thienylacetyl)hydrazonodeacetoxycephalosporanate (**4b,** R_1 = *p*-NO_2PhCH_2; R_2 = H; 0.61 g) was treated with potassium borohydride in the same manner as in the reduction of **4a.** TLC (silica gel, 1:4 Et_2O–CH_2Cl_2) of the workup showed starting material (**4b,** R_f 0.50) and a product (R_f 0.17). Column chromatography gave 0.35 g of unreacted **4b** (58% recovery) and a white crystalline solid (0.12 g, 20%) which is identical with **5** (R_1 = *p*-NO_2PhCH_2) based on melting point, IR, NMR, and TLC data.

7β-(2-Thienylacetyl)hydrazinodeacetoxycephalosporanic Acid 5 (R_1 = H). *p*-Nitrobenzyl 7β-(2-thienylacetyl)hydrazinodeacetoxycephalosporanate (**5,** R_1 = *p*-NO_2PhCH_2, 0.10 g) was dissolved in glacial acetic acid (20 ml) and hydrogenated (1 atm) at room temperature for 2 h in the presence of 10% Pd/C (0.4 g). The catalyst was removed by filtration and washed with glacial acetic acid. The solvent was partially removed at reduced pressure and then freeze-dried together with an excess of benzene, leaving a pale yellow solid, 60 mg: IR (KBr) 3500–2700, 1770, 1730–1650 cm^{-1}; NMR (Me_2SO-d_6) δ 9.83 (br, 1 H), 7.45 (m, 1 H), 7.05 (m, 2 H), 6.65 (br, 1 H), 5.10–4.80 (m, 2 H), 3.75–3.15 (m, 2 H), 2.10 (br s, 3 H).

***p*-Nitrobenzyl 7-Oxodeacetoxycephalosporanate 6 (R_1 = *p*-NO_2PhCH_2; R_2 = H).** *p*-Nitrobenzyl 7-hydrazonodeacetoxycephalosporanate (**3b,** 0.9 g, 2.49 mmol) was dissolved in 10% aqueous acetone (200 ml), and the solution was cooled in an ice bath. Pyridine (3.65 ml, 0.04 mol) and *N*-bromosuccinimide (0.97 g, 2.2 equiv) were added to the stirred solution. After 45 min the reaction mixture was diluted with methylene chloride and cold water. Extraction with cold methylene chloride was repeated three times. The organic layer was washed successively with cold hydrochloric acid (0.1 N), cold 5% sodium bicarbonate solution, and ice water, dried (Na_2SO_4), and evaporated to a yellow oil, 0.94 g. Chromatography on silicic acid eluted with 1:10 Et_2O–CH_2Cl_2 gave one major fraction, R_f 0.36 (1:10 Et_2O–CH_2Cl_2); 0.65 g (75%); IR (film) 1825, 1780, 1725, 1515 cm^{-1}; NMR of the product **6** (R_1 = *p*-NO_2PhCH_2; R_2 = H) after chromatography gave complicated signals suspected to be the result of a mixture of the ketone and the hydrate of the ketone. The same sample was refluxed in benzene under a Dean-Stark trap for 16 h and the following NMR was obtained after removal of solvent at reduced pressure: NMR ($CDCl_3$) δ 8.25–7.50 (q, 4 H), 5.40 (s, 2 H), 5.30 (s, 1 H), 3.78–3.10 (q, J = 19 Hz, 2 H), 2.25 (s, 3 H).

Benzhydryl 7-Oxocephalosporanate 6 (R_1 = Ph_2CH; R_2 = OAc). Compound **3b** (R_1 = Ph_2CH; R_2 = OAc) (0.5 g, 1.11 mmol) was treated with *N*-bromosuccinimide in the same way as **3b** (R_1 = *p*-NO_2PhCH_2; R_2 = H). A yellow oil was obtained after chromatography: 0.24 g, 49%; R_f 0.40 (1:9 Et_2O–CH_2Cl_2); IR (film) 1825, 1785, 1735, 1385, 1240 cm^{-1}; NMR of the product after chromatography indicated partial hydration. The sample after refluxing in benzene gave the following spectrum: NMR ($CDCl_3$) δ 7.39 (s, 10 H), 7.00 (s, 1 H), 5.21 (s, 1 H), 5.10–4.65 (q, J = 13 Hz, 2 H), 3.80–3.15 (q, J = 18 Hz, 2 H), 2.01 (s, 3 H).

Benzhydryl 7β-Hydroxycephalosporanate 7 (R_1 = Ph_2CH; R_3 = H). Crude **6** (R_1 = Ph_2H; R_2 = OAc) (2.95 g) was dissolved in THF (150 ml) and cooled to 0 °C. Potassium borohydride (0.74 g, 13.7 mmol) in 1:1 THF–H_2O (150 ml) was added quickly. The reaction was quenched after 2 min by addition of 1 N HCl to pH 2. The solution was diluted with water and extracted with methylene chloride, and the organic layer was washed with bicarbonate solution and salt solution. Drying and evaporation gave a yellow oil which was chromatographed to give 1.2 g of solid. Recrystallization from benzene gave mp 122–123 °C; IR (CH_2Cl_2) 3540, 1785, 1735, 1225 cm^{-1}; NMR ($CDCl_3$) δ 2.04 (s, 3 H), 3.45 (d, 2 H), 3.90 (s, 1 H), 4.62–5.20 (m, J_1 = 4.5, J_2 = 13 Hz, 3 H), 5.29 (d, J = 4.5 Hz, 1 H), 7.00 (s, 1 H), 7.39 (s, 10 H).

7β-Hydroxycephalosporanic Acid 7 (R_1 = R_3 = H). Compound **7** (R_1 = Ph_2H; R_3 = H) (0.3 g, 0.68 mmol) was dissolved in trifluoroacetic acid (7 ml) and anisole (1 ml) at 0 °C. After 1 h the solvents were evaporated and the residual oil washed with petroleum ether. The oil was dissolved in ethyl acetate and decolorized with charcoal. Crystallization from ethyl acetate gave 0.17 g (99%): mp 132 °C dec; IR (KBr) 3430, 3100, 1780–1700, 1625, 1380, 1220 cm^{-1}; NMR (acetone-d_6) δ 2.04 (s, 3 H), 3.55 (d, 2 H), 4.80–5.15 (m, J = 4.8, 13 Hz, 3 H), 5.40 (d, J = 4.8 Hz, 1 H).

Benzhydryl 7β-Phenoxyacetoxycephalosporanate 7 (R_1 = $CHPh_2$; R_3 = $PhOCH_2CO$). Compound **7** (R_1 = $CHPh_2$; R_3 = H) (0.8 g, 1.8 mmol) and phenoxyacetyl chloride (0.42 g, 1.5 equiv) were dissolved in CH_2Cl_2 (50 ml). Pyridine (0.15 ml, 1.5 equiv) was added to the cooled, stirred solution. After 3 h stirring at room temperature, the solution was washed with water, bicarbonate, and salt solution. The solution was dried and evaporated and the residue was chromatographed on silicic acid with Et_2O–CH_2Cl_2 (1:20) to give 0.85 g (88%) of an oil: IR (film) 1785, 1730, 1600, 1495, 1380, 1225 cm^{-1}; NMR ($CDCl_3$) δ 1.98 (s, 3 H), 3.38 (s, 2 H), 4.75 (s, 2 H), 4.65–5.20 (q, J = 4.8, 14 Hz, 3 H), 6.10 (d, J = 4.8 Hz, 1 H), 6.80–7.54 (m, 16 H).

7β-Phenoxacetoxycephalosporanic Acid 7 (R_1 = H; R_3 = $PhOCH_2CO$). Compound **7** (R_1 = $CHPh_2$; R_3 = $PhOCH_2CO$) was deblocked in the same way as **7** (R_1 = $CHPh_2$; R_3 = H) to give a 93% yield: IR (film) 3580, 3520–2500, 1785–1690, 1635, 1600, 1495, 1380, 1230 cm^{-1}; NMR (acetone-d_6) δ 2.02 (s, 3 H), 3.60 (d, 2 H), 4.92 (s, 2 H), 4.70–5.28 (q, J = 14 Hz, 2 H), 5.25 (d, J = 4.8 Hz, 1 H), 6.32 (d, J = 4.8 Hz, 1 H), 6.87–7.42 (m, 5 H), 8.10 (s, 1 H).

Benzhydryl 7β-(2-Thienyl)acetoxycephalosporanate 7 (R_1 = $CHPh_2$; R_3 = $C_4H_3SCH_2CO$). Compound **7** (R_1 = $CHPh_2$; R_3 = H) (0.45 g, 1.0 mmol), 2-thienylacetic acid (0.21 g, 1.5 equiv), and pyridine (0.1 ml, 1.2 equiv) were dissolved in CH_2Cl_2 (50 ml) at 0 °C. Diisopropylcarbodiimide (0.13 g, 1 equiv) was added and the solution stirred at 0 °C for 1 h and stored at 5 °C for 17 h. The solution was filtered, diluted with CH_2Cl_2, and washed with cold dilute HCl, bicarbonate, and salt solution. Drying and evaporation gave a yellow oil which was chromatographed on silicic acid with Et_2O–CH_2Cl_2 (1:20) to give 0.6 g (95%): IR (film) 1785, 1730, 1360, 1235 cm^{-1}; NMR ($CDCl_3$) δ 1.98 (s, 3 H), 3.36 (s, 2 H), 3.91 (s, 2 H), 4.60–5.20 (d on q, J = 4.8, 14 Hz, 3 H), 6.05 (d, J = 4.8 Hz, 1 H), 6.90–7.54 (m, 14 H).

7β-(2-Thienyl)acetoxycephalosporanic Acid 7 (R_1 = H; R_3 = $C_4H_3SCH_2CO$). Compound **7** (R_1 = $CHPh_2$; R_3 = $C_4H_3SCH_2CO$) was deblocked as described for **7** (R_1 = $CHPh_2$; R_3 = $PhOCH_2CO$). Freeze-drying from benzene gave 98%: IR (film) 3560–2540, 1780, 1725, 1380, 1225 cm^{-1}; NMR ($CDCl_3$) δ 2.13 (s, 3 H), 3.47 (s, 2 H), 4.00 (s, 2 H), 4.82–5.38 (d on q, J = 4.8, 15 Hz, 3 H), 6.19 (d, J = 4.8 Hz, 1 H), 7.00 (d, 1 H), 7.20–7.40 (m, 2 H), 7.73 (s, 1 H).

Benzhydryl 7β-Benzylsulfonylcephalosporanate 7 (R_1 = $CHPh_2$; R_3 = $PhCH_2SO_2$). Compound **7** (R_1 = $CHPh_2$; R_3 = H) was

benzylsulfonated with benzylsulfonyl chloride and pyridine as described for **7** (R_1 = $CHPh_2$; R_3 = $PhOCH_2CO$). The product was chromatographed on silica gel with Et_2O–CH_2Cl_2 (1:20) to give 74% of an oil: IR (film) 1780, 1725, 1625, 1495, 1450, 1370, 1220 cm^{-1}; NMR ($CDCl_3$) δ 2.05 (s, 3 H), 3.45 (s, 2 H), 4.58 (s, 2 H), 4.55–5.20 (d on q, J = 13, 21 Hz, 3 H), 5.70 (d, J = 4.5 Hz, 1 H), 6.95 (s, 1 H), 7.45 (m, 15 H).

7β-Benzylsulfonylcephalosporanic Acid 7 (R_1 = H; R_3 = $PhCH_2SO_2$). Compound **7** (R_1 = $CHPh_2$; R_3 = $PhCH_2SO_2$) was deblocked as described for **7** (R_1 = $CHPh_2$; R_3 = $PhOCH_2CO$) to give a yellow oil. Treatment with potassium 2-ethyl hexanoate gave 60 mg of the potassium salt: IR (KBr) 2910, 1755, 1725, 1600, 1360, 1225 cm^{-1}.

Benzhydryl 7β-(2-*tert*-Butoxycarbonylamino-D-phenylacetoxy)cephalosporanate 7 [R_1 = $CHPh_2$; R_3 = $PhCH(NHCO_2$-*t*-Bu)CO]. Compound **7** (R_1 = $CHPh_2$; R_3 = H) (2.8 g, 6.4 mmol) was esterified with 2-*tert*-butoxycarbonylamino-D-phenylacetic acid as described for **7** (R_1 = $CHPh_2$; R_3 = $C_4H_3SCH_2CO$). Chromatography on silicic acid with Et_2O–CH_2Cl_2 (1:20) gave 0.5 g (11%) of oil: IR (film) 3300, 2960, 1790, 1720, 1500 cm^{-1}; NMR ($CDCl_3$) δ 1.90 (s, 3 H), 4.06 (q, J_{gem} = 15 Hz, 2 H), 4.82 (d, J = 4 Hz, 2 H), 5.35 (d, J = 13 Hz, 1 H), 5.60 (m, 2 H), 6.03 (d, J = 4.8 Hz, 1 H), 6.86 (s, 1 H), 7.24 (m, 15 H).

7β-(2-Amino-D-phenylacetoxy)cephalosporanic Acid 7 [R_1 = H; R_3 = $PhCH(NH_2)CO$]. Compound **7** [R_1 = $CHPh_2$; R_3 = $PhCH(NHCO_2$-*t*-Bu)CO] (0.13 g, 0.149 mmole) was deblocked as described for **7** (R_1 = $CHPh_2$; R_3 = $PhOCH_2CO$). After evaporation of the solvents the residue was dissolved in 10 ml of cold dioxane and 20 ml of cold methylene chloride. Toluenesulfonic acid (29 mg) was added and the solution freeze-dried. The residue was crystallized from dioxane–ether to give a white solid **7** [R_1 = H; R_3 = D-$PhCH(NH_3^+CH_3PhSO_3^-)CO$]: mp 138–140 °C; IR (KBr) 3400, 2900, 1760, 1730, 1610, 1500, 1375 cm^{-1}; NMR (acetone-d_6) δ 1.80 (s), 2.13 (s, 3 H), 3.12 (m, 2 H), 4.70 (d, J = 4 Hz, 2 H), 4.90 (d, J = 5 Hz, 1 H), 5.33 (s, 1 H), 6.15 (d, J = 4 Hz, 1 H), 6.90–7.50 (m, 9 H).

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Registry No.—**2** (R_1 = p-NO_2PhCH_2; R_2 = H), 51056-21-4; **3** (R_1 = p-NO_2PhCH_2; R_2 = H), 61394-33-0; **3** (R_1 = Ph_2CH; R_2 = OAc), 61394-34-1; **4** (R_1 = p-NO_2PhCH_2; R_2 = H), 61394-35-2; **5** (R_1 = p-NO_2PhCH_2), 61394-36-3; **5** (R_1 = H), 61394-37-4; **6** (R_1 = p-NO_2PhCH_2; R_2 = H), 61394-38-5; **6** (R_1 = Ph_2CH; R_2 = OAc), 59128-53-9; **7** (R_1 = Ph_2CH; R_3 = H), 59128-54-0; **7** (R_1 = R_3 = H), 59128-55-1; **7** (R_1 = $CHPh_2$; R_3 = $PhOCH_2CO$), 59128-56-2; **7** (R_1 = H; R_3 = $PhOCH_2CO$), 57792-80-0; **7** (R_1 = $CHPh_2$; R_3 = $C_4H_3SCH_2CO$), 59128-57-3; **7** (R_1 = H; R_3 = $C_4H_3SCH_2CO$), 59128-58-4; **7** (R_1 = $CHPh_2$; R_3 = $PhCH_2SO_2$), 61394-39-6; **7** (R_1 = H; R_3 = $PhCH_2SO_2$), 61394-40-9; **7** (R_1 = $CHPh_2$; R_3 = $PhCHNHCO_2$-*t*-Bu)CO, 61436-64-4; **7** (R_1 = H; R_3 = $PhCHNH_2COMeC_6H_4SO_3H$), 61394-42-1; dinitrogen tetroxide, 10544-72-6; *p*-nitrobenzyl 7β-phenoxyacetamidodeacetoxycephalosporanate, 28974-31-4; benzhydryl 7β-(benzhydryl-5-*N*,*N*-phthaloyl-5-aminoadipamido)cephalosporanate, 16361-81-2; benzhydryl 7β-*N*-nitrosobenzhydryl-5-*N*,*N*-phthaloyl-5-aminoadipamidocephalosporanate, 61394-43-2; 2-thienylacetyl chloride, 50529-60-7; phenoxyacetyl chloride, 701-99-5; 2-thienylacetic acid, 1918-77-0; benzylsulfonyl chloride, 1939-99-7; 2-*tert*-butoxycarbonylamino-D-phenylacetic acid, 33125-05-2.

References and Notes

(1) For review see P. G. Sammes, *Chem. Rev.*, **76**, 113 (1976).
(2) L. D. Cama, R. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Am. Chem. Soc.*, **94**, 1408 (1972).
(3) J. S. Wiering and H. Wynberg, *J. Org. Chem.*, **41**, 1574 (1976).
(4) J. C. Sheehan, Y. S. Lo, J. Löliger, and C. C. Podewell, *J. Org. Chem.*, **39**, 1444 (1974); D. Hauser and H. P. Sigg, *Helv. Chim. Acta*, **50**, 1327 (1967).
(5) G. Lowe, German Patent 2 305 972 (1973); *Chem. Abstr.*, **79**, 115602 (1973).
(6) D. M. Brunwin and G. Lowe, *J. Chem. Soc., Chem. Commun.*, 192 (1972).
(7) F. Scheinmann, Ed., "An Introduction to Spectroscopic Methods for the Identification of Organic Compounds", Vol. I, Pergamon Press, Elmsford, N.Y. 1970, p 129.

1-Oxo-1,2,5-thiadiazolidin-3-ones. A Structural Reassignment

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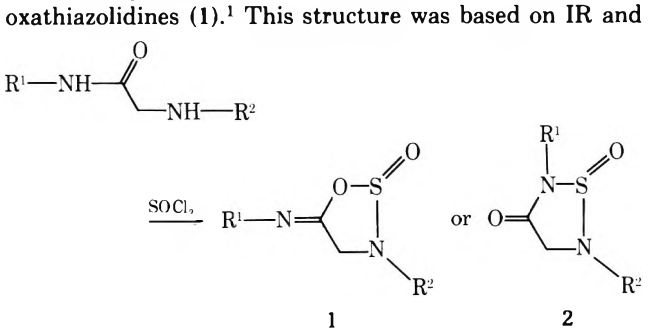
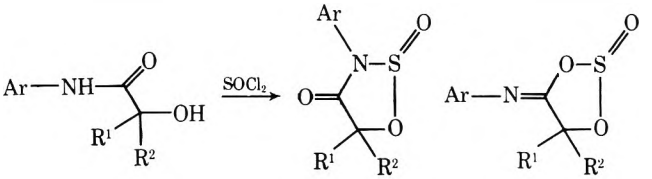
The structure of the products obtained from the reactions of 2-aminoamides with thionyl chloride has been reinvestigated by means of ^{13}C NMR spectroscopy. As a result of these investigations and comparisons with appropriate model compounds, the revised 1-oxo-1,2,5-thiadiazolidin-3-one structure has been assigned.

We reported previously the reaction of 2-aminoamides with thionyl chloride to produce 2-oxo-5-imino-1,2,3-oxathiazolidines (**1**).[1] This structure was based on IR and NMR spectral data as well as the mild acid hydrolysis of **1a** to its precursor 2-aminoamide. Subsequently, Chupp reported on a similar reaction between 2-hydroxyarylamides and thionyl chloride.[2] Consideration of the IR and NMR spectral data led this author to prefer the 2-oxo-1,2,3-oxathiazolidin-4-one structure (**3**) over the isomeric 2-oxo-4-imino-1,3,2-dioxathiolane structure (**4**). Chupp and Dahm later employed ^{18}O labeling and x-ray crystallography to confirm structure **3a** (Ar = 3,4-$Cl_2C_6H_3$; R^1 = CH_3; R^2 = H; 5-methyl group trans to the sulfinyl oxygen).[3] At the same time Chupp



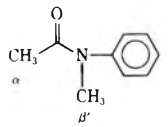
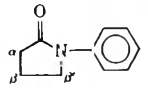
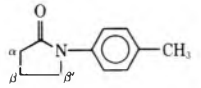
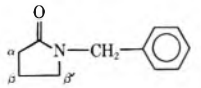
1 **2**

a, R^1 = o-$C_6H_4CH_3$; R^2 = *t*-Bu
b, R^1 = o-$C_6H_4CH_3$; R^2 = C_6H_5
c, R^1 = *t*-Bu; R^2 = C_6H_5
d, R^1 = $CH_2C_6H_5$; R^2 = *t*-Bu



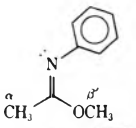
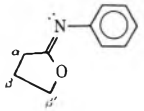
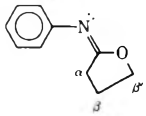
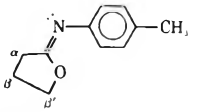
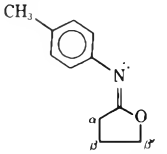
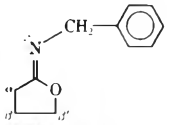
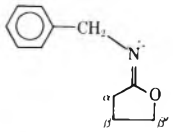
3 **4**

Table I. Amide and Lactam ^{13}C Chemical Shifts[a,b]

Structure	No.	C=O	C-α	C-β	C-β′
	7	170.0	22.3		37.0
	9	174.0	32.7	17.8	48.5
	10	173.8	32.6	17.8	48.6
	11	174.4	30.7	17.6	46.4[c]

[a] Chemical shifts are in parts per million downfield from Me_4Si. [b] Aromatic resonances between 119.6 and 144.7. [c] Assignment may be interchanged with a peak ($ArCH_2$) at 46.3.

Table II. Imidate and Iminolactone ^{13}C Chemical Shifts[a,b]

Structure	No.	C=N-	C-α	C-β	C-β′	CH_3 or CH_2Ar
	8-*Z*	161.5	15.7		53.0	
	12-*Z*	163.5	29.8	22.9	71.2	
	12-*E*	168.9	25.0[c]	23.4[c]	69.1	
	13-*Z*	163.1	29.8	22.9	71.1	20.8
	13-*E*	168.8	24.8[c]	23.4[c]	68.9	20.7
	14-*Z*	163.6	28.8	23.4	70.1	51.2
	14-*E*	169.2	23.6[c]	23.3[c]	67.9	54.5

[a] Chemical shifts are in parts per million downfield from Me_4Si. [b] Aromatic resonances between 121.0 and 149.5. [c] Assignment may be interchanged.

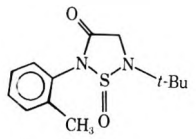
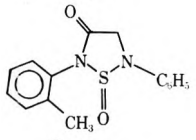
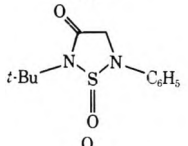
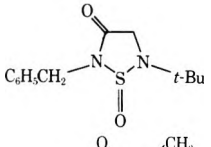
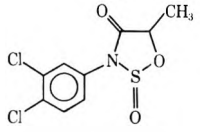
and Dahm also pointed out that our evidence for structure **1** was equally compatible with the isomeric 1-oxo-1,2-5-thiadiazolidin-3-one structure (**2**).

These observations led us to reexamine the structure of the 2-aminoamide–thionyl chloride products. Since the product structure could depend upon the precise nature of the amide nitrogen substituent, a more general technique than either ^{18}O labeling or x-ray crystallography was sought for differentiating between structures **1** and **2**.

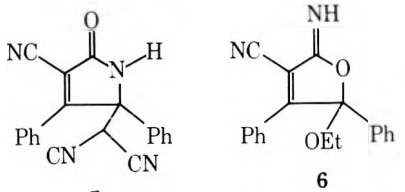
Observation that the 2-aminoamide–thionyl chloride product **1b** showed a peak at *m/e* 222 (8% of base peak) appeared to support the original assignment. This peak, which corresponds to the facile loss of SO_2 from the parent ion, would not be expected from structure **2b**. However, since the possibility of mass spectral rearrangement could not be excluded, we sought other evidence.

Ducker and Gunter recently reported the natural abundance ^{13}C chemical shifts for the C-2 carbons of lactam **5**

Table III. ^{13}C Chemical Shifts of 2-Aminoamide–Thionyl Chloride Products and 3a[a,b]

Structure	No.	C=O	C-α	CH_3	$C(CH_3)_3$	$C(CH_3)_3$	CH_2
	2a	170.9	46.1	18.0	55.8	27.9	
	2b	169.2	48.4	18.0			
	2c	171.0	49.8		58.4	28.7	
	2d	171.9	46.1[c]		55.4	27.9	43.5[c]
	3a	170.5	76.4	17.0			

[a] Chemical shifts are in parts per million downfield from Me_4Si. [b] Aromatic resonances between 116.9 and 139.6 ppm. [c] Assignments may be interchanged.



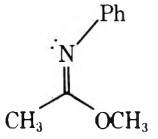
5 6

(170.4 ppm) and the iminolactone **6** (155.7 ppm).[4] Thus, it appeared that ^{13}C NMR spectroscopy might provide a simple, unambiguous method for differentiating between the amide and imidate moieties, and ultimately between structures **1** and **2**.

To test the validity of this approach, the ^{13}C NMR spectra were obtained for the following model compounds: *N*-methylacetanilide (**7**),[5] *O*-methyl *N*-phenylacetimidate (**8**),[6-8] the 1-substituted 2-pyrrolidinones (**9–11**),[9,10] and the N-substituted 2-iminotetrahydrofurans (**12–14**).[11,12] The assignments of the pertinent ^{13}C resonances of these model compounds are shown in Tables I and II.

The ^{13}C spectra for the acyclic amide **7** and the lactams **9–11** were all easily assigned with the lactam carbonyl carbons appearing ca. 4 ppm further downfield than the amido carbon of **7**.

The spectra of imidate **8** and the iminolactones **12–14** proved to be more complex because of syn–anti isomerism. Moriarty et al. reported that **8** exists as the configurationally stable *Z* isomer (**8-*Z***) on the basis of 100-MHz ^1H NMR

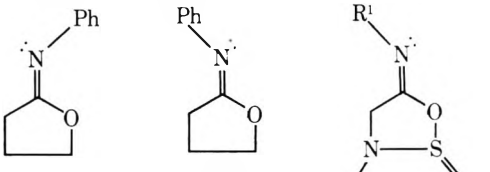


8-*Z*

studies.[8] Our ^{13}C spectrum of **8** confirms the presence of only one isomer. In contrast, Saito and Nukada reported that **12** exists as a mixture of syn–anti isomers **12-*Z*** and **12-*E***.[13] On the basis of their spectral studies, Saito and Nukada assigned the major isomer the *Z* configuration. Apparently, the effective size of the **12-*E*** methylene group is larger than the oxygen.

The ^{13}C and ^1H spectra of iminolactones **12–14** confirm the existence of syn–anti isomerism. For example, from the ^1H spectra the major isomer was shown to represent ca. 65 and 89% of **13** and **14**, respectively. The major isomer in each case is assigned the *Z* configuration based on the work of Saito and Nukada.[13,14] It is not clear why the chemical shifts for the imino carbon of the *E* isomers is deshielded relative to the same carbon in the *Z* isomer. It is possible that repulsive interaction between the α-methylene protons and the phenyl ring causes the angle between the C=N and the *N*-phenyl bond to become slightly larger than 120°. The concomitant rehybridization of the nitrogen atom from sp^2 toward sp would increase s character in the nitrogen orbital participating in the C–N σ bond and thereby cause a deshielding of the imino carbon.[21]

The ^{13}C spectra were obtained for a variety of our 2-aminoamide–thionyl chloride products **1a–d** or **2a–d** and for compound **3a**. These spectral results are summarized in Table III. An examination of these spectra reveals that the low-field resonance corresponding to the imino carbon in structure **1** or the amido carbon in structure **2** appears in the range of 169–172 ppm. This chemical shift range is in good agreement with the chemical shift of ca. 174 ppm observed for the amido carbon in lactams **9–11**. The slight shielding effect could be due to the adjacent sulfinyl group in structure **2**. The observed ^{13}C chemical shift of 170.5 ppm for the amido carbon of **3a** supports this assignment.[17] Of equal or greater significance is the failure to observe any sign of syn–anti isomerism in the



12-*Z* **12-*E*** **1-*E***

^{13}C spectra of these 2-aminoamide–thionyl chloride products.[22] The 169–172 ppm chemical shift range could be consistent with structure **1**, if the products existed solely as the configurationally stable *E* isomer **1**-*E*. It appears unlikely, however, that the configurational preference of these compounds should be completely opposite that of the iminolactones **12–14**. On the basis of these ^{13}C spectra, the 2-aminoamide–thionyl chloride products should be reassigned the 1-oxo-1,2,5-thiadiazolidin-3-one structure (**2**) rather than the initially assigned 2-oxo-5-imino-1,2,3-oxathiazolidine structure (**1**).

Experimental Section

Spectra. Carbon-13 spectra were recorded on a Varian XL-100-15 NMR spectrometer, equipped with a Transform Technology FT attachment, operating at 25.16 MHz under conditions of full proton decoupling at a probe temperature of about 38 °C. Samples were observed in 12-mm o.d. tubes as saturated solutions (for solid compounds) or approximately 50% solutions (for liquid compounds) in $CDCl_3$ containing Me_4Si as internal standard. ^1H NMR spectra were also recorded on $CDCl_3$ solutions using a Varian XL-100-15 NMR spectrometer. Chemical shifts are relative to internal Me_4Si.

Materials. The 2-aminoamide–thionyl chloride products (**2a–d**) were prepared as previously described.[1] Compound **3a** was prepared according to the procedure of Chupp.[2] Compound **7** was prepared by the acetylation of *N*-methylaniline with acetyl chloride.[5] Compound **8**[6–8] was prepared from acetanilide by methylation using methyl fluorosulfonate. Compounds **9**,[9] **10**,[9] and **11**[10] were prepared by potassium hydroxide fusion of *N*-phenyl- (**15**),[9] *N*-*p*-tolyl- (**16**),[9] and *N*-benzyl-4-chlorobutanamide (**17**),[10] respectively. Compounds **12**,[11,12] **13**,[11] and **14**[11] were prepared from **15**, **16**, and **17**, respectively, upon treatment with silver tetrafluoroborate, according to the general procedure of Eschenmoser et al.[20] as applied by Schmir and Cunningham[12] for the preparation of **12**. All of the compounds had IR and ^1H NMR spectra in agreement with the assigned structures.

Acknowledgments. The authors thank the National Science Foundation for partial support of this work and Dr. W. S. Brey, Jr., Dr. L. W. Jaques, and Mr. P. I. Yang for recording the ^{13}C spectra reported in this paper. H. L. G. thanks the Proctor & Gamble Co. for a graduate fellowship (1974–1975).

Registry No.—**2a**, 61218-56-2; **2b**, 61218-57-3; **2c**, 61218-58-4; **2d**, 61218-59-5; **3a**, 52559-50-9; **7**, 579-10-2; **9**, 4641-57-0; **10**, 3063-79-4; **11**, 5291-77-0; 8-*Z*, 31001-89-5; **12**-*Z*, 51229-48-2; **12**-*E*, 51229-49-3; **13**-*Z*, 61218-60-8; **13**-*E*, 61218-61-9; **14**-*Z*, 61218-62-0; **14**-*E*, 61218-63-1.

References and Notes

(1) J. A. Deyrup, J. C. Gill, T. LeBlanc, and H. L. Gingrich, *J. Org. Chem.*, **38**, 1645 (1973).
(2) J. P. Chupp, *J. Heterocycl. Chem.*, **11**, 1 (1974).
(3) J. P. Chupp and D. J. Dahm, *J. Heterocycl. Chem.*, **12**, 393 (1975).
(4) J. W. Ducker and M. J. Gunter, *Aust. J. Chem.*, **27**, 2229 (1974).
(5) A. W. Hoffman, *Ber.*, **7**, 525 (1874).
(6) A. Buhner, *Justus Liebigs Ann. Chem.*, **333**, 289 (1904).
(7) A. Pilotti, A. Reuterhall, and K. Torssell, *Acta Chem. Scand.*, **23**, 818 (1969).
(8) R. M. Moriarty, C. L. Yeh, K. C. Ramey, and P. W. Whitehurst, *J. Am. Chem. Soc.*, **92**, 6360 (1970).
(9) P. Lipp and F. Caspers, *Chem. Ber.*, **58**, 1011 (1925).
(10) W. E. Hanford and R. Adams, *J. Am. Chem. Soc.*, **57**, 921 (1935).
(11) T. Mukaiyama and K. Sato, *Bull. Chem. Soc. Jpn.*, **36**, 99 (1963).
(12) G. L. Schmir and B. A. Cunningham, *J. Am. Chem. Soc.*, **87**, 5692 (1965).
(13) H. Saito and K. Nukada, *Tetrahedron*, **22**, 3313 (1966).
(14) Possible support for this assignment comes from the observation that the α-methylene carbon of the minor isomer is ca. 5 ppm upfield from the α-methylene carbon of the major isomer in each case. This upfield shift is probably a steric compression shift similar to those observed for α-syn carbons of oximes.[15,16]
(15) G. C. Levy and G. L. Nelson, *J. Am. Chem. Soc.*, **94**, 4897 (1972).
(16) G. E. Hawkes, K. Herwig, and J. D. Roberts, *J. Org. Chem.*, **39**, 1017 (1974).
(17) Inspection of the ^{13}C chemical shifts of the aromatic ring carbons of the imidate **8** and the iminolactones **12** and **13**[18] reveals a pattern qualitatively consistent with nitrogen lone pair conjugation with the phenyl π system. In these spectra the ortho and para carbons are shielded by at least 5 ppm relative to the meta carbons.[19] Lactams **9** and **10** also show a similar shielding pattern due to amide–phenyl conjugation, while the ortho and para ring carbons of amide **7** are not shielded presumably due to steric inhibition of amide–phenyl conjugation. Inspection of the *o*-tolyl ring carbons of the 2-aminoamide–thionyl chloride products (**1a** or **2a** and **1b** or **2b**) reveals the absence of any appreciably shielded carbons. Molecular models of these compounds suggest that the *o*-tolyl methyl group should sterically inhibit the amide–phenyl conjugation in **2a** and **2b**, while not interfering with the nitrogen lone pair–phenyl conjugation in **1a** and **1b**. Thus, the absence of a shielded ortho or para carbon in the *o*-tolyl ring of these two compounds also favors assignment of structure **2** over structure **1**.
(18) H. L. Gingrich, Ph.D. Thesis, University of Florida, 1977.
(19) G. L. Nelson, G. C. Levy, and J. D. Cargioli, *J. Am. Chem. Soc.*, **94**, 3089 (1972).
(20) H. Peter, M. Brugger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **46**, 577 (1963).
(21) **Note Added in Proof.** Sauers and Relles have reported the ^{13}C chemical shifts of two *N*-aryl-2,2-dimethylsuccinisoimides, which exhibit syn–anti isomerism. As in the case of the iminolactones reported in this paper, the methylene carbon α to the imino group in the *E* isomer of these *N*-aryl-2,2-dimethylsuccinisoimides exhibits a steric compression shift: C. K. Sauers and H. M. Relles, *J. Am. Chem. Soc.*, **95**, 7731 (1973).
(22) **Note Added in Proof.** A referee suggested that the failure to observe any sign of syn–anti isomerism in the ^{13}C NMR spectra of our 2-aminoamide–thionyl chloride products could be consistent with structure **1** if syn–anti isomerization is fast at room temperature and/or the concentration of the minor isomer is too low to be detected by ^{13}C NMR, which is less sensitive than ^1H NMR. However, the proton spectrum of the 2-aminoamide–thionyl chloride product (**1d** or **2d**) failed to show any additional signals even upon cooling to −50 °C.

Heteroaromatic 10-π-Electron Systems. New *s*-Triazolo-*as*-triazines with a Bridgehead Nitrogen Atom

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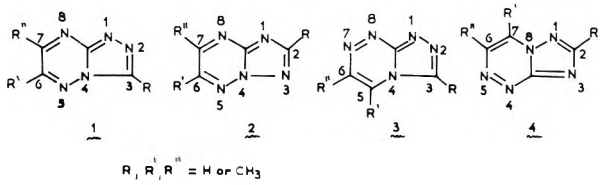
Four different polyazaindolizine systems of the *s*-triazolo-*as*-triazine type have been prepared either from 3-amino- or 3-hydrazino-*as*-triazines, or from 5-chloro-, 3,4-diamino-, or 3-hydrazino-*s*-triazoles.

s-Triazolo-*as*-triazine heterocycles are among the least known in the polyazaindolizine series. In particular *s*-triazolo[2,3-*b*]-*as*-triazines **2** have never been described and only *s*-triazolo[4,3-*b*]-*as*-triazines **1**, *s*-triazolo[3,4-c]-as-triazines **3**, and *s*-triazolo[3,2-c]-*as*-triazines **4** substituted with phenyl, amino, hydroxy, or mercapto groups are known.[1–8] The synthesis and properties of unsubstituted and methyl-substituted *s*-triazolo-*as*-triazines **1–4** (Chart I) were of interest in con-

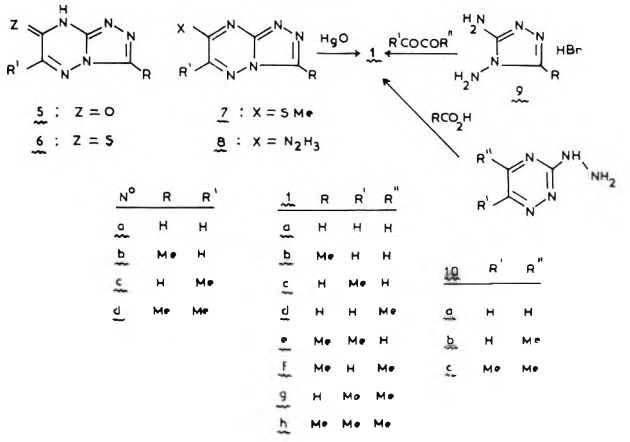
Chart I



junction with our previous investigations in the *as*-triazine[1] and azaindolizine[9] series.

Several routes to each system **1**–**4** were investigated. Unsubstituted and methyl-substituted *s*-triazolo[4,3-*b*]-*as*-triazines **1** have been obtained from the known 7-oxo-*s*-triazolo[4,3-*b*]-*as*-triazines **5**[3] using a multistep synthesis. The preparation involved successive thionylation of the carbonyl group, methylation at the sulfur atom, replacement of the methylthio group with hydrazine, and oxidation of the 7-hydrazino derivative with mercuric oxide (Chart II). Furthermore, it was found that a methyl group could be introduced into the 7 position upon treatment of compound **1** (R″ = H) with methylmagnesium iodide in tetrahydrofuran and diethyl ether. Under the reaction conditions the intermediate 7,8-dihydro-*s*-triazolo[4,3-*b*]-*as*-triazines are rather unstable and decompose easily to **1** (R″ = Me) except in the case of **1b** and **1c**, where controlled reaction conditions allowed their isolation.

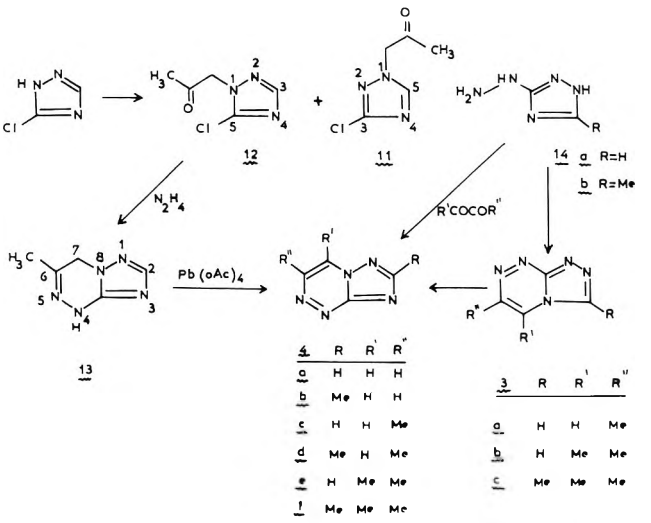
Chart II



3,4-Diamino-*s*-triazole hydrobromide (**9**) reacted with α-dicarbonyl compounds in acetic acid to afford the corresponding compounds **1**. Thus diacetyl yields **1g** whereas methylglyoxal gives only one of the two possible positional isomers; this was identified as **1c** already obtained from **5c** via **6c**, **7c**, and **8c**. Cyclization of 3-hydrazino-*as*-triazines **10** with carboxylic acids or otho esters may result in the formation of two isomeric *s*-triazolo-*as*-triazines, **1** or **3**, depending on the nuclear nitrogen involved[1] in the cyclization step. However, only isomer **1** was obtained when condensing **10a**–**c** with formic acid, acetic acid, or triethyl orthoformate, regardless of the conditions used. This exclusive ring closure mode of 3-hydrazino-*as*-triazines can be explained by the enhanced nucleophilicity of N-2 as compared to N-4.[11]

Based on the behavior of homologous "azaindolizine" systems[1,10,11] we expected *s*-triazolo[3,4-*c*]-*as* triazines **3** to isomerize easily to compounds **4** through fission of bond N-4–C-5 and Dimroth rearrangement, contrary to system **1**. Hence an unequivocal synthesis of **4** was carried out (Chart III). Reaction of 3-chloro-*s*-triazole with chloroacetone affords two isomeric 1-acetonyl-3- or -5-chloro-*s*-triazoles **11** and **12**. These compounds have been identified by comparison of their fragmentations under electron impact with those of recently studied[12] 1-methyl-3- or -5-chloro-*s*-triazoles. Thus the molecular ions of **11** and **12** fragment mostly into ketene and the

Chart III



1-methyl-3- or -5-chloro-*s*-triazoles ion, respectively. These ions have characteristic fragmentation patterns.[12] The action of hydrazine on **12** leads to 6-methyl-4,7-dihydro-*s*-triazolo[3,2-*c*]-*as*-triazine (**13**). This compound was dehydrogenated to **4c** with lead tetraacetate under conditions which preclude any rearrangement.

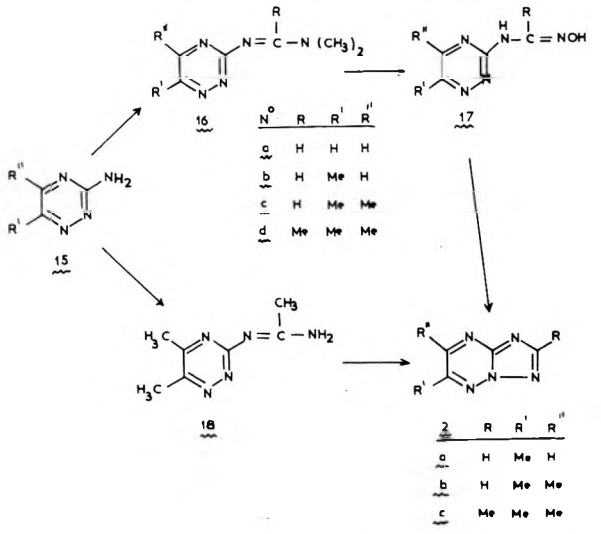
Condensations of 3-hydrazino-*s*-triazoles **14** with α-dicarbonyl compounds are not unequivocal syntheses of either **3** or **4**. The transformation may involve cyclization either at the N-2 or N-4 atom of the *s*-triazole ring. The situation is further complicated by the possible occurrence of the Dimroth rearrangement of **3** to **4** as stated before. Under controlled reaction conditions the reaction of diacetyl and **14a** or **14b** in ethanol leads to only one product in each case. However, if the temperature is increased or a longer reaction time used the former product is transformed into an isomeric compound. Moreover, a fast and complete conversion is also achieved if the initial product is treated with an aqueous solution of sodium hydroxide at room temperature. These results suggest that the thermodynamically more stable products are **4e** and **4f**[10] (Chart III). Methylglyoxal and **14a** afforded one product to which structure **3a** was assigned since it rearranges easily to **4c** obtainable also from **13**. Compound **14b** and methylglyoxal gave only **4d**. Similarly, even under controlled reaction conditions, glyoxal gives only one product to which the structure **4a** (or **4b**) is assigned by analogy.

The last *s*-triazolo-*as*-triazine system of interest, namely, the previously unknown *s*-triazolo[2,3-*b*]-*as*-triazines **2**, were obtained from 3-amino-*as*-triazine derivatives using two methods known to effect cyclization in related systems.[13-16]

Treatment of 3-amino-*as*-triazines **15** with *N,N*-dimethylformamide or *N,N*-dimethylacetamide acetal yielded the corresponding amidines **16** (Chart IV). These compounds react with hydroxylamine to give the amidoximes **17**. These, except **17a**, when treated with phosphorus oxychloride led in each case to only one *s*-triazolo-*as*-triazine different in every aspect from the corresponding *s*-triazolo[3,2-*c*]-*as*-triazine **4** already prepared from **14**. Therefore, the structure of the cyclization products must be **2**. This is consistent with the higher nucleophilic character of the ring nitrogen atom N-2 (as compared to N-4) as observed in the cyclization of 3-hydrazino-*as*-triazines. In contrast, attempts to cyclize **17a** using phosphorus oxychloride or lead tetraacetate were unsuccessful; polyphosphoric acid hydrolyzed the amidoxime to 3-formylamino-*as*-triazine.

3-Amino-*as*-triazines **15** reacted with acetonitrile in the presence of aluminum chloride to afford triazinylacetamidines similar to **18**. However, the compounds are fairly unstable and

Chart IV



did not undergo oxidative cyclization to **2** with the exception of compound **18**. The latter when treated with lead tetraacetate in benzene gave **2c** obtainable also from the amidoxime **17d**.

Experimental Section

NMR spectra were determined on a Varian HA-100 spectrometer and are listed in Table I. Mass spectra were recorded on a JEOL JMS D100 instrument.

The following starting materials were obtained according to procedures described in the literature: 3,4-diamino-*s*-triazoles,[8] 7-oxo-*s*-triazolo[4,3-*b*]-*as*-triazines,[1] 3-hydrazino-*as*-triazines,[17] 3-chloro-*s*-triazoles,[12] and 3-hydrazino-*s*-triazoles.[18,19] Details concerning the purification and characterization of new compounds are reported in Table II.

***s*-Triazolo[4,3-*b*]-*as*-triazines 1. A.** A suspension of **5** (0.03 mol) and phosphorus pentasulfide (5 g) in 200 ml of acetonitrile was heated for 1 h. After evaporation to dryness the residue was poured in 30 ml of hot water and the precipitate of **6** was removed by filtration.

A stirred solution of **6** (0.02 mol) in 20 ml of 4% aqueous sodium hydroxide and 1.5 ml of methyl iodide was allowed to stand at room temperature for 30 min. The organic product was then extracted with chloroform and the extracts evaporated to dryness giving compound **7**.

A solution of **7** (0.01 mol) and hydrazine hydrate (0.02 mol) in 45 ml of ethanol was refluxed for 1 h. After cooling, **8** precipitated and was removed by filtration. Mercuric oxide (10 g) was added to 150 ml of absolute ethanol in which 0.01 mol of finely powdered **8** had been suspended. The mixture was stirred and refluxed for 24 h. The solid phase was filtered and the filtrate concentrated to dryness, leaving the corresponding compound **1**.

B. A solution of **1b** (R″ = H) (0.004 mol) in 30 ml of tetrahydrofuran was slowly added at room temperature to a solution of methylmagnesium iodide (0.012 mol) in diethyl ether (50 ml). The solution was refluxed for 6 h and, after cooling, a saturated solution of ammonium chloride in water was added. The product of reaction was extracted with chloroform. After evaporation a solid was obtained and purified through crystallization. Thus, 3,7-dimethyl-7,8-dihydro-*s*-triazolo[4,3-*b*]-*as*-triazine (or its tautomer) was obtained from **1b**: mp 128–129 °C (from benzene–ethyl acetate); yield 48%; mass spectrum M$^+$ *m/e* 151; NMR (CDCl$_3$) δ 1.48 (d, Me-7), 2.40 (s, Me-3), 4.38 (m, H-7), 7.08 (d, H-6), J_{H_6,H_7} = 2, J_{Me_7,H_7} = 7 Hz.

Anal. Calcd for $C_6H_9N_5$: C, 47.67; H, 6.00; N, 46.33. Found: C, 47.28; H, 6.03; N, 46.42.

6,7-Dimethyl-7,8-dihydro-*s*-triazolo[4,3-*b*]-*as*-triazine (or its tautomer) was obtained from **1c**: mp 136–137 °C (from benzene–ethyl acetate); yield 52%; mass spectrum M$^+$ *m/e* 151; NMR (CDCl$_3$) δ 1.43 (d, Me-7), 2.11 (s, Me-6), 4.25 (q, H-7), 7.95 (s, H-3), J_{Me_7,H_7} = 7 Hz.

Anal. Calcd for $C_6H_9N_5$: C, 47.67; H, 6.00; N, 46.33. Found: C, 47.32; H, 5.94; N, 46.25.

On the contrary, if the crude products obtained from **1a, 1b, 1c,** and **1e** are chromatographed on neutral alumina, only the compounds **1d, 1f, 1g,** and **1h** are obtained, respectively (Table II).

C. A solution of 3,4-diamino-*s*-triazole hydrobromide (0.9 g) and the α-dicarbonyl compound (0.005 mol) in acetic acid (5 ml) was allowed to stand at room temperature for 3 h. After evaporation 20 ml of water was added and the solution neutralized with sodium bicarbonate. The product was extracted with chloroform and the residue after evaporation purified by crystallization.

D. Compound **10** (0.02 mol) in 5 ml of formic or acetic acid was cyclized after 40 min of reflux. The same results were obtained from a solution of **10** in ethyl orthoformate (10 ml) and ethanol (35 ml) after 24 h of reflux.

***s*-Triazolo[3,4-*c*]-*as*-triazines 3 and *s*-Triazolo[3,2-*c*]-*as*-triazines 4. A.** A solution of 3-chloro-*s*-triazole (1.0 g) and chloroacetone (11 g) in 30 ml of 1-butanol was refluxed for 8 h, then evaporated to dryness. Water (30 ml) was added and the solution neutralized with 5% aqueous sodium bicarbonate. After extraction with chloroform and evaporation the isomers **11** and **12** were separated by chromatography on a column of alumina (eluent petroleum ether–benzene, 1:1, R_f **11** > R_f **12**).

Compound **11** in 48% yield: mp 90–91 °C (from benzene–hexane); mass spectrum M$^+$ *m/e* 159 and 161; NMR (CDCl$_3$) δ 2.26 (s, CH$_3$), 5.05 (s, CH$_2$), 8.11 (s, H$_5$).

Anal. Calcd for $C_5H_6N_3OCl$: C, 37.61; H, 3.76; N, 26.33; Cl, 22.25. Found: C, 37.66; H, 3.84; N, 26.36; Cl, 22.09.

Compound **12** in 32% yield: mp 128–130 °C (from benzene–hexane); mass spectrum M$^+$ *m/e* 159 and 161; NMR (CDCl$_3$) δ 2.26 (s, CH$_3$), 5.05 (s, CH$_2$), 7.96 (s, H$_3$).

Anal. Calcd for $C_5H_6N_3OCl$: C, 37.61; H, 3.76; N, 26.33; Cl, 22.25. Found: C, 37.53; H, 3.81; N, 26.27; Cl, 22.12.

A solution of **12** (0.10 g) and hydrazine hydrate (1.25 g) in methanol (5 ml) was heated at 150 °C in a sealed tube for 5 h. The residue was triturated with 10 ml of ether and the hydrochloride of **13** precipitated and was filtered off and crystallized: mp 177–178 °C (from methanol); yield 50%; NMR (Me$_2$SO-d_6) δ 1.90 (s, CH$_3$), 4.73 (s, CH$_2$), 7.70 (s, H$_2$).

The hydrochloride of **13** (2.0 g) was dissolved in 50 ml of water at 50 °C. The solution was neutralized with sodium bicarbonate. An extraction with chloroform yielded **13**: mp 112–113 °C (from benzene–ethyl acetate); yield 85%; mass spectrum M$^+$ *m/e* 137; NMR (CDCl$_3$) δ 2.05 (s, CH$_3$), 4.75 (s, CH$_2$), 7.73 (s, H$_2$).

Anal. Calcd for $C_5H_7N_5$: C, 43.79; H, 5.14; N, 51.07. Found: C, 43.81; H, 5.12; N, 51.02.

Lead tetraacetate (0.7 g) was added to a solution of **13** (0.1 g) in anhydrous benzene (20 ml) and the stirred mixture was refluxed for 30 min. The hot filtrate was neutralized with sodium bicarbonate. The product (**4c**) was extracted with chloroform and chromatographed on a column of alumina (eluent benzene–chloroform, 3:2): mp 80–81 °C; mass spectrum M$^+$ *m/e* 135.

Anal. Calcd for $C_5H_5N_5$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.22; H, 3.45; N, 51.42.

B. A stirred solution of 3-hydrazino-*s*-triazole hydrochloride (0.05 mol) and α-dicarbonyl compound (0.07 mol) in 10 ml of ethanol was

Table I. NMR Spectra of *s*-Triazolo-*as*-triazines 1–4[a]

No.	R	R′	R″
1a	9.13	8.61 d (J = 1.5 Hz)	8.45 d
1b	2.83	8.56 d (J = 1.5 Hz)	8.47 d
1c	8.99	2.72	8.49
1d	9.00	8.26	2.75
1e	2.76	2.72	8.43
1f	2.78	8.29	2.72
1g	8.88	2.64	2.67
1h	2.72	2.63	2.65
2a	8.59	2.78	8.67
2b	8.55	2.75	2.70
2c	2.61	2.70	2.67
3a	8.78	3.00	8.43
3b	8.62	2.90 q (J = 0.6 Hz)	2.93 q
3c	2.73	2.93	2.93
4a	7.83	6.94 d (J = 2.4 Hz)	6.16 d
4b	2.34	6.94 d (J = 2.4 Hz)	6.12 d
4c	7.80	2.22	6.05
4d	2.36	2.16	6.00
4e	7.80	2.10	2.07
4f	2.43	2.10	2.07

[a] Chemical shifts in parts per million (Me$_4$Si as internal standard); solvent CDCl$_3$.

Table II. Purification and Characterization of New Compounds[a]

Registry no.	Compd	Mp, °C	Method of prepn	Yield, %	Crystn solvent	M^+ MS	Mol formula
275-01-4	**1a**	165–166	I A	56	Benzene and ethyl acetate	121	$C_4H_3N_5$
61139-68-2	**1b**	186–187	I A	62	Benzene and ethyl acetate	135	$C_5H_5N_5$
61139-69-3	**1c**	139–140	I A	55	Benzene and *n*-hexane	135	$C_5H_5N_5$
			I B	60			
61139-70-6	**1d**	234–235	I C	65	Benzene and ethanol	135	$C_5H_5N_5$
			I D	41			
			I D[a]	85			
61139-71-7	**1e**	136–137	I A	72	Benzene and ethyl acetate	149	$C_6H_7N_5$
61139-72-8	**1f**	215–216	I B	65	Benzene and ethanol	149	$C_6H_7N_5$
			I D	32			
			I B	62			
61139-73-9	**1g**	123–124	I C	38	Benzene and ethyl acetate	149	$C_6H_7N_5$
			I D	41			
			I D[a]	53			
61139-74-0	**1h**	173–174	I B	60	Benzene and ethyl acetate	163	$C_7H_9N_5$
			I D	54			
61139-75-1	**2a**	146–148	III A	25	Benzene and ethyl acetate	135	$C_5H_5N_5$
61139-76-2	**2b**	122–124	III A	31	Benzene and ethanol	149	$C_6H_7N_5$
61139-77-3	**2c**	86–87	III A	50	Benzene and *n*-hexane	163	$C_7H_9N_5$
			III B	75			
61139-78-4	**3a**	137–138	II B	45	Benzene and ethyl acetate	135	$C_5H_5N_5$
61139-79-5	**3b**	114–115	II B	42	Benzene and ethyl acetate	149	$C_6H_7N_5$
61139-80-8	**3c**	144–145	II B	48	Benzene and ethyl acetate	163	$C_7H_9N_5$
452-28-8	**4a**	176–177	II B	42	Benzene and ethyl acetate	121	$C_4H_5N_5$
61139-81-8	**4b**	189–190	II B	62	Benzene and ethyl acetate	135	$C_5H_5N_5$
61139-82-0	**4c**	80–81	II A	28	Benzene and ethanol	135	$C_5H_5N_5$
			II B	31			
61139-83-0	**4d**	169–170	II B	35	Benzene and ethyl acetate	149	$C_6H_7N_5$
61139-84-2	**4e**	148–149	II B	33	Benzene and ethanol	149	$C_6H_7N_5$
61139-85-3	**4f**	162–163	II B	37	Benzene and ethyl acetate	163	$C_7H_9N_5$
21119-72-2	**6a**	205 dec		85	Water	153	$C_4H_3N_5S$
61139-86-4	**6b**	225 dec		85	Water	167	$C_5H_5N_5S$
14742-98-4	**6c**	248–250		85	Water	167	$C_5H_5N_5S$
14894-20-3	**6d**	237–238		85	Water	181	$C_6H_7N_5S$
61139-87-5	**7a**	219–220		90	Benzene and ethyl acetate	164	$C_5H_5N_5S$
61139-88-6	**7b**	199–200		90	Benzene and ethanol	181	$C_6H_7N_5S$
25623-90-9	**7c**	171–172		90	Benzene and petroleum ether	181	$C_6H_7N_5S$
61139-89-7	**7d**	198–199		90	Benzene and ethyl acetate	195	$C_7H_9N_5S$
21119-77-7	**8a**	236–237		70	Water–ethanol	151	$C_4H_5N_7$
61139-90-0	**8b**	252–253		70	Water–ethanol	165	$C_5H_7N_7$
14742-99-5	**8c**	247–248		70	Methanol	165	$C_5H_7N_7$
14894-21-4	**8d**	242–243		70	Water–ethanol	179	$C_6H_9N_7H_2O$
61139-91-1	**16a**	72–75		51	Benzene and *n*-hexane	151	$C_6H_9N_5$
61139-92-2	**16b**	102–104		40	Benzene and *n*-hexane	165	$C_7H_{11}N_5$
61139-93-3	**16c**	94–95		92	Benzene and *n*-hexane	179	$C_8H_{13}N_5$
61139-94-4	**16d**	84–86		92	Benzene and *n*-hexane	193	$C_9H_{15}N_5$
61139-95-5	**17a**	161–162		31	Water and ethanol	139	$C_4H_5N_5O$
61139-96-6	**17b**	210–211		37	Water and ethanol	153	$C_5H_7N_5O$
61139-97-7	**17c**	226–227		78	Water and ethanol	167	$C_6H_9N_5O$
61139-98-8	**17d**	208–209		55	Water and ethanol	181	$C_7H_{11}N_5O$
61139-99-9	**18**	133–134		30	Benzene and *n*-hexane	165	$C_7H_{11}N_5$

[a] Satisfactory analytical data were obtained for all compounds listed.

allowed to stand for 2 h at room temperature (at −5 °C for glyoxal). Compound **3a** could be separated at this stage whereas **3b** was obtained after 16 h of refluxing. If, on the contrary, the solution was refluxed for at least 24 h the isomer **4** was obtained. After evaporation of the solvent the residue was dissolved in 50 ml of water and the solution neutralized with sodium bicarbonate. After extraction with chloroform the product was purified by column chromatography on alumina.

***s*-Triazolo[2,3-*b*]-*as*-triazines 2. A.** A solution of compound **15** (0.03 mol) and *N,N*-dimethylaminoformamide or -acetamide (0.03 mol) in 150 ml of toluene was refluxed for 4–6 h, then evaporated to dryness leaving the amidine **16.** To a solution of **16** (0.01 mol) and hydroxylamine hydrochloride (0.70 g) in 60 ml of methanol, 3 ml of methanolic sodium methoxide (0.5 M) was added and the resulting solution refluxed for 2 h. After cooling the amidoxime **17** was removed by filtration and crystallized. A hot solution of **17** (0.01 mol) in phosphorus oxychloride (4.5 ml) was refluxed for 10 min, cooled, poured on ice, and neutralized with aqueous sodium hydroxide (5 N). After extraction with chloroform and evaporation of the solvent, 2 was separated and chromatographed on a column of alumina (eluent chloroform).

Formamidoxine **17a** (0.5 g) was slowly added to 20 ml of polyphosphoric acid and the solution heated at 70 °C for 15 min. After cooling the mixture was poured on ice and the solution neutralized with sodium bicarbonate. 3-Formylamino-*as*-triazine was extracted with ethyl acetate and crystallized: mp 188–190 °C (from ethanol); yield 22%; mass spectrum M^+ *m/e* 124; NMR (Me_2SO-d_6) δ 8.61 (d, H_5), 9.15 (d, H_6), 9.36 (s, HCO), J_{H_5,H_6} = 2 Hz.

Anal. Calcd for $C_4H_4N_4O$: C, 38.71; H, 3.25; N, 45.15. Found: C, 38.68; H, 3.15; N, 44.98.

B. Aluminum chloride (1.33 g) was slowly added to a stirred mixture of **15c** (0.01 mol) and acetonitrile (0.7 g) at −5 °C. The mixture was then heated at 150 °C in a sealed tube for 1 h. Water (30 ml) was added and the resulting solution neutralized with sodium bicarbonate. The

acetamidine **18** was extracted with chloroform and after evaporation of the solvent the residue was chromatographed on a column of alumina (eluent benzene).

A stirred suspension of **18** (0.2 g) and lead tetraacetate (0.8 g) in 20 ml of anhydrous benzene was refluxed for 20 min. The hot solution was filtered and cooled and 20 ml of 30% aqueous sodium hydroxide was added. The product was extracted with chloroform, the solvent evaporated, and the separated compound **2c** purified by chromatography on alumina (eluent chloroform).

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Registry No.—**5a,** 874-40-8; **5b,** 875-84-3; **5c,** 19542-10-0; **5d,** 877-27-0; **9** (R = H), 23160-99-8; **9** (R = Me), 54557-76-5; **10a,** 28735-23-1; **10b,** 28735-26-4; **10c,** 19542-09-7; **11,** 61140-00-9; **12,** 61140-01-0; **13,** 61140-02-1; **13** HCl, 61140-03-2; **14a** HCl, 21126-64-7; **15a,** 1120-99-6; **15b,** 18915-36-1; **15c,** 17584-12-2; phosphorus pentasulfide, 1314-80-3; 3,7-dimethyl-7,8-dihydro-*s*-triazolo[4,3-*b*]-*as*-triazine, 61140-04-3; 6,7-dimethyl-7,8-dihydro-*s*-triazolo[4,3-*b*]-*as*-triazine, 61140-05-4; ethanedial, 107-22-2; 2-oxopropanal, 78-98-8; 2,3-butanedione, 431-03-8; 3-chloro-*s*-triazolo, 6818-99-1; chloroacetone, 78-95-5; *N,N*-dimethylformamide, 68-12-1; acetamide, 60-35-5; 3-formylamino-*as*-triazine, 61140-06-5.

References and Notes

(1) J. Daunis, R. Jacquier, and P. Viallefont, *Bull. Soc. Chim. Fr.*, 2492, 3670 (1969), and references cited therein.
(2) T. Sasaki and K. Minamoto, *Chem. Ber.*, **100** 3467 (1967).
(3) T. Sasaki, K. Minamoto, and S. Fukuda, *Chem. Ber.*, **101,** 2747 (1968).
(4) T. Sasaki and M. Murata, *Chem. Ber.*, **102,** 3818 (1969).
(5) H. G. O. Becker, D. Beyer, G. Israel, R. Muller, W. Riediger, and H. J. Timpe, *J. Prakt. Chem.*, **312,** 669 (1970).
(6) K. Lempert and K. Zauer, *Acta Chim. Acad. Sci. Hung.*, **71,** 371 (1972).
(7) A. Messmer, G. Hajos, P. Benko, and L. Pallos, *J. Heterocycl. Chem.*, **10,** 575 (1973).
(8) F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1,* 1221 (1972).
(9) R. Jacquier, H. Lopez, and G. Maury, *J. Heterocycl. Chem.*, **10,** 755 (1973).
(10) P. Guerret, R. Jacquier, and G. Maury, *J. Heterocycl. Chem.*, **8,** 643 (1971).
(11) J. Daunis and M. Follet, *Bull. Soc. Chim. Fr.*, 857 (1975).
(12) A. Bernardini, P. Viallefont, and J. Daunis, *J. Heterocycl. Chem.*, **12,** 655 (1975).
(13) J. D. Bower and G. R. Ramage, *J. Chem. Soc.*, 4506 (1957).
(14) G. M. Badger, P. J. Nelson, and K. T. Potts, *J. Org. Chem.*, 29, 2542 (1964).
(15) M. Zupan, B. Stanovnik, and M. Tisler, *Tetrahedron Lett.* 4179 (1972).
(16) S. Polanc, B. Vercek, B. Sek, B. Stanovnik, and M. Tisler, *J. Org. Chem.*, **39,** 2143 (1974).
(17) W. W. Paudler and T. K. Chen, *J. Heterocycl. Chem.*, **7,** 767 (1970).
(18) E. Lieber, S. Schiff, R. A. Henry, and W. G. Finnegan, *J. Org. Chem.*, **18,** 218 (1953).
(19) British Patent 1 157 256; *Chem. Abstr.*, **71,** 102230 (1969).

Phosphorus-Containing Cyclohexanes. Stereochemical Analysis of *cis*- and *trans*-2-Phenyl-2-oxo-5-*tert*-butyl-1,3,2-dithiaphosphorinanes

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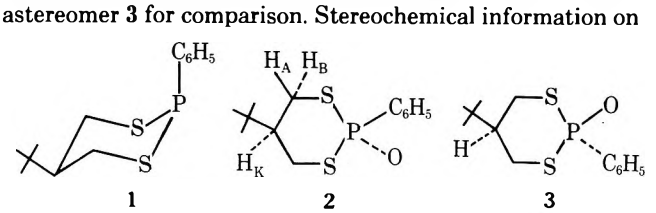
Assignments of configuration to *cis*- and *trans*-2-phenyl-2-oxo-5-*tert*-butyl-1,3,2-dithiaphosphorinanes (**2** and **3**) were accomplished through analysis of ^{1}H NMR spectral data and an LIS study with Eu(fod)$_3$. Cis diastereomer **2** was found to be conformationally heterogeneous with a considerable contribution made to the conformational equilibrium by the twist-boat conformer **4c**; the other major conformer was the chair structure with equatorial *tert*-butyl and axial phenyl groups. Complexation of **2** with Eu(fod)$_3$ had no significant influence on the conformational distribution. Trans diastereomer **3** adopted essentially one chair conformation with equatorial *tert*-butyl and phenyl substituents.

Although substituents attached to carbon or nitrogen atoms in saturated six-membered rings usually prefer an equatorial orientation, the same groups display this tendency to a much weaker degree when attached to other atoms such as sulfur,[1] phosphorus,[2-4] selenium,[5a] and arsenic;[5b] in fact, axial preferences are often encountered. This conformational novelty has stimulated much interest and study,[6] especially with regard to diverse phosphorus-containing cyclohexane systems.[2-4,7]

Previously, we reported[4a] that the more stable isomer (85% at 200 °C; ca. 97% at 25 °C) of 2-phenyl-5-*tert*-butyl-1,3,2-dithiaphosphorinane (**1**) possesses a cis configuration with the *P*-phenyl group axially disposed. In order to further support the stereochemical assignment, we converted **1** stereospecifically to cis 2-oxo derivative **2** and synthesized the trans diastereomer **3** for comparison. Stereochemical information on these compounds was obtained by ^{1}H NMR spectroscopy and ^{1}H NMR lanthanide-induced shift (LIS) studies. Our results, which yielded configurational assignments for **2** and **3**, as well as an analysis of their conformational behavior, are presented in this article.



1 **2** **3**

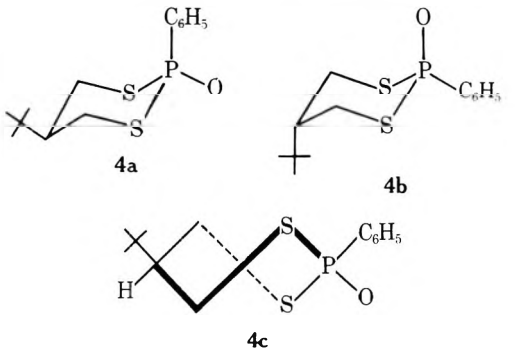
Results and Discussion

Oxidation of **1** with hydrogen peroxide[8] (presumably stereospecific with retention[9]) afforded a single diastereomer (mp 105–106 °C); there was no evidence for the presence of the other possible isomer. Spectral and analytical data were consistent with **2**. The 100-MHz ^{1}H NMR spectrum of **2** exhibited a complex AA'BB'KX (X = ^{31}P) pattern which was treated as an A_2B_2KX approximation[10] to provide the parameters presented in Table I.[11] The nearly identical, middling values of J_{AK} and J_{BK} (e.g., 7.2 and 5.9 Hz) suggest that **2** is a mixture of conformational isomers in solution ($CDCl_3$ and C_6D_6); the axial and equatorial orientations of H_A, H_B, and H_K are interchanged, thereby averaging the ^{1}H NMR spectral parameters. This observation can be accommodated by a mixture of chair conformers (**4a** and **4b**), a twist-boat form (**4c**), or an equilibrium mixture of chair and boat forms.

Table I. ^{1}H Nmr Data at 100 MHz for 2 and 3[a]

Compd	δH_K	δH_A[f]	δH_B[f]	δt-Bu	J_{AK}	J_{BK}	J_{AX}	J_{BX}	$J_{AX} + J_{BX}$
2[b]	2.07	2.97	3.29	0.96	7.3	5.9	14.2	22.2	36.5
2[c,d]	1.63	2.59	2.94	0.55	7.2	6.0	14.5	22.5	37.0
3[b]	2.01	3.45	3.20	1.01	9.4	3.5	12.7	19.9	32.6
3[c]	1.66	3.13	2.64	0.56	9.6	3.5	11.6	19.6	31.2

[a] Chemical shifts are reported in parts per million downfield from Me_4Si. J values are in hertz. J_{AB} was 14.0 ± 0.5 Hz. Spectral data were obtained at 100 MHz, except as noted. [b] Measured in $CDCl_3$. [c] Measured in C_6D_6. [d] The parameters defining the A_2B_2KX pattern were used as input for the LAOCN3 NMR program. The computed spectrum agreed well with the experimental spectrum (21 lines) with iteration. [e] Recorded at 60 MHz. [f] A reversal in the relative order of the chemical shifts of H_A and H_B is observed.

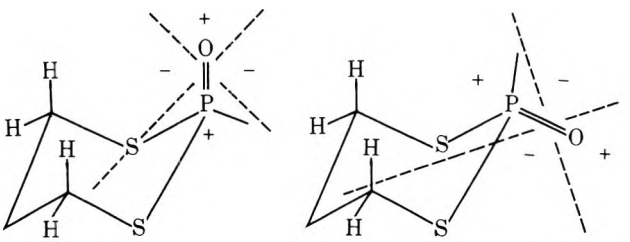


Evidently, the expected axial preference of an oxygen on phosphorus vs. a phenyl group[12] competes effectively with the equatorial preference of the 5-*tert*-butyl group; the result is a mixture of conformers **4a, 4b,** and/or **4c.**

Condensation of 2-*tert*-butyl-1,3-propanedithiol with phenylphosphonic dichloride gave mostly the other possible stereoisomer **3** (mp 141.5–142.5 °C). The 100-MHz ^{1}H NMR spectrum of **3** revealed an AA′BB′KX (X = ^{31}P) pattern which provided the parameters in Table I when approximated as an A_2B_2KX spin system. The large J_{AK} (9.7–10.0 Hz, $H_{4,6\text{-axial}}$–$H_{5\text{-axial}}$ coupling) and small J_{BK} (3.6–3.8 Hz, $H_{4,6\text{-equat}}$–$H_{5\text{-axial}}$ coupling) are typical for a highly biased equilibrium favoring a chair conformer with the *tert*-butyl group equatorial. This analysis is consistent with the $^3J_{PSCH}$ values for **3** (Table I).[11b] Given the aforementioned axial preference of the phosphoryl group against the phenyl group,[12] the conformational bias for **3** suggests that **3** has the trans configuration.

The downfield shift of the axial 4,6 protons (H_A) relative to the equatorial 4,6 protons (H_B) in **3** (Table I) can be explained by a predominant axial disposition of the phosphoryl group. This reversal in the relative order of the chemical shifts of H_A and H_B (cf. **2** and **3**) is similar to that reported for *cis*- and *trans*-2-oxo-5-*tert*-butyl-1,3,2-dioxaphosphorinanes.[2,13,14] Deshielding of protons in proximity to a phosphoryl group, as in **3,** is apparently a general phenomenon[15] and is analogous to the action of the sulfinyl moiety in cyclic sulfites.[16]

In an axial position, the P=O bond exerts a deshielding influence on *both* sets of 4,6 protons and, conversely, in an equatorial position it exerts a shielding influence (see diagram below). In either circumstance, it is the axial set of 4,6 protons which senses a greater effect, because of proximity in the case



first case—axial P=O second case—equatorial P=O

of an axial P=O, and directionality in the other case. A conformational equilibrium between chair structures or a twist form would naturally tend to average this effect. In **3** the axial protons resonate at a lower field than the equatorial protons and at a lower field than either set of 4,6 protons in **2** (same solvent for comparison). This qualitative result agrees with a predominantly axial P=O bond in **3.** On the contrary, the axial 4,6 protons in **2** resonate at a higher field than the equatorial protons, which indicates a fair amount of the equatorial phosphoryl conformation **4a** and strongly militates against a significant contribution from **4b.** The shielding of H_A in **2** may be reinforced by the axial phenyl group in **4a.**[17] The tentative inference is that stereoisomer **2** is chiefly composed of a fairly balanced mixture of **4a** and **4c,** to the virtual exclusion of **4b.**

The oxygen of the phosphoryl group in **2** and **3** provides a handle for obtaining additional structural information by complexation of it with lanthanide shift reagents, the use of which in the evaluation of molecular spatial arrangements is well established.[19] Tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium (III), $Eu(fod)_3$, was employed[20] and the induced proton shifts were monitored. Upon treatment of a solution of **3** with incremental amounts of $Eu(fod)_3$ all protons experienced the usual accompanying downfield shift as the shift reagent complexed the strongly basic phosphoryl oxygen.[21] A plot of the chemical shifts of H_A, H_B, and H_K vs. added $Eu(fod)_3$ (Figure 1) demonstrates that the axial 4,6 protons (H_A) were deshielded to a much greater extent than H_B and H_K. This can only be consistent with a predominantly axial position of the phosphoryl group, which brings the Eu complex in proximity with the syn-axial protons. Analogous results and conclusions have been reported for *trans*-2-methyl-2-oxo-5-*tert*-butyl-1,3,2-dioxaphosphorinane[13] and related compounds.[14b,15b,19e-g]

Treatment of **2** with incremental amounts of $Eu(fod)_3$ also caused downfield shifts of the three sets of 4,6 and 5 protons (Figure 1) but in this case all sets were deshielded to approximately the same degree. In fact, the 4,6 protons were shifted about the same extent as the equatorial protons in **3** (see sensitivity values in Table II). Apparently, the chair conformer with an axial P=O (**4b**) must not make an appreciable contribution to the conformational profile of **2,** otherwise the contiguity of the europium atom to H_A should have induced a greater average deshielding for this pair of protons, as for **3.** Thus, cis diastereomer **2** exists in a conformation or conformations in which the remote 4,6 protons (H_A and H_B) are located at similar average distances from the phosphoryl oxygen. This condition is satisfied by the flexible twist form **4c** or possibly a mixture of **4c** and chair form **4a.** The relatively large chemical shift differences for H_A and H_B, Δ_{AB}, suggest the latter interpretation since pseudorotation in flexible forms usually averages chemical shifts to a greater extent.[22] The ^{1}H NMR data for the LIS studies are collected in Table II.

In view of the substantial amount of twist form apparently present in **2,** the following summation obtains. The unfavorable disposition of the groups on phosphorus in **2** (axial phenyl

Table II. ^{1}H NMR Eu(fod)$_3$-Shift Data for 2 and 3[a]

Compd[b]	Mg Eu(fod)$_3$	νt-Bu	νH_A	νH_B	νH_K	J_{AK}	J_{BK}	J_{AX}	J_{BX}	Δ_{AB}
2	0	42.2	162.8	181.2	106.0	7.4	6.3	14.5	21.7	18.5
	10	46.0	186.9	213.3	123.0					26.3
	20	56.5	205.5	237.9	137.8					32.4
	25	60.0	216.2	252.4	145.2					36.2
	35	66.6	236.2	278.2	161.0					42.1
	40	69.0	243.4	288.0	166.8	7.0	6.5	15.0	24.0	44.6
		48.5[c]	145.9[c]	193.4[c]	110.1[c]					
3	0	45.0	199.4	174.0	107.5	9.8	3.7	12.1	20.2	25.4
	10	60.0	275.2	203.8	139.0					71.4
	20	73.7	346.0	230.0	167.5					116.0
	25	78.3	371.0	239.0	178.0	10.8	3.0	12.8	21.0	132.0
		96.5[c]	497.1[c]	188.3[c]	204.2[c]					

[a] The LIS study was carried out at 60 MHz. Coupling constants are in hertz and have an estimated error of $\leq \pm 0.5$ Hz. The proton frequencies are reported in hertz downfield from Me_4Si. $\Delta_{AB} = \nu_A - \nu_B$. J_{AB} varied between 13.7 and 14.2 Hz. [b] Solutions were 0.155 M in 1:1 CCl_4–C_6D_6. [c] Sensitivity given in proton shift (Hz) per molar equivalent of Eu(fod)$_3$.

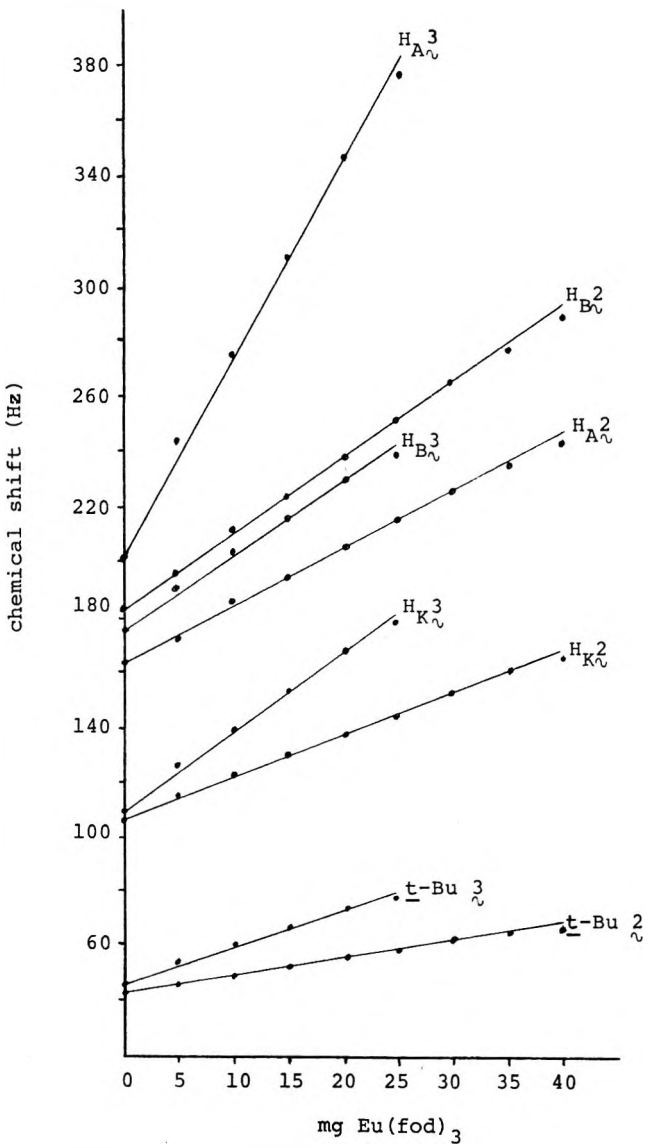


Figure 1. Induced chemical-shift changes upon incremental addition of Eu(fod)$_3$ to solutions of **2** and **3**.

and equatorial phosphoryl) is enough to force the molecule to adopt a necessarily low energy (perhaps as low as ca. 0.5 kcal/mol) twist conformer[23] to a large extent with the virtual exclusion of any axial phosphoryl–axial *tert*-butyl form. The low energy twist conformation is in agreement with the results of Bentrude and co-workers on 1,3,2-dioxaphosphorinane derivatives.[2,24]

By employing the europium-shift technique the configurational assignments for the title stereoisomers have been bolstered. Moreover, important conformational information has been obtained on one of the isomers, namely **2**, which is conformationally heterogeneous. It is noteworthy that the conformational equilibrium is not altered by complexation of **2** with Eu(fod)$_3$ as evidenced by the nearly identical vicinal H–H coupling constants with and without added Eu(fod)$_3$ (see Table II). Both $^3J_{PSCH}$ values follow suit, although they are observed to increase slightly with increasing Eu(fod)$_3$ concentration.[25] This conformational consistency with the addition of shift reagent is in harsh contrast to observations of Bentrude and co-workers with the *cis*-2-oxo-1,3,2-dioxaphosphorinanes,[14b,19e] in which complexation generally caused a concomitant displacement in the conformational equilibria.

Phosphorus-31 chemical shifts were measured for **2** and **3**. The values of −55.1 and −47.3 ppm for the cis and trans isomers, respectively, illustrate that the different configurations engender a large (8 ppm) difference in δ^{31}P. The resonance of trans isomer **3** at higher field than cis isomer **2** is opposite to the order of resonance for pairs of (corresponding[26]) cis/trans isomers of 5-*tert*-butyl-1,3,2-dioxaphosphorinanes,[19e] 5-*tert*-butyl-2-oxo-1,3,2-dioxaphosphorinanes,[19e] 1-methyl-4-*tert*-butyl-4-phosphoranol,[3d] and 2-phenyl-5-methyl-1,3,2-dithiaphosphorinanes.[4b] The meaning of this result is not clear at this point, but the anomalous chemical shift order may be attributable to a large proportion of twist boat conformer present in **2** in solution. Additional ^{31}P NMR data for other 2-oxo-1,3,2-dithiaphosphorinane derivatives is required to illuminate this problem.

Conclusion

Assignment of the cis configuration to **2**, through analysis of ^{1}H NMR spectral and europium-shift data for **2** and **3**, supports the cis assignment advanced for **1**,[4a,b] with its axial phenyl substituent. By extension, the suggestion of an axial preference for a variety of P substituents (CH_3, C_2H_5, OCH_3, Cl, C_6H_5) in the 1,3,2-dithiaphosphorinanes is reinforced.[4a,b] Cis diastereomer **2** is conformationally heterogeneous in solution and the twist-boat conformation is populated to a considerable extent. Complexation of **2** with the europium-shift reagent Eu(fod)$_3$ had a negligible effect on the conformational equilibrium.[27]

Experimental Section

All melting points (determined on a Mel-Temp hot-stage appara-

tus) and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 457 spectrophotometer. Proton nuclear magnetic resonance spectra were obtained on Varian A-60 and HA-100 spectrometers. Chemical shifts are reported in parts per million downfield from tetramethylsilane (internal reference); coupling constants are reported in hertz. Proton decoupling was achieved on the HA-100 instrument; europium-shift studies were carried out at 60 MHz. Phosphorus-31 NMR spectra were recorded at 40.5 MHz on a HA-100 spectrometer using a reference capillary containing 85% H_3PO_4. The spectra were calibrated by the sideband technique.[28] The ^{31}P chemical shifts are an average of at least two scans and have a standard deviation of about ±0.3 ppm. Analyses of ^1H NMR spectra were performed using a modified version of the LAOCN3 NMR program;[29] calculated spectra were plotted by assigning a Lorentzian line shape.[30] Determination of the chemical shifts of A and B protons of AB patterns was performed by utilizing the following equation: $\Delta\nu_{AB} = \sqrt{(\nu_1 - \nu_4)(\nu_2 - \nu_3)}$.[31]

Mass spectra were recorded on a Perkin-Elmer Hitachi RMU-6 mass spectrometer at an electron energy of 70 eV. Microanalyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, West Germany. Molecular weight determinations (osmometry in benzene) were made by Schwartzkopf Microanalytical Laboratories, Woodside, N.Y.

All reactions involving trivalent phosphorus compounds were conducted under an atmosphere of dry nitrogen. Phenylphosphonic dichloride (phenyldichlorophosphine oxide) was obtained as a free sample from Stauffer Chemical Co. (Specialties), New York, N.Y. Triethylamine was distilled from potassium hydroxide and stored over molecular sieves (3A). Europium $(fod)_3$ was purchased from Pierce Chemical Co., Rockford, Ill., and was stored in a desiccator.

2-*tert*-Butyl-1,3-propanedithiol. This compound was prepared according to the procedure of Eliel and Hutchins.[22] Distillation afforded the product in 60% yield, bp 53–55 °C (0.75–0.85 mm) [lit.[22] bp 40 °C (0.04 mm)], $n^{25}D$ 1.5095. GLC analysis indicated the material to be ca. 96% pure. An improved procedure is now available.[22b]

2-Phenyl-5-*tert*-butyl-1,3,2-dithiaphosphorinane (1). In a 300-ml flask was placed 100 ml of dry ether and triethylamine (8.1 g, 0.080 mol). The flask was fitted with a drying-tube-protected condenser, nitrogen inlet, and two dropping funnels. A magnetic stirring bar was placed in the flask and the contents were cooled to ca. 0 °C in an ice bath. In one funnel was placed 2-*tert*-butyl-1,3-propanedithiol (3.3 g, 0.020 mol) and 40 ml of dry ether; the other was charged with phenyldichlorophosphine (3.6 g, 0.020 mol) and 40 ml of dry ether. Both solutions were added slowly and synchronously to the cold, stirred solution. After addition, the contents were stirred for 1 h while being allowed to warm to ambient temperature. The mixture was filtered and the residue was rinsed with dry ether. The total filtrate was stripped at reduced pressure, leaving an almost colorless oil which solidified on standing in vacuo. The solid was fractionally sublimed (80 °C, 0.0006 mm) and product was collected in portions as indicated in Table III.

A sample of fraction 5 was slowly recrystallized from 70% ethanol to afford shiny, opalescent leaflets, mp 94–95 °C (sharp), which turned out to be pure 1. Fractions 1, 2, 6, and 7 were combined with the sublimation residue and distilled: bp 159–163 °C (0.08 mm); mp 69–90.5 °C; cis/trans isomer ratio 85/15; IR (KBr) ν_{max} 3070, 3050, 2965, 2930, 2870, 1498, 1473, 1440, 1375, 1230, 1090, 860, 810, 755, 705 cm^{-1}; MS *m/e* (rel abundance) 270 (100, M^+).

Anal. Calcd for $C_{13}H_{19}PS_2$: C, 57.74; H, 7.08; P, 11.46. Found: C, 57.66; H, 6.92; P, 11.56.

Stereospecific Oxidation of 1 with 3% Aqueous Hydrogen Peroxide. Phosphine 1 (81 mg, 0.30 mmol) was combined with 1 ml of 3% H_2O_2 and 2 ml of CH_2Cl_2 under an atmosphere of nitrogen. The mixture was stirred for 12 h at ambient temperature. The CH_2Cl_2 solution was separated by pipet and the solvent was evaporated. The resultant colorless oil crystallized upon treatment with *n*-pentane. The white solid was recrystallized by adding enough ether to dissolve it warm and then cooling to 0 °C. The yield of long, gleaming needles, mp 105–106 °C, was 68 mg. Concentration and cooling of the mother liquor yielded another 10 mg, for a total yield of 78 mg (91%). This material proved to be **2**, IR (KBr) ν_{max} (P=O) 1202 cm^{-1}. Sublimation furnished an analytical sample. Mol wt (osmometry in benzene): calcd, 286; found, 279.

Anal. Calcd for $C_{13}H_{19}OPS_2$: C, 54.52; H, 6.69. Found: C, 54.36; H, 6.84.

Reaction of 2-*tert*-Butyl-1,3-propanedithiol with Phenyldichlorophosphine Oxide. In the manner described for the preparation of **1**, 2-*tert*-butyl-1,3-propanedithiol (0.82 g, 5.0 mmol) in dry ether (20 ml) and phenyldichlorophosphine oxide (0.98 g, 5.0 mmol) in dry ether (20 ml) were added slowly to an ice-cooled solution of triethylamine (2.02 g, 0.020 mol) in dry ether (20 ml). After addition, the reaction mixture was stirred for 3 h at ambient temperature and then filtered. the filter cake was washed with 25 ml of dry ether–THF (1:1). The cooled filtrate deposited a white solid which was filtered off; it weighed 35 mg and had mp 137–140 °C. To the clean filtrate was added 20 ml of *n*-pentane and the solution was cooled to 0 °C and filtered, giving 40 mg of solid, mp 137–139 °C. The filtrate was concentrated and minute, prismatic needles separated from solution; these were filtered off with the assistance of an ice-cold mixture of ether–pentane (2:1). This crop weighed 0.371 g and had mp 134–138 °C. A fourth fraction was obtained, 0.256 g, mp 86–91 °C. A portion of the third crop was recrystallized from hexane–ethyl acetate (1:1) as colorless, clear, elongated prisms (very slow) or prismatic needles (faster). The first subcrop had mp 141–142.5 °C; the second had mp 140–141.5 °C. The first-crop material proved to be pure **3**, IR (KBr) ν_{max} (P=O) 1195 cm^{-1}. Mol wt (osmometry in benzene): calcd, 286; found 283.

Anal. Calcd for $C_{13}H_{19}OPS_2$: C, 54.52; H, 6.69. Found: C, 54.39; H, 6.62.

Table III

Fraction	Yield, g	Mp, °C
1	0.360	
12	0.23	
3	1.22	84.5–91.5
4	0.56	84–91
5	0.90	84–90.5
6	0.68	76–90
7	0.18	
	4.13	

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work and Mrs. Carol Folk of the University of Pennsylvania for ^{31}P and 100-MHz ^1H NMR spectra.

Registry No.—*cis*-**1**, 61009-66-3; *trans*-**1**, 61009-67-4; **2**, 61009-68-5; **3**, 61009-69-6; 2-*tert*-butyl-1,3-propanedithiol, 24330-57-2; phenyldichlorophosphine, 644-97-3; phenyldichlorophosphine oxide, 824-72-6.

References and Notes

(1) (a) J. B. Lambert, D. S. Bailey, and C. E. Mixan, *J. Org. Chem.*, **37**, 377 (1972); (b) J. B. Lambert and R. G. Keske, *ibid.*, **31**, 3429 (1966); (c) J. B. Lambert, C. E. Mixan, and D. H. Johnson, *J. Am. Chem. Soc.*, **95**, 4634 (1973); (d) J. B. Lambert, C. E. Mixan, and D. S. Bailey, *ibid.*, **94**, 208 (1972); (e) E. L. Eliel, R. L. Willer, A. T. McPhail, and K. D. Onan, *ibid.*, **96**, 3021 (1974).

(2) 1,3,2-Dioxaphosphorinanes: W. G. Bentrude, H.-W. Tan, and K. C. Yee, *J. Am. Chem. Soc.*, **97**, 573 (1975), and references cited therein.

(3) Phosphorinanes: (a) S. I. Featherman and L. D. Quin, *J. Am. Chem. Soc.*, **97**, 4349 (1975); (b) A. T. McPhail, J. J. Breen, J. H. Somers, J. C. H. Steele, Jr., and L. D. Quin, *Chem. Commun.*, 1020 (1971); (c) A. T. McPhail, J. J. Breen, J. C. H., Steele, Jr., and L. D. Quin, *Phosphorus*, **1**, 255 (1972); (d) A. T. McPhail, P. A. Lukan, S. I. Featherman, and L. D. Quin, *J. Am. Chem. Soc.*, **94**, 2126 (1972).

(4) 1,3,2-Dithiaphosphorinanes: (a) R. O. Hutchins and B. E. Maryanoff, *J. Am. Chem. Soc.*, **94**, 3266 (1972); (b) B. E. Maryanoff, Ph.D. Dissertation, Drexel University, 1972. Also see (c) J. Martin and J. B. Robert, *Org. Magn. Reson.*, **7**, 76 (1975); J. Martin, J. B. Robert, and C. Taleb, *J. Phys. Chem.*, **80**, 2417 (1976).

(5) (a) J. B. Lambert, C. E. Mixan, and D. H. Johnson, *Tetrahedron Lett.*, 4335 (1972); ref 1c; (b) J. B. Lambert, D. A. Netzel, H.-n. Sun, and K. K. Lilianstrom, *J. Am. Chem. Soc.*, **98**, 3778 (1976); B. A. Arbuzov, I. V. Anonimova, S. G. Vul'fson, L. K. Yuldasheva, N. A. Chadaeva, and A. N. Vereshchagin, *Phosphorus*, **5**, 17 (1974); J. B. Lambert and H.-N. Sun, *J. Organometal. Chem.*, **117**, 17 (1976).

(6) J. B. Lambert and S. I. Featherman, *Chem. Rev.*, **75**, 611 (1975).

(7) 1,3,2-Diazaphosphorinanes: (a) R. O. Hutchins, B. E. Maryanoff, J. P. Albrand, A. Cogne, D. Gagnaire, and J. B. Robert, *J. Am. Chem. Soc.*, **94**, 9151 (1972); (b) J. A. Mosbo, *Tetrahedron Lett.*, 4789 (1976).

(8) Other methods of oxidation were tried, such as N_2O_4 [J. R. Cox, Jr. and F. H. Westheimer, *J. Am. Chem. Soc.*, **80**, 5441 (1958); D. B. Denney and S. L. Varga, *Tetrahedron Lett.*, 4931 (1966); J. Michalski, A. Okruszek, and W. Stec, *Chem. Commun.*, 1495 (1970); D. Z. Denney, G. Y. Chen, and D. B. Denney, *J. Am. Chem. Soc.*, **91**, 6838 (1969); W. G. Bentrude and K. C. Yee, *Tetrahedron Lett.*, 3999 (1970); ref 19e, 19f] and *t*-BuOCl [D. B. Denney and R. R. DiLeone, *J. Am. Chem. Soc.*, **84**, 4737 (1962); D. B. Denney and J. W. Hanifin, Jr., *Tetrahedron Lett.*, 2177 (1963)], but extensive decomposition of the substrate was observed [see A. Lippert and E. E. Reid, *J. Am. Chem. Soc.*, **60**, 2370 (1938)].

(9) L. Horner, *Pure Appl. Chem.*, **9**, 225 (1964); W. Stec, A. Okruszek, and J. Michalski, *Angew. Chem., Int. Ed. Engl.*, **10**, 494 (1971).
(10) This approximation was successfully utilized in a similar system; see footnote 5 in ref 11.
(11) The assignment of the $C_{4,6}$ protons was made on the basis that the larger $^3J_{PSCH}$ value occurs with the equatorial protons (H_B). For example, see (a) L. D. Hall and R. B. Malcolm, *Chem. Ind. (London)*, 92 (1968); (b) J. R. Campbell and L. D. Hall, *ibid.*, 1138 (1971). Also note footnote 7 in ref 19e.
(12) In 2-phenyl-2-oxo-1,3,2-dioxaphosphorinanes, the P=O bond prefers an axial disposition vs. phenyl in $CDCl_3$ and CS_2. The preference varies with the polarity of the solvent and is ca. 250–700 cal/mol in nonpolar solvents; see J. P. Majoral, R. Pujol, and J. Navech, *C. R. Acad. Sci.*, **274**, 213 (1972).
(13) K. C. Yee and W. G. Bentrude, *Tetrahedron Lett.*, 2775 (1971).
(14) (a) W. G. Bentrude and J. H. Hargis, *Chem. Commun.*, 1113 (1969); (b) W. G. Bentrude, H. Tan, and K. C. Yee, *J. Am. Chem. Soc.*, **94**, 3264 (1972).
(15) (a) F. Ramirez, A. V. Patwardham, N. B. Desai, and S. R. Heller, *J. Am. Chem. Soc.*, **87**, 549 (1965); (b) Y. Kashman and O. Awerbouch, *Tetrahedron*, **27**, 5593 (1971).
(16) W. Wucherpfennig, *Justus Liebigs Ann. Chem.*, **737**, 144 (1970); J. G. Pritchard and P. C. Lauterbur, *J. Am. Chem. Soc.*, **83**, 2105 (1961); L. Cazaux and P. Maroni, *Tetrahedron Lett.*, 3667 (1969); C. H. Green and D. G. Hellier, *J. Chem. Soc., Perkin Trans. 2*, 458 (1972).
(17) Δ_{AB} values for **2** and **3** ($CDCl_3$) are −0.32 and 0.25, respectively. Bentrude and Yee have found Δ_{AB} values for *cis*- and *trans*-2-phenyl-2-oxo-5-*tert*-butyl-1,3,2-dioxaphosphorinanes (CCl_4) to be −0.40[14b] and 0.28,[18] respectively.
(18) W. G. Bentrude, private communication, 1972.
(19) Reports describing the use of NMR shift reagents with compounds containing the phosphoryl group include (a) ref 13; ref 14b; ref 15b; (b) T. M. Ward, I. L. Allcox, and G. H. Wahl, Jr., *Tetrahedron Lett.*, 4421 (1971); B. D. Cuddy, K. Treon, and B. J. Walker, *ibid.*, 4433 (1971); (c) J. K. M. Saunders and D. H. Williams, *ibid.*, 2813 (1971); (d) J. R. Corfield and S. Trippett, *Chem. Commun.*, 721 (1971); (e) W. G. Bentrude and H.-W. Tan, *J. Am. Chem. Soc.*, **95**, 4666 (1973); (f) J. A. Mosbo and J. G. Verkade, *ibid.*, **95**, 4659 (1973); (g) P. Finocchiaro, A. Recca, W. G. Bentrude, H.-W. Tan, and K. C. Yee, *J. Am. Chem. Soc.*, **98**, 3537 (1976). General references to the use of NMR shift reagents for assignment of molecular geometry may be found in J. R. Campbell, *Aldrichimica Acta*, **4**, 55 (1971); I. Y. Slonim and A. K. Bulai, *Russ. Chem. Rev. (Engl. Transl.)*, **42**, 904 (1973); R. E. Sievers, Ed., "Nuclear Magnetic Resonance Shift Reagents", Academic Press, New York, N. Y., 1973.
(20) Tris(dipivaloylmethanato)europium(III) gave poorly resolved, broad lines with **2** and **3** at high chelate to substrate ratios.
(21) The phosphoryl oxygen should be the preferential site of complexation for lanthanides; see (a) J. L. Burdett and L. L. Burger, *Can. J. Chem.*, **44**, 11 (1966); (b) S. C. Goodman and J. G. Verkade, *Inorg. Chem.*, **5**, 498 (1966); (c) ref 19g.
(22) (a) E. L. Eliel and R. O. Hutchins, *J. Am. Chem. Soc.*, **91**, 2703 (1969); (b) E. L. Eliel, V. S. Rao, S. Smith, and R. O. Hutchins, *J. Org. Chem.*, **40**, 524 (1975).
(23) Introduction of sulfur atoms into a six-membered ring can significantly lower the chair–boat energy difference. For instance, 1,3-dioxane has an energy difference (ΔG°) of ca. 8.3 ± 0.5 kcal/mol [R. M. Clay, G. M. Kellie, and F. G. Riddell, *J. Am. Chem. Soc.*, **95**, 4632 (1973)], whereas 1,3-dithiane has a value of only ca. 1.7 kcal/mol.[22] The corresponding chair–boat energy difference for cyclohexane is ca. 5.3 kcal/mol [M. Squillacote, R. S. Sheridan, O. L. Chapman, and F. A. L. Anet, *J. Am. Chem. Soc.*, **97**, 3244 (1975)]; see also K. Pihlaja, *J. Chem. Soc., Perkin Trans. 2*, 890 (1974).
(24) The chair–boat energy difference for *cis*-2,5-di-*tert*-butyl-2-oxo-1,3,2-dioxaphosphorinane may be as low as ca. 1 kcal/mol [W. G. Bentrude and K. C. Yee, *J. Chem. Soc., Chem. Commun.*, 169 (1972); ref 19e], and the value for *trans*-2-methoxy-5-*tert*-butyl-1,3,2-dioxaphosphorinane is suggested to be 1.5–2.0 kcal/mol (see ref 2).
(25) There is precedent for an increase in ^{31}P–H coupling constants in phosphoryl compounds upon complexation with transition metals.[21a]
(26) The cis/trans designation may vary from compound to compound. In the discussion, we are comparing compounds correspondent by their alkyl/phenyl or alkyl/alkyl substitution.
(27) An example has been reported where a conformational equilibrium was not appreciably affected by europium chelates. See J. T. Groves and M. Van Der Puy, *Tetrahedron Lett.*, 1949 (1975).
(28) M. M. Crutchfield, C. H. Dungan, J. H. Letcher, V. Mark, and J. R. Van Wazer, *Top. Phosphorus Chem.*, **5**, 40–41 (1967).
(29) A. A. Bothner-by and S. M. Castellano in "Computer Programs for Chemistry", Vol. 1, D. F. Detar, Ed., W. A. Benjamin, New York, N.Y., 1968, Chapter 3.
(30) The program was first modified to operate on a Burroughs 5500 computer with the help of Mr. William Slegeir and was subsequently improved by Mr. Brandt Kramer. We are especially indebted to Mr. Kramer for carrying out spectral computations and for obtaining plots of calculated spectra.
(31) N. Bhacca and D. Williams, "Application of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, p 43.

Preparation, Stereochemistry, and Nuclear Magnetic Resonance Spectroscopy of Methyl 1,3-Dimethyl-2-oxocyclohexaneacetates and Related Derivatives

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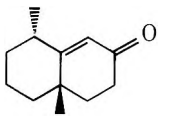
The two diastereomeric methyl 1,3-dimethyl-2-oxocyclohexaneacetates, **9b** and **10b**, as well as the related epimeric derivatives (**2–7**) have been prepared and their stereochemistry rigorously established via chemical correlation with the previously known enone **8**. During the correlation, oxidative cleavage of a variety of carbon–carbon double bonds was effected with $RuO_4/NaIO_4$ without concomitant epimerization either at incipient or remote ketone functionalities. Finally, the stereochemical assignments, in accord with the 60- and 220-MHz NMR spectral data, require reversal of the assignment previously made by Muller and Jeger[5] for diastereomers of **7**.

During the course of our studies on the thermal[1] and acid-catalyzed[2] decomposition of β,γ-unsaturated diazo ketones, we required an efficient approach to authentic samples of both diastereomers of methyl 1,3-dimethyl-2-oxocyclohexaneacetate (**1**). In this report we wish to document the preparation and rigorous stereochemical assignment of these esters as well as the related epimeric derivatives (**2–7**). Our stereochemical assignment involves a chemical correlation of **1–7** with the well-known enone (**8**) prepared first by the Marshall group[3] and improved several years later by Caine and co-workers.[4] Interestingly, the diastereomers of **7** were recently isolated and their structures defined employing NMR criteria.[5] The present chemical interrelationships require the reversal of these assignments. Finally, we note the synthetic utility of $RuO_4/NaIO_4$ in aqueous acetone for the oxidative cleavage of olefinic bonds without concomitant epimerization either at incipient or remote carbonyl functionalities.[6]

Our synthetic approach to the diastereomers of **1** involves the facile monoalkylation of 2,6-dimethylcyclohexanone with allyl bromide, utilizing lithium diisopropylamide as the base.[7] The resultant epimeric ketones **9a** and **10a**, produced in equal amounts, were each fully characterized after separation via vapor phase chromatography (VPC). Subsequent oxidation[6] of **9a** and **10a** with $RuO_4/NaIO_4$ in aqueous acetone followed by diazomethane esterification of the resultant acids provided **9b** and **10b**, the desired diastereomers of **1**. In each case, oxidation yielded only a single γ-keto ester, demonstrating that the oxidation conditions do not result in equilibration. On the

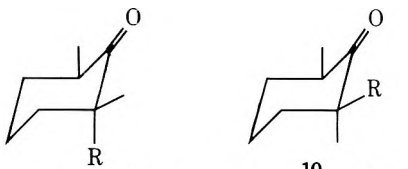
Chart I

1, X = O; R = $CH_2CO_2CH_3$
2, X = O; R = $CH_2CH{=}CH_2$
3, X = O; R = $CH_2CH_2CO_2CH_3$
4, X = CH_2; R = $CH_2CO_2CH_3$
5, X = CH_2; R = $CH_2CH_2CO_2CH_3$
6, X = CH_2; R = CH_2COCH_3
7, X = O; R = CH_2COCH_3

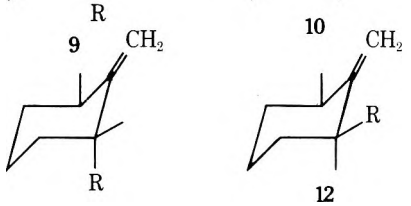


8

Chart II

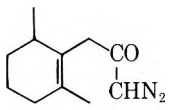


9 10



11 12

a, R = $CH_2CH{=}CH_2$
b, R = $CH_2CO_2CH_3$
c, R = $CH_2CH_2CO_2CH_3$
d, R = CH_2COCH_3



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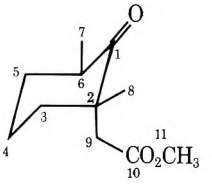
other hand, treatment of either **9b** or **10b** with $NaOCH_3$ in boiling methanol led to the same equilibrium mixture, i.e., 65:35, respectively.

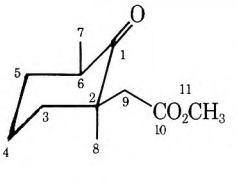
A stereochemical assignment, albeit tentative, of diastereomers **1** and **2** based on the 220-MHz ^1H NMR data was possible at this point. For example, the resonance for the equatorial methyl substituent at C-1 in **9a** and **9b** experiences a small[8,9] upfield shift (Δ ~0.20 ppm) relative to that of the C-1 axial methyls in **10a** and **10b.** Likewise, the equatorial methylene group at C-1 in **10b** appears upfield (Δ ~0.20 ppm) compared to the axial counterpart in **9b.** We next turned to ^{13}C NMR to support these assignments. Table I records the carbon chemical shifts for **9b** and **10b** along with the multiplicity obtained during off-resonance decoupling. The carbon assignments were straightforward based on analogy with literature data for cyclohexane[10] and cyclohexanone[11] derivatives. For comparison we list the chemical shifts of 2,2,6-trimethylcyclohexanone.[11] Most noteworthy here is the lack of significant chemical shift differences between the respective carbons of **9b** and **10b,** thereby preventing verification by carbon NMR of the above stereochemical assignments.

With the ready availability of **9b** and **10b,** there remained only a chemical correlation with enone **8** to complete a rigorous stereochemical assignment. We envisioned here a simple

Table I. ^{13}C NMR Spectral Data of Diastereomers 9b and 10b



9b



10b

Carbon assignments	Chemical shifts, ppm from Me_4Si		
	9b	10b	2,2,6-Trimethylcyclohexanone
1	214.6 (s)	215.0 (s)	216.4
10	171.5 (s)	172.5 (s)	
11	51.6 (q)	51.2 (q)	
2	47.6 (s)	47.3 (s)	45.0
9	42.7 (t)	42.6 (t)	(25.2 or 25.6)
6	41.2 (d)	41.1 (d)	40.6
3	40.6 (t)	38.7 (t)	41.8
5	36.6 (t)	35.9 (t(	36.7
8	22.9 (q)	23.7 (q)	(25.2 or 25.6)
4	21.0 (t)	21.4 (t)	21.6
7	15.1 (q)	15.0 (q)	15.0

Arndt–Eistert homologation of **9b** and **10b** to esters **9c** and **10c,** coupled with conversion of enone **8** to one of these esters. Approach to the desired δ-keto acid derivatives, **9c** and **10c,** from enone **8** has ample precedent. For example, Caspi[12] and Pelletier[13] reported recently the high-yield conversion of a variety of α,β-unsaturated steroidal ketones to δ-keto acid derivatives using ruthenium tetroxide oxidation. This strategy requires that both the oxidation of **8** and the homologation of **9b** and **10b** proceed without equilibration. Although our previous work indicates that $RuO_4/NaIO_4$ oxidation in aqueous acetone is sufficiently mild to avoid epimerization, prevention of equilibration in the chain homologation sequence, specifically ester hydrolysis preliminary to diazo ketone formation, appeared more difficult. This potential problem was circumvented by the availability in our laboratory of the epimeric esters **11b** and **12b,** the major and minor products, respectively, of the vinylogous Wolff rearrangement[1] of diazo ketone **13.** Correlation of these esters with **9b** and **10b** was effected without incident by oxidation with ruthenium tetroxide.

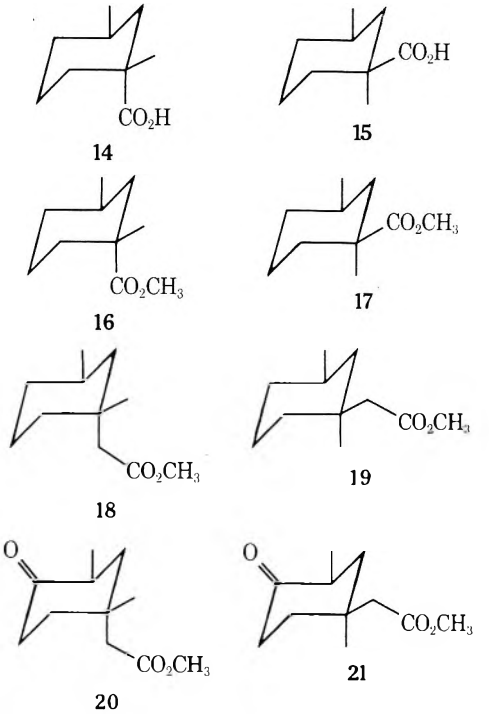
Employing esters **11b** and **12b,** side chain homologation followed by oxidative conversion of the methylene functionality to a carbonyl group without concomitant equilibration was now straightforward. To this end **11b** and **12b** were subjected to a photochemical[14] version of the Arndt–Eistert chain homologation. Each was transformed to the corresponding diazo ketone in the usual manner, and these in turn were irradiated in methanol through Pyrex (λ >280 nm) to give **11c** and **12c** in 94 and 85% yield. Subsequent ruthenium tetroxide oxidation gave **9c** and **10c,** respectively. The final chemical correlation, completing the stereochemical assignment of diastereomers **1–5,** was effected by the successful conversion [(a) $RuO_4/NaIO_4$; (b) CH_2N_2] of enone **8**[4] to a single γ-keto ester which was identical in all respects (IR, 220-MHz NMR, and VPC data) with **10c.**

The above stereochemical assignments are in complete accord with the 60- and 220-MHz ^1H NMR spectra. Table II lists the observed chemical shifts of the axial and equatorial C-1 methyl and methylene groups obtained for diastereomers **1–7** as well as the related epimeric derivatives (**14–21**) recently assigned by Wolff and Agosta.[15] Evident here is the generalization, observed originally by Johnson[8] and later by Musher[9] and Grant[10] that proton resonances for equatorial methyl and

Table II. ^{1}H NMR Data for Diastereomers 1–11

Diastereomer	Isomer	Registry no.	Chemical shifts, δ C-1 CH_3	C-1 CH_2
1	**9b**	61140-22-5	1.05	2.57
	10b	61140-23-6	1.23	2.42
2	**9a**	61140-24-7	0.97	
	10a	61140-25-8	1.13	
3	**9c**	61140-26-9	0.98	
	10c	61140-27-0	1.17	
4	**11b**	61140-28-1	1.20	2.42
	12b	61140-29-2	1.20	2.43
5	**11c**	61140-30-5	1.02	
	12c	61140-31-6	1.05	
6	**11d**	61140-32-7	1.17	2.52
	12d	61140-33-8	1.20	2.55
7	**9d**	58254-23-2	1.02	2.70
	10d	58254-24-3	1.18	2.48
	14	38864-02-7	1.20	
	15	38864-08-3	1.23	
	16	38864-04-9	1.09	
	17	38864-09-4	1.17	
	18	60415-83-0	0.96	2.21
	19	38864-10-7	0.98	2.06
	20	23733-86-0	1.08	2.58
	21	23733-85-9	1.32	2.24

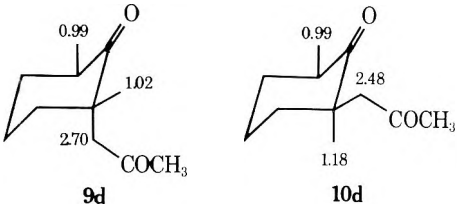
Chart III



methylene substituents experience a small upfield shift (~0.02–0.25 ppm) relative to that of the corresponding C-1 axial substituents. Exceptions occur for diastereomers **4** and **6** where the shifts are either extremely small or nonexistent. Interestingly, the magnitude of the observed shifts are somewhat larger when the ring contains a carbonyl group. This augmentation in effect appears to be independent of location of the carbonyl group on the ring. Finally, it should be noted that this generalization is the exact reverse of the well-known empirical correlation that equatorial cyclohexyl protons appear at lower field relative to axial protons.[16]

While this work was in progress, Muller and Jeger[5] reported the isolation and stereochemical assignment of the related 1,4-diketones, **9d** and **10d.** However, their stereochemical assignments did not conform with the reported NMR observations. To clarify this discrepancy, we transformed esters **11b** and **12b,** now of known stereochemistry, to **9d** and **10d,** respectively. Each ester was first hydrolyzed to the corresponding carboxylic acid and then treated in ether with 2 equiv of methyllithium to yield **11d** and **12d.**[17] All attempts at this point to transform these unsaturated ketones to **9d** and **10d** with ruthenium tetroxide lead to overoxidation. Successful conversion was finally accomplished via microozonolysis at −78 °C, followed by reductive workup with triphenylphosphine.[18] Gas chromatography revealed in each case the formation of a single 1,4-diketone. The spectral data for **9d** and **10d,** as shown in Chart IV, were in complete agreement

Chart IV



with the data reported by Muller and Jeger[5] upon reversal of their stereochemical assignments.

Experimental Section

Materials and Equipment. All VPC separations were accomplished on a Varian Aerograph Model 920 gas chromatograph employing one of the following columns: A, 25% QF-1, 10 ft × 0.375 in.; B, 25% QF-1, 50 ft × 0.25 in.; C, 25% DEGS, 10 ft × 0.375 in. The column oven was operated at 140–190 °C and the helium carrier gas flow rate was 100–120 ml/min. Compounds purified by VPC were obtained as colorless liquids. IR and NMR spectra were obtained for CCl_4 solutions, the former on a Perkin-Elmer Model 337 spectrophotometer and the latter on a Varian A-60 (60 MHz) or HR-220 (220 MHz) spectrometer. ^{13}C NMR spectra were obtained in $CDCl_3$ on a JEOL PS-100 spectrometer. The internal standard for both ^{1}H and ^{13}C NMR spectroscopy was Me_4Si. Solutions were dried over $MgSO_4$; melting points are corrected; boiling points are uncorrected. Photochemical experiments were carried out with a Hanovia Model L mercury lamp (no. 679A-36) in a quartz immersion well using Pyrex 7740 as filter. Ruthenium dioxide ($RuO_2 \cdot x H_2O$, 57.95%) was obtained from Englehard Laboratories.

2,*t*-6- and 2,*c*-6-Dimethyl-*r*-2-allylcyclohexan-1-one[19] (9a and 10a). To a solution containing 25 ml of dry THF and 5.3 g (1.2 equiv) of diisopropylamine distilled from KOH and cooled under N_2 to 0–5 °C was added with stirring 21 ml (1.2 equiv, 2.5 M) of *n*-BuLi. After the addition was complete the solution was cooled to −78 °C and 9.4 g (1.2 equiv) of HMPA distilled from CaH_2 was added. Approximately 30 min later a solution containing 5.5 g (44 mmol) of 2,6-dimethylcyclohexanone and 20 ml of THF was added slowly followed 45 min later by the addition of 8.7 g (1.2 equiv) of allyl bromide. The resulting solution was stirred for 1 h at −78 °C and then overnight at room temperature. The reaction mixture was then poured into 80 ml of saturated aqueous NH_4Cl and extracted with ether; the combined organic phases were washed with H_2O and brine and dried. Removal of the solvent in vacuo followed by distillation afforded 4.4 g (63%) of a 1:1 mixture of **9a** and **10a.** Preparative VPC on column B gave pure **9a** and **10a.** The first was **10a:** IR 3075 (w), 2975 (s), 2940 (s), 1705 (s), 1640 (w), 995 (s), 905 cm^{-1} (s); NMR (220 MHz) δ 0.95, 1.13 (d, s, J = 6 Hz, 6 H), 1.16–2.36 (m, 8 H), 2.55 (m, 1 H), 4.98 (m, 2 H), 5.75 (m, 1 H); mass spectrum *m/e* 166.1361 (M^+, calcd for $C_{11}H_{18}O$, 166.1357). The second was **9a:** IR 3075 (w), 2975 (s), 2940 (s), 1705 (s), 1640 (w), 915 cm^{-1} (s); NMR (220 MHz) δ 0.92, 0.97 (d, s, J = 6 Hz, 6 H), 1.05–2.54 (m, 9 H), 5.00 (m, 2 H), 5.55 (m, 1 H); mass spectrum *m/e* 166.1347 (M^+, calcd for $C_{11}H_{18}O$, 166.1357).

Methyl 1,*t*-3-Dimethyl-2-oxo-*r*-1-cyclohexaneacetate (9b). A solution containing 80 mg of RuO_2, 500 mg of $NaIO_4$, 20 ml of H_2O, and 35 ml of reagent acetone was stirred (ca. 1 h) at room temperature until the organic phase assumed a distinct yellow coloration (RuO_4). To this mixture was added a solution containing 50 mg (0.30 mmol)

of pure **9a** in 10 ml of acetone. The resultant mixture was then stirred at room temperature for 4 h, whereupon 500 μl of 2-propanol was added and the black precipitate filtered after 15 min. The filtrate was poured into 60 ml of H_2O and extracted with ether. The combined organic phases were washed with H_2O and brine and dried. Removal of the solvent in vacuo gave 51.5 mg (93%) of acid [IR 3600–2500 (s, br), 1710 cm^{-1} (s)] which was esterified with excess ethereal diazomethane (CH_2N_2). After 60 min the excess CH_2N_2 was removed on a steam bath and the solution dried. Removal of the solvent in vacuo gave 80 mg of crude **9b**. An analytical sample was obtained by VPC on column A: IR 2975 (s), 2943 (s), 1749 (s), 1723 (s), 1207 cm^{-1} (s); NMR (60 MHz) δ 0.98, 1.05 (d, s, J = 6 Hz, 6 H), 1.13–3.03, 2.57 (m, dd, J = 14 Hz, 9 H), 3.57 (s, 3 H).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.88; H, 9.08.

Methyl 1,*c*-3-Dimethyl-2-oxo-*r*-1-cyclohexaneacetate (10b). By a procedure similar to that listed for **9b**, 35 mg (0.21 mmol) of **10a** was oxidized and esterified to afford 39 mg (93%) of **10b**. An analytical sample was obtained by VPC on column B: IR 2970 (s), 2940 (s), 2875 (s), 1740 (s), 1708 (s). 1171 (s), 1004 cm^{-1} (s); NMR (60 MHz) δ 1.00 (d, J = 7 Hz, 3 H), 1.23 (s, 3 H), 1.33–2.83, 2.42 (m, dd, J = 16 Hz, 9 H), 3.59 (s. 3 H).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.89; H, 9.17.

Equilibration of Diastereomers 9b and 10b. On a 50-mg scale, pure keto ester **10b** was dissolved in 6 ml of a freshly prepared solution of NaOMe in MeOH (~0.6 M) and heated at reflux under N_2 for 16 h. After workup vapor phase chromatography on column A indicated a mixture of keto esters **9b** and **10b** in a ratio of 65:35, respectively. Keto ester **9b** isolated from this mixture by preparative VPC on column A was identical (VPC retention time, 60-MHz NMR) with keto ester **9b** prepared previously.

In a similar manner pure keto ester **9b** (40 mg) was dissolved in 6 ml of a freshly prepared solution of NaOMe in MeOH and heated to reflux under N_2 for 16 h. After workup VPC on column A indicated a mixture of keto esters **9b** and **10b** in a ratio of 65:35, respectively.

Oxidation of Methyl 1,*t*-3-Dimethyl-2-methylene-*r*-1-cyclohexaneacetate (11b). A suspension containing 104 mg of RuO_2, 580 mg of $NaIO_4$, 20 ml of H_2O, and 35 ml of acetone was stirred for 1 h at room temperature until the organic phase assumed a distinct yellow coloration (i.e., RuO_4). To this mixture was added a solution containing 54 mg (0.28 mmol) of ester **11b** in 10 ml of acetone. The resultant mixture was then stirred at room temperature for 4 h, whereupon 500 μl of 2-propanol was added and the black RuO_2 filtered after 15 min. The filtrate was poured into H_2O and extracted with ether. The organic phase was washed and dried. Removal of the solvent in vacuo gave 50.3 mg (91%) of a γ-keto ester which, after VPC purification on column A, was identical in all respects (i.e., IR, 220-MHz NMR, and VPC retention properties) with ester **9b**.

Oxidation of Methyl 1,*c*-3-Dimethyl-2-methylene-*r*-1-cyclohexaneacetate (12b). In a manner similar to the above, 33 mg (0.17 mmol) of ester **12b** was oxidized (RuO_2, $NaIO_4$, aqueous acetone) yielding 26 mg (79%) of a γ-keto ester which, after VPC purification of column A, was identical in all respects (i.e., IR, 220-MHz NMR, and VPC retention properties) with ester **10b**.

Methyl 1,*t*-3- and 1,*c*-3-Dimethyl-2-methylene-*r*-1-cyclohexaneacetate (11b and 12b). A solution consisting of 358.6 mg (1.88 mmol) of diazo ketone **13**, 27.1 mg of $Cu(AcAc)_2$, 123 μl of MeOH (1.5 equiv), and 100 ml of cyclohexane was heated at reflux for 60 min. After cooling the reaction mixture was washed successively with 1 N HCl, H_2O, and brine, and dried. Removal of the solvent in vacuo afforded 344 mg of an oily residue containing 150 mg (41%, by VPC calibration) of a 9:1 mixture of **11b** and **12b**, respectively. Preparative VPC on column C gave pure **11b** and **12b**. The first was **11b**: IR 3110 (w), 2930 (s), 1740 (s), 1640 (w), 1475 (m), 1212 (s), 1181 (s), 898 cm^{-1} (s); NMR (60 MHz) δ 0.87, 1.20, 1.29–2.06 (d, s, m, J = 7 Hz, 13 H), 2.42 (dd, J = 13 Hz, 2 H), 3.53 (s, 3 H), 4.75 (m, 2 H).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.34; H, 10.13.

The second was **12b**: IR 3110 (w), 2930 (s), 1740 (s), 1640 (w), 1470 (m), 1210 (s), 1115 (s), 1007 (s), 890 cm^{-1} (s); NMR (60 MHz) δ 1.05, 1.20, 1.26–2.03 (d, s, m, J = 7 Hz, 13 H), 2.43 (s, 2 H), 3.60 (s, 3 H), 4.67 (m, 2 H); mass spectrum m/e 196.1472 (M^+, calcd for $C_{12}H_{20}O_2$, 196.1462).

Methyl 1,*t*-3-Dimethyl-2-methylene-*r*-1-cyclohexanepropionate (11c). A solution containing 360 mg (1.84 mmol) of ester **11b**, 12 ml of MeOH, and 4.4 ml of 5% (w/v) aqueous NaOH was heated at reflux under nitrogen for 2 h, yielding upon workup 324 mg (97%) of the corresponding acid [IR 3400–2600 (s, broad), 1700 (s), 1640 (w), 900 cm^{-1} (s)].

A solution containing 324 mg (1.78 mmol) of this acid in 2 ml of benzene was treated with 300 μl (2.0 equiv) of oxalyl chloride and stirred for 4 h at room temperature. Distillation (Kuglerohr) of the residue after removal in vacuo of the benzene and excess oxalyl chloride afforded 334 mg (94%) of the corresponding acid chloride [IR 2940 (s), 1800 (s), 1640 (w), 900 cm^{-1} (s)]. This acid chloride was dissolved in 20 ml of ether and added dropwise with stirring to an ethereal solution of CH_2N_2 (3.5 equiv) yielding 360 mg (100%) of the corresponding diazo ketone [IR 3100 (w), 2940 (s), 2100 (s), 1645 (s), 900 cm^{-1} (s)]. The diazo ketone was dissolved in 70 ml of MeOH and irradiated for 90 min. The photolysate was poured into 50 ml of H_2O and extracted with ether and the organic phase washed with H_2O and brine and dried. Removal of the solvent in vacuo gave 328 mg (94%) of **11c**. An analytical sample was obtained by VPC on column C: IR 3110 (w), 2940 (s), 1740 (s), 1640 (w), 1195 (s), 1173 (s), 895 cm^{-1} (s); NMR (60 MHz) δ 0.93–2.5, 1.02, 1.04 (m, s, d, J = 6 Hz, 17 H), 3.58 (s, 3 H), 4.75 (m, 2 H).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H 10.54. Found: C, 74.20; H, 10.57.

Methyl 1,*c*-3-Dimethyl-2-methylene-*r*-1-cyclohexanepropionate (12c). By a similar procedure ester **12b** was homologated to ester **12c** in 87% overall yield. Preparative VPC on column C gave pure **12c**: IR 3100 (w), 2940 (s), 1740 (s), 1640 (w), 1198 (s), 1170 (s), 895 cm^{-1} (s); NMR (60 MHz) δ 0.96–2.67, 1.05, 1.06 (m, s, d, J = 7 Hz, 17 H), 3.65 (s, 3 H), 4.78 (s, 2 H).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.23; H, 10.46.

Methyl 1,*t*-3-Dimethyl-2-oxo-*r*-1-cyclohexanepropionate (9c). A mixture of 80 mg of RuO_2, 450 mg of $NaIO_4$, 20 ml of H_2O, and 35 ml of acetone was stirred at room temperature for 60 min followed by dropwise addition of 49.2 mg (0.23 mmol) of ester **11c** in 10 ml of acetone. After stirring for 4.5 h at room temperature, 500 μl of 2-propanol was added and the RuO_2 was removed by filtration. The filtrate was poured into H_2O and extracted with ether; the combined organic phases were washed with H_2O and brine and dried. Removal of the solvent in vacuo afforded 34 mg (70%) of crude **9c**. After purification by VPC on column C, **9c** had the following spectral data; IR 2970 (s), 2940 (s), 1740 (s), 1710 (s), 1255 cm^{-1} (s); NMR (60 MHz) δ 0.96, 0.98 (d, s, J = 6 Hz, 6 H), 1.05–2.66 (m, 11 H), 3.63 (s, 3 H); mass spectrum m/e 212.1425 (M^+, calcd for $C_{12}H_{20}O_3$, 212.1411).

Methyl 1,*c*-3-Dimethyl-2-oxo-*r*-1-cyclohexanepropionate (10c). In a manner similar to that listed for ester **9c**, 27.6 mg (0.13 mmol) of ester **12c** was oxidized (80 mg of RuO_2, 253 mg of $NaIO_4$, aqueous acetone, 4 h) affording 20 mg (71%) of crude **10c**. After purification by VPC on column C, **10c** had the following spectral data: IR 2940 (s), 1740 (s), 1715 (s), 1200 (s), 1170 cm^{-1} (s); NMR (220 MHz) δ 0.96 (d, J = 6 Hz, 3 H), 1.17 (s, 3 H), 1.24–2.41 (m, 10 H), 2.42–2.73 (m, 1 H), 3.66 (s, 3 H); mass spectrum m/e 212.1412 (M^+, calcd for $C_{12}H_{20}O_3$, 212.1411).

Oxidation of 4,4a,5,6,7,8-Hexahydro-4aβ,8α-dimethyl-2(3*H*)-naphthalenone (8). In a manner similar to the previously listed oxidations, 70.5 mg (0.4 mmol) of enone 8 was oxidized to the corresponding keto acid which was then esterified with excess CH_2N_2 for 60 min to yield 75 mg (88%) of a keto ester (**10c**). After VPC purification on column C this keto ester was identical in all respects (IR, 220-MHz NMR, and VPC retention properties) with **10c** prepared from ester **12c**.

2,*t*-6-Dimethyl-*r*-2-(2′-oxoprop-1′-yl)-1-methylenecyclohexane (11d). A solution containing 360 mg (1.8 mmol) of pure **11b**, 12 ml of MeOH, and 4.4 ml of 5% (w/v) aqueous NaOH was heated at reflux under nitrogen for 2 h. The reaction mixture was then cooled, poured into water, and extracted with ether. Acidification of the aqueous phase, extraction with ether, drying, and removal of the solvent in vacuo gave as an oil 324 mg (97%) of the corresponding carboxylic acid.

A solution containing 142 mg (0.78 mmol) of this acid and 10 ml of anhydrous ether was treated at 0 °C under N_2 with 950 μl (2.5 equiv) of MeLi (2.06 M). The resulting solution was stirred at room temperature for 13 h, and then added dropwise to a stirred saturated aqueous solution of NH_4Cl. The reaction mixture was extracted with ether and the combined organic phases washed with H_2O and brine and then dried. Removal of the solvent in vacuo gave 137.2 mg (93%) of **11d**. An analytical sample was prepared by VPC on column C: IR 3110 (w), 2970 (s), 2940 (s), 1710 (s), 1640 (w), 900 cm^{-1} (s); NMR (60 MHz) δ 1.00–1.92, 1.08, 1.17 (m, d, s, J = 6 Hz, 12 H), 1.93–2.98, 1.97, 2.52 (m, s, d, J = 14 Hz, 6 H), 4.97 (m, 2 H); mass spectrum m/e 180.1498 (M^+, calcd for $C_{12}H_{20}O$, 180.1513).

2,*c*-6-Dimethyl-*r*-2-(2′-oxoprop-1′-yl)-1-methylenecyclohexane (12d). A solution containing 147 mg (0.75 mmol) of pure **12b**, 12 ml of MeOH, and 2 ml of 5% (w/v) aqueous NaOH was heated at reflux

under nitrogen for 3 h. The reaction mixture was then cooled, poured into water, and extracted with ether. Acidification of the aqueous phases, extraction with ether, drying, and removal of the solvent in vacuo gave as an oil 126 mg (93%) of the corresponding carboxylic acid.

A solution containing 74 mg (0.41 mmol) of this acid and 10 ml of anhydrous ether was treated at 0 °C under nitrogen with 0.63 ml (3.2 equiv) of MeLi (2.06 M). The resulting solution was stirred at room temperature for 19 h and then worked up as above to give 68 mg (93%) of **12d.** An analytical sample was obtained by VPC on column C: IR 3110 (w), 2970 (s), 2930 (s), 1710 (s), 1640 (w), 890 cm^{-1} (s); NMR (60 MHz) δ 1.07, 1.20 (d, s, J = 7 Hz, 6 H), 1.23–2.06 (m, 7 H), 2.08 (s, 3 H), 2.55 (s, 2 H), 4.62 (m, 2 H); mass spectrum m/e 180.1497 (M^+, calcd for $C_{12}H_{20}O$, 180.1513).

2,*t*-6-Dimethyl-*r*-2-(2′-oxoprop-1′-yl)-1-cyclohexanone (9d). A solution containing 55 mg (0.31 mmol) of ketone **11d** and 6 ml of spectroquality hexane was cooled to −78 °C. Ozone was then passed slowly through the solution for 75 min after which 95 mg of triphenylphosphine was added. After warming to room temperature the resulting suspension was filtered and the filtrate chromatographed on silica gel. Elution with ether–hexane (1:1) gave 46 mg (82%) of **9d.** A pure sample prepared by VPC on column C possessed the IR and NMR data listed below, which were identical with those reported for *trans*-2,6-dimethyl-2-(2-oxoprop-1-yl)cyclohexan-1-one by Muller and Jager:[5] IR 2975 (s), 2940 (s), 1720 (s, br), 1360 (s), 1015 (s), 975 (w), 950 cm^{-1} (w); NMR (60 MHz) δ 0.99, 1.02 (d, s, J = 6 Hz, 6 H), 1.13–2.67, 2.04 (m, s, 10 H), 2.70 (s, 2 H); (220 MHz) δ 0.98–1.91, 0.99, 1.02 (m, d, s, J = 6 Hz, 10 H), 1.92–2.36, 2.05 (m, s, 5 H), 2.56–2.82, 2.70 (m, dd, J = 16 Hz, 3 H).

2,*c*-6-Dimethyl-*r*-2-(2′-oxoprop-1′-yl)-1-cyclohexanone (10d). In a manner similar to the above, 29 mg (0.16 mmol) of **12d** was ozonized to give 29 mg (94%) of **10d.** A pure sample of **10d** prepared by VPC on column C possessed the IR and NMR data listed below which were identical with those reported for *cis*-2,6-dimethyl-2-(2-oxoprop-1-yl)cyclohexan-1-one by Muller and Jager:[5] IR 2975 (s), 2940 (s), 1710 (s, br), 1360 (s), 1168 (s), 1142 (s), 1125 (s), 1000 (s), 978 (m), 955 cm^{-1} (w); NMR (60 MHz) δ 1.02 (d, J = 6 Hz, 3 H), 1.20 (s, 3 H), 1.50–2.16, 2.09 (m, s, 9 H), 2.16–2.75, 2.51 (m, dd, J = 17 Hz, 3 H); (220 MHz) δ 0.99 (d, J = 6 Hz, 3 H), 1.18 (s, 3 H), 1.20–2.13, 2.09 (m, s, 9 H), 2.42, 2.48 (m, dd, J = 17 Hz, 3 H).

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Registry No.—8, 17990-00-0; **10c** free acid, 61140-34-9; **11b** free acid, 61140-35-0; **11b** acid chloride, 61140-36-1; **12b** free acid, 61140-37-2; **12b** acid chloride, 61140-38-3; **13**, 61140-39-4; 2,6-dimethylcyclohexanone, 2816-57-1; allyl bromide, 106-95-6.

References and Notes

(1) A. B. Smith, III, *J. Chem. Soc., Chem. Commun.*, 695 (1974).
(2) A. B. Smith, III, *J. Chem. Soc., Chem. Commun.*, 274 (1975); A. B. Smith, III, S. J. Branca, and B. H. Toder, *Tetrahedron Lett.*, 4225 (1975).
(3) J. A. Marshall and D. J. Schaeffer, *J. Org. Chem.*, **30**, 3642 (1965).
(4) D. Caine and F. N. Tuller, *J. Org. Chem.*, **34**, 222 (1969). We are grateful to Professor Caine for the generous sample of enone **8.**
(5) E. P. Muller and O. Jeger, *Helv. Chim. Acta*, **58**, 2173 (1975).
(6) For leading references on ruthenium tetroxide oxidations of (a) unsaturated compounds see R. Pappo and A. Becker, *Bull. Res. Counc. Isr., Sect. A*, **5**, 300 (1956); L. M. Berkowitz and P. N. Rylander, *J. Am. Chem. Soc.*, **80**, 6682 (1958); S. Sarel and Y. Yanuka, *J. Org. Chem.*, **24**, 2018 (1959); G. Stork, A. Meisels, and J. E. Davies, *J. Am. Chem. Soc.*, **85**, 3419 (1963); G. Snatzke and H. W. Fehlhaber, *Justus Liebigs Ann. Chem.*, **663**, 123 (1963); F. Sondheimer, R. Mechulan, and M. Sprecher, *Tetrahedron* **20**, 2473 (1964); J. A. Caputo and R. A. Fuchs, *Tetrahedron Lett.*, 4729 (1967); (b) alcohols see E. J. Corey, J. Casanova, Jr., P. A. Vatakencherry, and R. Winter, *J. Am. Chem. Soc.*, **85**, 169 (1963); H. Nakata, *Tetrahedron*, **19**, 1959 (1963); P. J. Benyon, P. M. Collins, P. T. Doganyes, and W. G. Overend, *J. Chem. Soc. C*, 1131 (1966); H, Kaufmann and T. Reichstein, *Helv. Chim. Acta*, **50**, 2280 (1967).
(7) For a detailed study on the alkylation of simple ketones with LDA see H. O. House, M. Gall, and H. D. Olmstend, *J. Org. Chem.*, **36**, 2361 (1971). For the use of the LDA–HMPA complex in the alkylation of esters see J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Lett.*, 2433 (1973).
(8) F. Johnson and N. A. Starkovsky, *Tetrahedron Lett.*, 1173 (1962); F. Johnson, N. A. Starkovsky, and W. D. Gurowitz, *J. Am. Chem. Soc.*, **87**, 3492 (1965).
(9) A. Segre and J. I. Musher, *J. Am. Chem. Soc.*, **89**, 706 (1967).
(10) D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.*, **89**, 6612 (1967).
(11) J. B. Stothers and C. T. Tan, *Can. J. Chem.*, **52**, 308 (1974).
(12) D. M. Piatak, H. B. Bhat, and E. Caspi, *J. Org. Chem.*, **34**, 112 (1969).
(13) S. W. Pelletier, K. N. Iyer, and C. W. . Chang, *J. Org. Chem.*, **35**, 3535 (1970).
(14) L. Horner and E. Spietschka, *Chem. Ber.*, **88**, 934 (1955).
(15) S. Wolff and W. C. Agosta, *J. Org. Chem.*, **38**, 1694 (1973).
(16) L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, Oxford, 1969, pp 238–241, and references cited therein.
(17) M. J. Jorgenson, *Org. React.*, **18**, 1 (1970).
(18) M. Beroza and B. A. Bierl, *Anal. Chem.*, **38**, 1976 (1966).
(19) Diastereomers **1–7** are named according to IUPAC Tentative Rules; see *J. Org. Chem.*, **35**, 2849 (1970).

Analogues of Phosphoenol Pyruvate. 3.[1] New Synthetic Approaches to α-(Dihydroxyphosphinylmethyl)acrylic acid and Unequivocal Assignments of the Vinyl Protons in Its Nuclear Magnetic Resonance Spectrum

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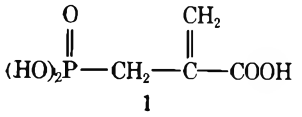
Three new synthetic routes to α-(dihydroxyphosphinylmethyl)acrylic acid (1), the phosphonic acid analogue of phosphoenolpyruvic acid, have been developed. One of these routes was devised so that a carbon-13 label could be introduced specifically in the carboxylate carbon position of 1. By measurement of $^3J_{^1H-^{13}C}$ coupling constants in the NMR spectrum of 1, unequivocal assignments for the vinyl protons have been made.

Phosphoenolpyruvic acid (PEP) is one of the most important biological substances with a high phosphate group-transfer potential.[4] In 1972, Stubbe and Kenyon reported the synthesis of the nonhydrolyzable phosphonate analogue of PEP, α-(dihydroxyphosphinylmethyl)acrylic acid (1). This analogue has been found to replace PEP as a substrate in the enolase reaction[1,5] and to serve as a weak competitive inhibitor of rabbit muscle pyruvate kinase.[6] In the case of both enzymes,

distance measurements between enzyme-bound Mn(II) at the active sites and fixed protons of bound 1 were made using



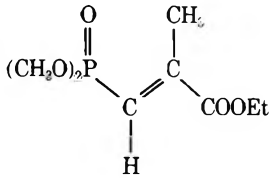
1

NMR techniques. The distance values obtained permitted models to be constructed of the enzyme–Mn(II)–inhibitor ternary complexes.[5,6] Although the tentative NMR assignments made to the vinyl protons of 1 were not crucial to the arguments made in either paper, there was disagreement about these assignments.[5,6] In this paper we present unequivocal assignments for these two vinyl protons, assignments which support the arguments of James and Cohn,[6] and which do not support those of Nowak, Mildvan, and Kenyon.[5]

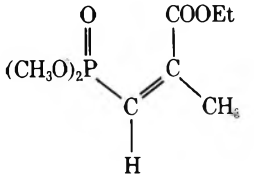
In addition, new, more efficient synthetic approaches to 1 and some related compounds are presented.

Results and Discussion

One synthetic approach to phosphonate analogues of phosphoenolpyruvic acid which was explored used the Wadsworth–Emmons–Horner (modified Wittig) reaction.[7,8] When the preformed α anion of bis(dimethoxyphosphinyl)methane (2) was treated with ethyl pyruvate in a manner similar to the procedure of Huff et al.,[9] a 50:50 mixture of (*E*)- and (*Z*)-ethyl (α-methyl-β-dimethoxyphosphinyl)-acrylates (*E*- and *Z*-4) was isolated in 91% yield. In an analo-



E-4



Z-4

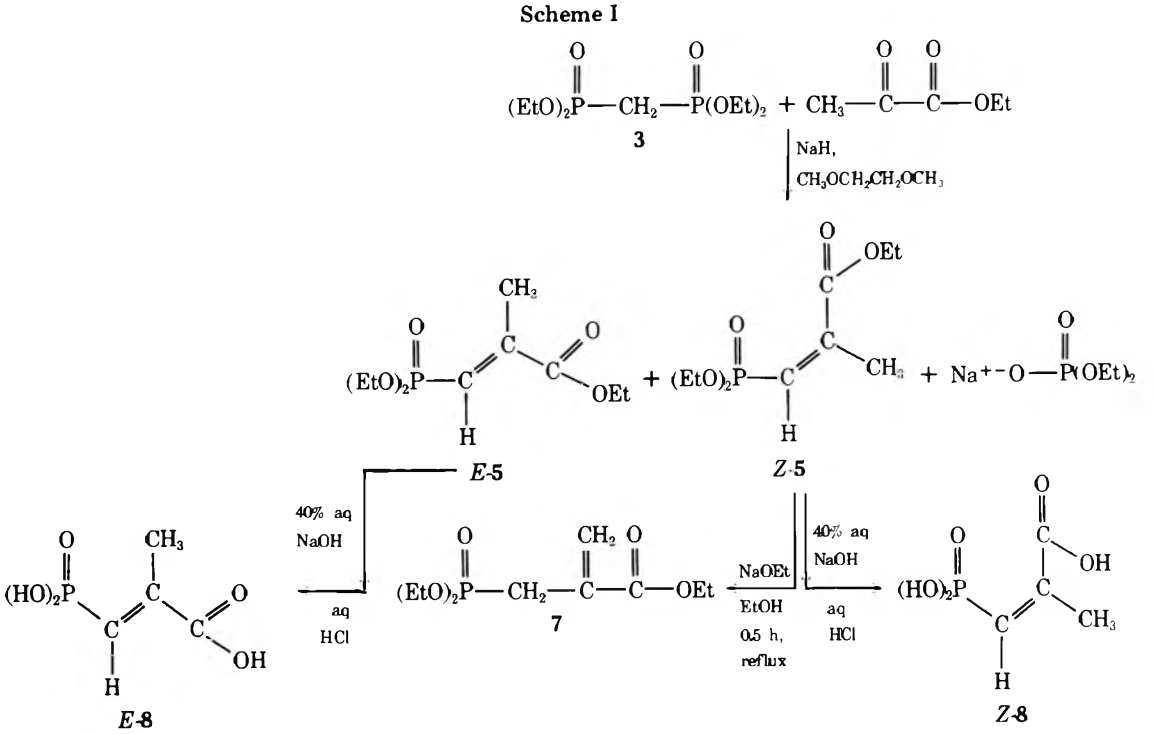
gous fashion using bis(diethoxyphosphinyl)methane (3), a 50:50 mixture of (*E*)- and (*Z*)-ethyl (α-methyl-β-diethoxyphosphinyl)acrylates (*E*- and *Z*-5) was generated in 88% yield (Scheme I).

When the former reaction was conducted with an excess of sodium hydride, substantial amounts of the known itaconate analogue, ethyl (α-dimethoxyphosphinylmethyl)acrylate[1] (6), were formed along with *E*- and *Z*-4, as judged by examining the NMR spectrum of the product mixture. This type of base-catalyzed rearrangement was also observed when a 40:60 mixture of *E*- and *Z*-5 was treated with refluxing sodium ethoxide in ethanol. The course of the rearrangement was followed by NMR spectroscopy, and it was observed that *only* isomer *Z*-5 readily rearranged to ethyl α-(diethoxyphosphinylmethyl)acrylate (7) (see Scheme I). Isomer *E*-5 remained unchanged. Presumably, the driving force for this stereoselective *Z*-5 → 7 conversion is release of relatively unfavorable steric interactions between the cis ethoxycarbonyl and diethoxyphosphinyl substituents of the *Z*-5 molecule. In compound *E*-5 these bulky substituents are trans to one another.

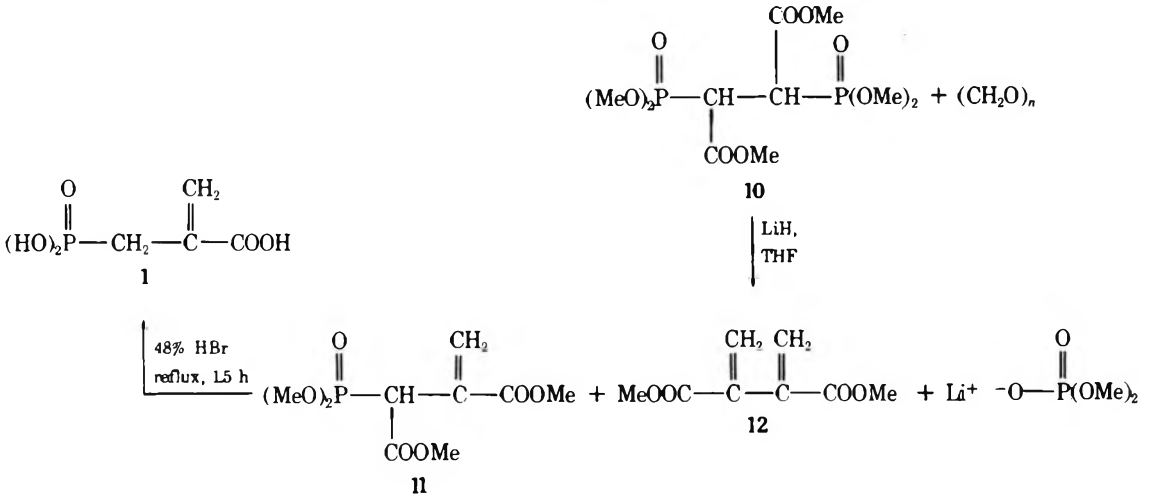
A definitive assignment of the geometries of *E*- and *Z*-5 has been made on the basis of the following observations (Scheme I). A 40:60 mixture of *E*- and *Z*-5 was stirred for 3 days at room temperature in an aqueous solution containing 1 molar equiv of NaOH; the solution was then acidified with HCl to pH 2 and thoroughly extracted with CH_2Cl_2. The aqueous layer was found to contain only *Z*-8 in the amount consistent with essentially its quantitative production from *Z*-5. The CH_2Cl_2 layer, in contrast, was found to contain only *E*-(α-methyl-β-diethoxyphosphinyl)acrylic acid (*E*-9) in the amount consistent with its production from *E*-5. Compound *E*-9 could be hydrolyzed to unesterified *E*-8 in 71% yield by heating at reflux for 36 h in 6 N HCl. The relatively rapid conversion of *Z*-5 to *Z*-8 at room temperature is strongly indicative of carboxyl group participation in the hydrolysis of the phosphonate ethyl ester groups via intramolecular nucleophilic catalysis.[10,11] Only the *Z* isomer of 5, with the carboxylate and phosphonate substituents cis to one another, would be expected to exhibit this hydrolytic behavior. Precedents for such intramolecular carboxyl-group participation leading to accelerated rates of hydrolysis of phosphonate esters may be found in the work of both Gordon et al.[12] and Blackburn and Brown.[13]

Observations of anisotropic deshielding effects in the ^1H NMR spectra[14] of both *E*- and *Z*-5 also support the given

Scheme I



Scheme II



structural assignments. For example, as predicted, the vinyl proton of *E*-**5** resonates at a lower field than the vinyl proton of *Z*-**5**, presumably owing to its cis relationship to an ethoxycarbonyl group.[14] Also, the allylic methyl protons of *E*-**5** resonate at a lower field than those of *Z*-**5**, again presumably owing to their cis relationship to a diethoxyphosphinyl group.

By treatment with aqueous HBr, esters of the type **6** and **7** may be hydrolyzed to the free α-(dihydroxyphosphinylmethyl)acrylic acid (**1**).[1] In the present study, **6** was converted to **1** in 54% isolated yield.

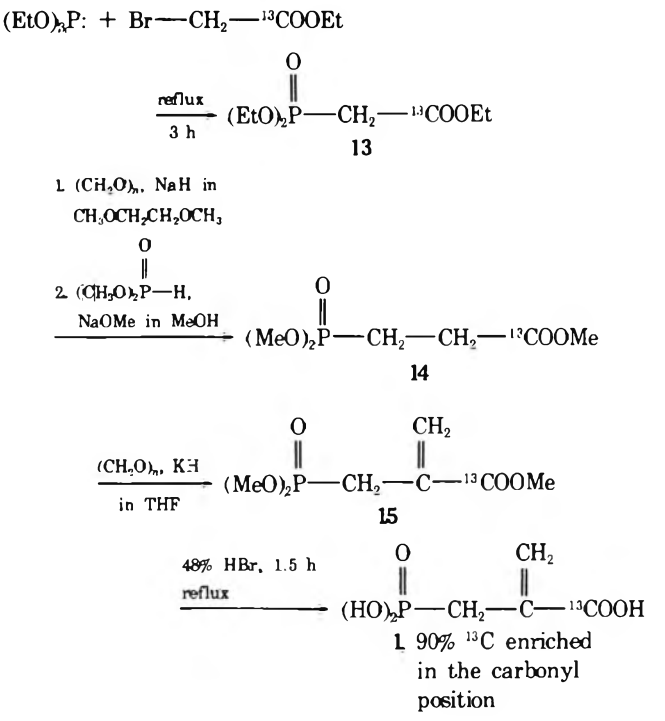
In Scheme II is outlined another modified Wittig reaction examined as a synthetic route to **1**. In this case the known compound dimethyl α,β-bis(dimethoxyphosphinyl)succinate[15] (**10**) was treated with formaldehyde under strongly basic conditions. A mixture of what appeared to be both dimethyl (α-methylidene-β-dimethoxyphosphinyl)succinate (**11**) and the known compound dimethyl α,β-bis(methylidene)succinate (**12**) was generated. Compound **12** was always the major product regardless of the conditions (e.g., base, temperature, reaction time, sequence of addition, solvent, stoichiometry) employed. Upon hydrolysis, **11** underwent decarboxylation without apparent double-bond rearrangement to give a 36% yield of **1**.

Still another synthetic approach to **1**, outlined in Scheme III, was developed so that selective carbon-13 enrichment could be made in the carboxyl carbon position. The finding of a commercial source of ethyl bromoacetate, 90% ^{13}C enriched in the carbonyl carbon position, led to the adoption of this scheme.

A Michaelis–Arbusov reaction of the labeled ethyl bromoacetate with triethyl phosphite gave labeled ethyl (diethoxyphosphinyl)acetate (**13**) in 96% yield. The modified Wittig procedure with formaldehyde then generated labeled ethyl acrylate. This ethyl acrylate was next treated without isolation with an excess of dimethyl phosphite in the presence of 1 molar equiv of sodium methoxide in methanol, following the procedure of Pudovik and Kitaev,[16] to generate labeled dimethyl β-methoxycarbonylethylphosphonate (**14**) in 62% yield. This in turn was converted to labeled methyl α-(dimethoxyphosphinylmethyl)acrylate (**15**) by treatment with KH in tetrahydrofuran followed by condensation with formaldehyde. Martin et al.[17] had earlier shown that such Stobbe condensations of diethyl β-ethoxycarbonylethylphosphonate with a variety of ketones gave a series of β,γ-unsaturated phosphonates. No evidence was observed for subsequent base-catalyzed rearrangement to α,β-unsaturated phosphonates.[17]

Compound **15** was converted to labeled **1** by acid-catalyzed

Scheme III



hydrolysis. The ^1H NMR spectra showing the vinyl proton regions of both labeled and unlabeled **1** are illustrated in Figure 1. In unlabeled **1** each of the vinyl proton signals is split by $^4J_{^1H-^{31}P}$ couplings of 4.3 and 4.7 Hz for the downfield and upfield protons, respectively. The smaller splitting of each peak is due to geminal ^1H–^1H coupling.[5] These ^1H–^{31}P and ^1H–^1H vinyl proton couplings were verified earlier by Nowak et al.[5] using both heteronuclear and homonuclear spin decoupling experiments. In the ^{13}C-labeled sample of **1** additional $^3J_{^1H-^{13}C}$ couplings of 6.7 and 11.5 Hz were observed for the downfield and upfield vinyl protons, respectively. Similarly, for the trimethyl ester precursor **15** $^3J_{^1H-^{13}C}$ values of 7.0 and 13.5 Hz were observed for the corresponding vinyl protons in the spectrum.

For spin–spin coupling between two nuclei substituted directly on the carbons of a carbon–carbon double bond it has been shown experimentally *without exception*[18] that J trans > J cis. This observation has also received some theoretical justification.[19] Thus it is clear from Figure 1 that the vinyl proton which is cis to the ^{13}C-enriched carboxyl group in both **1** and **15** resonates at a lower field (relative to tetramethylsilane) than that which is trans.

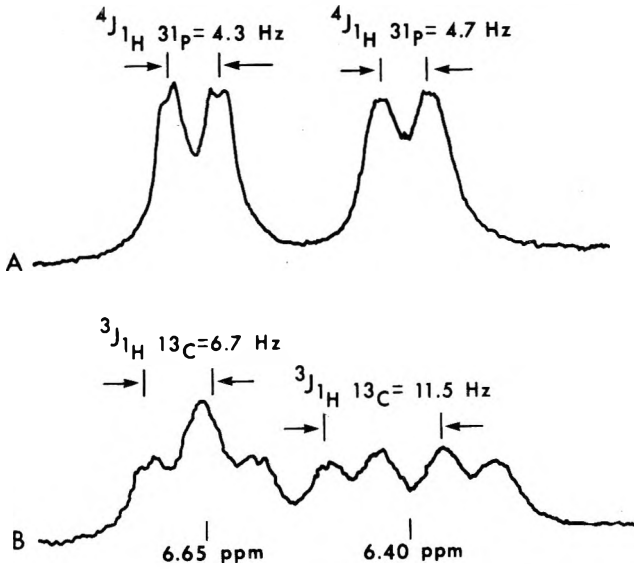


Figure 1. A: the ^1H NMR spectrum in D_2O at 60 MHz showing the vinyl proton region of the dilithium salt of **1**. B: the same, with 90% ^{13}C enrichment in the carboxyl carbon position.

Nowak, Mildvan, and Kenyon[5] had earlier made a tentative assignment of these vinyl protons in **1** on the basis of the observed differences in the $^4J_{1H-31P}$ values. It was pointed out that trans coupling is often greater than cis coupling in such systems, but known exceptions were noted,[20] and it was stated that there was "uncertainty in the assignments of the vinyl protons" [5]

James and Cohn[6] later made the opposite tentative assignments of the vinyl protons of **1** based on analogy to the well-established vinyl proton assignments made earlier for phosphoenolpyruvic acid.[21] In phosphoenolpyruvic acid the vinyl proton cis to the carboxyl group resonates downfield relative to the corresponding trans vinyl proton. James and Cohn argued that the same should probably be true for **1**. Indeed, many examples are known where the anisotropic deshielding effect of a carbonyl group substituted on a carbon–carbon double bond results in the vinyl proton substituted cis to be downfield from the geometrical isomer with the corresponding vinyl proton substituted trans.[14] The results in Figure 1 support the assignments of James and Cohn,[6] and, at least for this limited number of cases, show that the anisotropic deshielding of a vinyl proton by a carboxyl group attached to a carbon–carbon double bond is greater than that of a phosphinylmethyl group similarly attached to such a double bond.

The most efficient synthesis of unlabeled **1** which emerges from these studies is to prepare unlabeled **14** and then to carry out the last two steps of Scheme III. Alternatively, diethyl β-ethoxycarbonylethylphosphonate, the triethyl ester related to **14**, can be prepared by the method of Garner et al.[22] and used in the same sequence.

Experimental Section

General. All melting and boiling points are uncorrected. NMR spectra were determined at 60 MHz using either a Varian Model A-60A or Perkin-Elmer R12B spectrometer; δ values are relative to Me_4Si. IR spectra were recorded on a Beckman Acculab 4 spectrometer. Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley.

Bis(dimethoxyphosphinyl)methane (2) was prepared by the methods of Roy[23] and Nicholson et al.,[24] bp 80–85 °C (0.02 Torr) [lit.[24] bp 87–90 °C (0.05 Torr)]. The method of Roy[23] was also employed for the synthesis of **bis(diethoxyphosphinyl)methane (3)**, bp 85–90 °C (0.02 Torr) [lit.[24] bp 90–94 °C (0.1 Torr)].

A mixture of **(*E*) and (*Z*)-ethyl (α-methyl-β-dimethoxyphosphinyl)acrylates** (*E*- and *Z*-**4**) was prepared as follows. Sodium hydride (3.2 g of a 56% suspension in mineral oil, 75 mmol, Metal Hydrides, Inc.) was washed with hexane under N_2, and 100 ml of dimethoxyethane, freshly distilled from NaH, was added. Compound **2** (18.5 g, 92.5 mmol) dissolved in 25 ml of the distilled dimethoxyethane was added dropwise at 0 °C and allowed to stir for 2 h at room temperature under N_2. Freshly distilled ethyl pyruvate (9.3 g, 74 mmol, Aldrich) in 25 ml of dimethoxyethane was added dropwise at 0 °C, and the mixture was stirred for 0.5 h at 0 °C after addition was complete. Then cold, saturated aqueous KH_2PO_4 (50 ml) was added, and the reaction mixture was extracted thoroughly with five 100-ml portions of CH_2Cl_2. The extract was dried using Na_2SO_4 and filtered, and the solvent was removed in vacuo. Short-path distillation at 85–90 °C (0.03 Torr) gave 14.9 g (91% yield) of a 50:50 mixture of *E*- and *Z*-**4**. ***E*-4:** NMR ($CDCl_3$) δ 1.33 (t, J = 7 Hz, 3 H), 2.25 (d of d, $^4J_{H-H}$ = 1.3 Hz, $^4J_{H-^{31}P}$ = 3.6 Hz, 3 H), 3.73 (d, J = 11 Hz, 6 H), 4.25 (q, J = 7 Hz, 2 H), 6.6 (d of q, $^2J_{H-^{31}P}$ = 16.4, $^4J_{H-H}$ = 1.3 Hz, 1 H). ***Z*-4:** NMR ($CDCl_3$) δ 1.33 (t, J = 7 Hz, 3 H), 2.11 (apparent t, $^4J_{H-H}$ = 1.8, $^4J_{H-^{31}P}$ = 1.8 Hz, 3 H), 3.75 (d, $^3J_{H-^{31}P}$ = 11 Hz, 6 H), 4.25 (q, J = 7 Hz, 2 H), 5.8 (d of q, $^2J_{H-^{31}P}$ = 15, $^4J_{H-H}$ = 1.8 Hz, 1 H).

Anal. Calcd for $C_8H_{15}O_5P$: C, 43.25; H, 6.80. Found: C, 43.21; H, 6.77.

A mixture of **(*E*)- and (*Z*)-ethyl (α-methyl-β-diethoxyphosphinyl)acrylates** (*E*- and *Z*-**5**) was prepared in an analogous fashion using **3** instead of **2**. Short-path distillation at 100–110 °C (0.03 Torr) gave 16.2 g (88% yield) of an analytically pure sample of *E*- and *Z*-**5** in a 50:50 ratio. ***E*-5:** NMR ($CDCl_3$) δ 1.33 (t, J = 7 Hz, 3 H), 1.35 (t, J = 7 Hz, 6 H), 2.25 (d of d, $^4J_{H-H}$ = 1.0, $^4J_{H-^{31}P}$ = 3.6 Hz, 3 H), 4.15 (m, J = 7 Hz, 6 H), 6.58 (d of q, $^2J_{H-^{31}P}$ = 15.8, $^4J_{H-H}$ = 1.0 Hz, 1 H). ***Z*-5:** NMR ($CDCl_3$) δ 1.33 (t, J = 7 Hz, 3 H), 1.35 (t, J = 7 Hz, 6 H), 2.11 (apparent t, $^4J_{H-H}$ = 1.4, $^4J_{H-^{31}P}$ = 1.4 Hz, 3 H), 4.15 (m, J = 7 Hz, 6 H), 5.78 (d of q, $^2J_{H-^{31}P}$ = 14.6, $^4J_{H-H}$ = 1.4 Hz, 1 H).

Anal. Calcd for $C_{10}H_{19}O_5P$: C, 48.00; H, 7.65. Found: C, 47.68; H, 7.73.

Rearrangement of *E*- and *Z*-4 to ethyl α-(dimethoxyphosphinylmethyl)acrylate (6) could be achieved either by (1) conducting the reaction described above to prepare *E*- and *Z*-**4** with a 20% molar excess of NaH and stirring for 6 h at room temperature or (2) adding a 5.0-g mixture of isolated *E*- and *Z*-**4** dropwise to a 5% molar equivalent of hexane-washed NaH in 100 ml of dry dimethoxyethane at 0 °C and stirring for 6 h at room temperature before workup. With the second method 2.05 g (41% yield) of product **6** was obtained, bp 90–95 °C (0.03 Torr) [lit.[1] bp 103–105 °C (1 Torr)], with an NMR spectrum ($CDCl_3$) identical with that reported previously.[1]

Rearrangement of *E*- and *Z*-5 to ethyl α-(diethoxyphosphinylmethyl)acrylate (7) could be demonstrated by NMR spectroscopy. A 5.0-g mixture of *E*- and *Z*-**5** in a 40:60 ratio was treated with NaH using the second method described above. The product mixture distilled at bp 100–110 °C (0.03 Torr) giving 2.8 g (58% recovery) of approximately 65% **7** and 35% of unrearranged *E*- and *Z*-**5**, as judged by integration of the allylic proton region of the NMR spectrum. Compound **7** had the following NMR ($CDCl_3$): δ 1.33 (t, J = 7 Hz, 3 H), 1.35 (t, J = 7 Hz, 6 H), 2.94 (d, $^2J_{H-^{31}P}$ = 22 Hz, 2 H), 4.15 (m, J = 7 Hz, 6 H), 5.81 (d, J = 5 Hz, 1 H), 6.21 (d, J = 4 Hz, 1 H).

Hydrolysis of 6 to form α-(dihydroxyphosphinylmethyl)acrylic acid (1) was achieved as follows. A mixture (5.0 g, 22.5 mmol) of **6**, *E*-**4**, and *Z*-**4** in a 60:20:20 ratio was heated at reflux for 1.5 h in 48% HBr according to the procedure of Stubbe and Kenyon.[1] Product **1** (1.21 g, 54% yield based on **6**) was isolated using fractional crystallization from water as white flakes, mp 168–170 °C (lit.[1] mp 118–120 °C). Samples would occasionally melt at 118–120 °C on recrystallization, suggesting that either polymorphism exists or that thermal dehydration to a cyclic anhydride is possibly occurring.[25] The NMR spectrum (D_2O) was identical with that previously reported for **1**.[1]

Stereoselective rearrangement of *Z*-5 to ethyl α-(diethoxyphosphinylmethyl)acrylate (7) was determined as follows. A mixture of *E*- and *Z*-**5** in the ratio 40:60 (1.0 g) was added dropwise to 40 ml of 0.1 M sodium ethoxide in ethanol, and the solution was heated at reflux for 0.5 h under N_2. The reaction mixture was then cooled to 0 °C, 225 ml of saturated aqueous KH_2PO_4 was added, and the solution was extracted with four 100-ml portions of CH_2Cl_2. After drying the solution over $MgSO_4$, the solvent was removed in vacuo. The NMR spectrum ($CDCl_3$) of the resulting yellow oil (0.76 g, 76% recovery) showed the presence of only *E*-**5** and **7** in a ratio of 40:60.

Hydrolysis of *Z*-5 to generate (*Z*)-(α-methyl-β-dihydroxyphosphinyl)acrylic acids (8) was carried out as follows. A mixture (5.0 g, 22.5 mmol) of *E*- and *Z*-**5** in the ratio of 40:60 was dissolved in 5 ml of H_2O and stirred at 0 °C while 2.0 g of 40% aqueous NaOH was added. The resulting mixture was stirred at room temperature for 48 h and then acidified with 12 N HCl to pH 2 and allowed to stir for an additional 3 h before extracting with five 25-ml portions of CH_2Cl_2.

The aqueous layer was observed to form a white, crystalline precipitate which was isolated by filtration. After recrystallization from water, 1.89 g of the hemihydrate of product *Z*-8 (94% yield based on *Z*-5) was obtained as hygroscopic, colorless needles: mp 179–181 °C; IR (Nujol) 6.06, 7.6, 8.05, 8.53, 9.00, 9.86, 11.11 μ; NMR (D_2O) δ 2.02 (apparent t, $^4J_{H-H}$ = 1.4, $^4J_{H-^{31}P}$ = 1.4 Hz, 3 H), 6.11 (d of q, $^4J_{H-H}$ = 1.4, $^2J_{H-^{31}P}$ = 10.2 Hz, 1 H).

Anal. Calcd for $C_4H_7O_5P{\cdot}0.5H_2O$: C, 27.44; H, 4.61. Found: C, 27.3; H, 4.93.

Hydrolysis of *E*-5 to generate (*E*)-(α-methyl-β-dihydroxyphosphinyl)acrylic acid (*E*-8) began with crude (*E*)-(α-methyl-β-diethoxyphosphinyl)acrylic acid (*E*-9, 1.65 g) which was obtained upon evaporating the CH_2Cl_2 layer from the preceding reaction. This ethyl ester *E*-9 was heated at reflux for 36 h in 25 ml of 6 N HCl. Product *E*-8 (1.06 g, 71% yield based on the crude *E*-9) was isolated by recrystallization from water as hygroscopic, colorless plates: mp 153–158 °C; IR (Nujol) 5.91, 7.88, 8.47, 9.71, 10.82 μ; NMR (D_2O) δ 2.13 (d of d, $^4J_{H-^{31}P}$ = 3.6, $^4J_{H-H}$ = 1.4 Hz, 3 H), 6.57 (d of q, $^4J_{H-H}$ = 1.4, $^2J_{H-^{31}P}$ = 16.4 Hz, 1 H).

Anal. Calcd for $C_4H_7O_5P{\cdot}0.25H_2O$: C, 28.17; H, 4.43. Found: C, 28.21; H, 4.20.

Dimethyl α,β-bis(dimethoxyphosphinyl)succinate (10) was prepared by the method of Kirillova and Kukhtin,[15] bp 150–160 °C (0.03 Torr) [lit.[15] bp 208–210 °C (4 mm)].

Synthesis of 1 from 10 using a modified Wittig reaction with formaldehyde was achieved as follows. Compound **10** (30.0 g, 82.9 mmol), previously dried overnight over P_4O_{10}, was dissolved in 500 ml of dry tetrahydrofuran. Lithium hydride (1.0 g, 125 mmol) was added with stirring under N_2. The reaction mixture was then heated at reflux for 15 min. After cooling, 2.5 g (83.3 mmol) of paraformaldehyde (Eastman, previously dried in vacuo overnight) dissolved in 200 ml of tetrahydrofuran was added rapidly at room temperature. After 2 h of additional stirring, the reaction mixture was filtered, and the solvent was removed from the filtrate in vacuo at 25 °C. Short-path distillation at 65–85 °C (0.05 Torr) gave 8.45 g of a mixture of what appeared from examination of the NMR spectrum to be a 20:80 mixture of dimethyl (α-methylidene-β-dimethoxyphosphinyl)succinate (11) and dimethyl α,β-bis(methylidene)succinate[26] (12). This mixture could be partially resolved by further vacuum distillation, which yielded two fractions, bp 45–55 °C (0.1 Torr) and 100–110 °C (0.1 Torr). Judging from its NMR spectrum, the lower boiling fraction was mostly the dimethyl α,β-bis(methylidene)succinate [lit.[26] bp 52–65 °C (1 Torr)]. The higher boiling fraction, presumably mostly 11 (2.05 g, 9.3% yield), was then heated at reflux for 1.5 h in 20 ml of 48% HBr. After several recrystallizations from water, 0.46 g (36% yield based upon impure **11**) of **1** was obtained as white flakes, mp 168–170 °C. The NMR spectrum was identical with that previously reported.[1]

Preparation of Ethyl (Diethoxyphosphinyl)acetate (13) 90% ^{13}C Enriched in the Carbonyl Position. Ethyl bromoacetate (90% ^{13}C enriched in the carbonyl position, 5.0 g, 29.8 mmol, Koch Isotopes, Inc.) was heated at reflux for 3 h with 15 g (90.4 mmol) of freshly distilled triethyl phosphite (Aldrich). The ^{13}C-enriched product, ethyl (diethoxyphosphinyl)acetate (**13**, 6.45 g, 96% yield), was short-path distilled: bp 105–110 °C (1 Torr) [lit.[27] bp 142–145 °C (9 Torr)]; NMR ($CDCl_3$) δ 1.3 (t, J = 7 Hz, 3 H), 1.36 (t, J = 7 Hz, 6 H), 2.98 (d of d, $^2J_{H-^{13}C}$ = 7.5, $^2J_{H-^{31}P}$ = 21.7 Hz, 2 H), 4.2 (m, J = 7 Hz, 6 H).

Preparation of Dimethyl β-Methoxycarbonylethylphosphonate (14) 90% ^{13}C Enriched in the Carbonyl Position. A modified version of the procedure of Pudovik and Kitaev[16] was employed. Sodium hydride (1.44 g, 33.6 mmol, 56% suspension in mineral oil) was washed with hexane and placed in a 500-ml four-neck flask equipped with a mechanical stirrer, thermometer, 125-ml pressure-equalized addition funnel, and an N_2 bubbler. Dimethoxyethane (100 ml, freshly distilled from NaH) was added and the mixture was cooled to 0 °C. The ^{13}C-enriched **13** (6.45 g, 28.9 mmol) in 50 ml of the dry dimethoxyethane was added dropwise and allowed to stir for 1 h at 0 °C. The mixture was then cooled to −20 °C, 15 g (500 mmol) of paraformaldehyde (dried in vacuo overnight) was added rapidly, and the solution was allowed to stir at 0 °C. The reaction mixture, while still cold, was then filtered under an N_2 purge through a fine-fritted sintered glass filter into a 300-ml three-neck flask. The residue was washed with 25 ml of dry dimethoxyethane, and this solution was also added to the filtrate. Dimethyl phosphite (12 g, 109 mmol, Aldrich, freshly distilled from CaH_2) was added followed by the dropwise addition of 15 ml of 1 M sodium methoxide over 1 h at room temperature. After being stirred for an additional 1 h, the reaction mixture was cooled to 0 °C, 25 ml of saturated, aqueous KH_2PO_4 was added, and the solution was extracted with five 100-ml portions of CH_2CL_2/ After the extract was dried over Na_2SO_4, the solvent was removed in vacuo. The crude product was distilled, bp 95–103 °C (1 Torr) [lit.[16] bp 137–138 °C (10 Torr)], yielding 3.47 g of ^{13}C-enriched **14** (61% yield).

Preparation of Methyl α-(Dimethoxyphosphinylmethyl)-acrylate (15) 90% ^{13}C Enriched in the Carbonyl Position. Product **14** (3.44 g, 17.5 mmol) was dissolved in 60 ml of dry tetrahydrofuran and stirred under N_2 while potassium hydride (4.18 g of 25% suspension in mineral oil, 26.7 mmol) was added at room temperature. The mixture was allowed to stir at room temperature for 3 h. Paraformaldehyde (5.0 g, 16.7 mmol) was added to the mixture rapidly, and the slurry was stirred vigorously for 6 h. Excess paraformaldehyde was removed by filtration, and the solvent was removed in vacuo leaving a yellow oil which soon separated into two layers. The upper layer of mineral oil was removed by decantation leaving 1.43 g of product as a yellow oil. The NMR spectrum ($CDCl_3$) showed the presence of at least two products, compound **15** comprising better than 75% of the mixture. It was used in the next step of the synthesis without further purification. NMR ($CDCl_3$) δ 2.98 (d of d, $^2J_{H-^{31}P}$ = 22, $^3J_{H-^{13}C}$ = 4.6 Hz, 2 H), 5.95 (d of d, $^4J_{H-^{31}P}$ = 5.5 Hz, $^3J_{H-^{13}C}$ = 13.5 Hz, 1 H), 6.35 (apparent t, $^4J_{H-^{31}P}$ = 5.5, $^3J_{H-^{13}C}$ = 7.0 Hz, 1 H).

Preparation of Dilithium α-(Dihydroxyphosphinylmethyl)-acrylate (Dilithium Salt of 1) 90% ^{13}C Enriched in the Carbonyl Position. Impure ^{13}C-enriched **15** (1.43 g, 5.1 mmol) was heated at reflux for 1.5 h in 48% HBr (freshly distilled from $SnCl_2$). After removal of the solvent, an oil remained which was dissolved in 5 ml of H_2O. Barium acetate was then added until the pH was 4.3. Then 25 ml of absolute ethanol was added to yield 1.85 g of precipitated crude barium salt of **1**. This salt was suspended in water and subjected to ion exchange using a Dowex 50-W-X cation resin in the lithium form. The water was removed in vacuo leaving 0.95 g of crude dilithium salt of **1**. Recrystallization from aqueous ethanol gave 0.65 g of dilithium salt of ^{13}C-enriched **1**, the properties of which corresponded to those of the dilithium salt of **1** prepared from authentic, unlabeled **1**: NMR (D_2O) δ 3.19 (d of d, $^3J_{H-^{13}C}$ = 4, $^2J_{H-^{31}P}$ = 20.5 Hz, 2 H), 6.40 (d of d, $^3J_{H-^{13}C}$ = 11.5, $^4J_{H-^{31}P}$ = = 4.7 Hz, 1 H), 6.65 (apparent t, $^3J_{H-^{13}C}$ = 6.7, $^4J_{H-^{31}P}$ = 4.3 Hz, 1 H). The vinyl proton region of this spectrum is shown in Figure 1B.

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Registry No.—**1**, 4538-02-7; **1** dilithium salt, 61203-65-4; **1** ^{13}C derivative dilithium salt, 61203-61-0; **2**, 16001-93-7; **3**, 1660-94-2; *E*-**4**, 61203-62-1; *Z*-**4**, 61203-63-2; *E*-**5**, 34220-75-2; *Z*-**5**, 34220-74-1; **7**, 61203-64-3; *E*-**8**, 34220-77-4; *Z*-**8**, 34220-76-3; *E*-**9**, 61203-66-5; **10**, 2901-37-3; **11**, 61203-68-7; **12**, 38818-30-3; **13**, 61203-67-6; **14**, 61203-69-8; **15**, 61203-70-1; ethyl pyruvate, 617-35-6; ^{13}C-enriched ethyl bromoacetate, 61203-71-2; triethyl phosphite, 122-52-1.

References and Notes

(1) Part 2: J. A. Stubbe and G. L. Kenyon, *Biochemistry*, **11**, 338 (1972).
(2) National Institutes of Health Predoctoral Trainee, 1973–1976.
(3) Recipient of a Career Development Award, AM 00014, from the National Institute of Arthritis, Metabolism and Digestive Diseases.
(4) A. L. Lehninger, "Bioenergetics", 2d ed, W. A. Benjamin, Menlo Park, Calif., 1971, pp 67–68.
(5) T. Nowak, A. S. Mildvan, and G. L. Kenyon, *Biochemistry*, **12**, 1690 (1973).
(6) T. L. James and M. Cohn, *J. Biol. Chem.*, **249**, 3519 (1974).
(7) W. D. Emmons and W. S. Wadsworth, *J. Am. Chem. Soc.*, **83**, 1733 (1961).
(8) J. Boutagy and R. Thomas, *Chem. Rev.*, **74**, 87 (1974).
(9) R. K. Huff, C. E. Moppett, and J. K. Sutherland, *J. Chem. Soc.*, 2726 (1968).
(10) A. R. Fersht and A. J. Kirby, *Prog. Bioorg. Chem.*, **1**, 2 (1971).
(11) R. Kluger and P. D. Adawadkar, *J. Am. Chem. Soc.*, **98**, 3741 (1976).
(12) M. Gordon, V. A. Notaro, and C. E. Griffin, *J. Am. Chem. Soc.*, **86**, 1898 (1964).
(13) G. M. Blackburn and M. J. Brown, *J. Am. Chem. Soc.*, **91**, 525 (1969).
(14) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, Oxford, 1969.
(15) L. M. Kirillova and V. A. Kukhtin, *Zh. Obshch. Khim.*, **35**, 1146 (1965).
(16) N. Pudovik and Y. P. Kitaev, *Zh. Obshch. Khim.*, **22**, 473 (1952).
(17) D. J. Martin, M. Gordon, and C. E. Griffin, *Tetrahedron*, **23**, 1831 (1967).
(18) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, N.Y., 1969.
(19) M. Karplus, *J. Chem. Phys.*, **33**, 1842 (1960).
(20) J. A. Stubbe and G. L. Kenyon, *Biochemistry*, **10**, 2669 (1971).
(21) M. Cohn, J. E. Pearson, E. L. O'Connell, and I. A. Rose, *J. Am. Chem. Soc.*, **92**, 4095 (1970).

(22) A. Y. Garner, E. C. Chapin, and P. M. Scanlon, *J. Org. Chem.*, **24**, 532 (1959).
(23) C. H. Roy, U.S. Patent 3 251 907 (1966); *Chem. Abstr.*, **65**, 3908*d* (1966).
(24) D. A. Nicholson, W. A. Cilley, and O. T. Quimby, *J. Org. Chem.*, **35**, 3149 (1970).
(25) G. M. Blackburn and M. J. Brown, *J. Am. Chem. Soc.*, **91**, 525 (1969).
(26) W. J. Bailey, R. L. Hudson, and E. T. Yates, *J. Org. Chem.*, **28**, 828 (1963).
(27) E. Blumenthal and J. M. Herbert, *Trans. Faraday Soc.*, **41**, 611 (1945).

Acetylenic Analogues of the Cyanine Dyes. 2.[1] Synthesis of Isomeric Acetylenic Dyes

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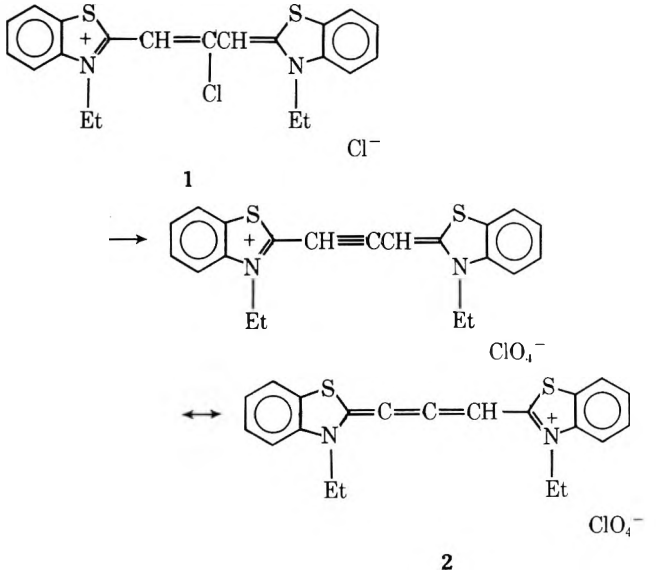
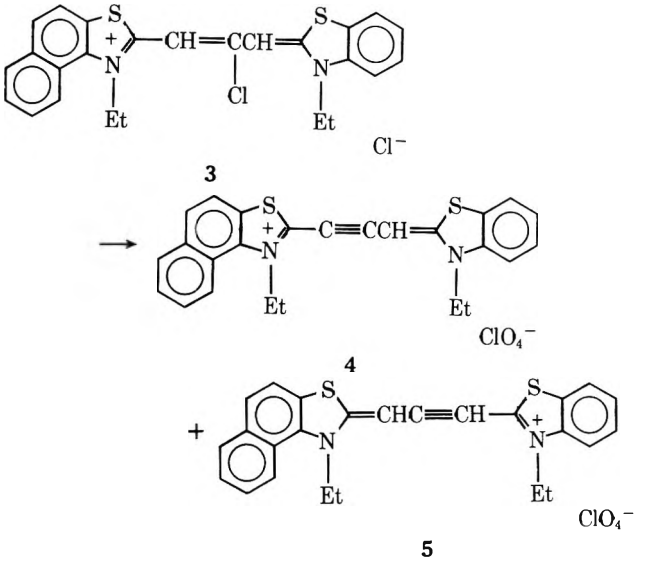
A new synthesis of acetylenic analogues of cyanine dyes is described, and the mechanism of the reaction is discussed in terms of ynenamines as reactive intermediates. This approach makes possible the separate synthesis of isomeric acetylenic dyes such as **4** and **5**.

The first examples of acetylenic cyanine analogues were described recently.[1] These compounds, which possess a formal triple bond in the conjugated system, were obtained through a reaction sequence in which the final step was the dehydrochlorination of a *meso*-chloro carbocyanine, as in the formation of **2** from **1**. This route leads to dyes of unambiguous structure only when the terminal heterocyclic nuclei are identical. In cases where this condition is not met, for example in **3**, elimination of hydrogen chloride can occur in two alternative modes to give the two isomeric dyes **4** and **5**.



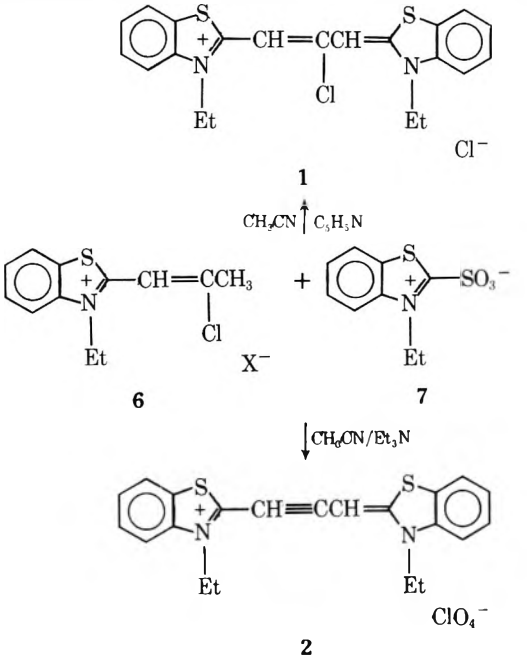
1 → **2**



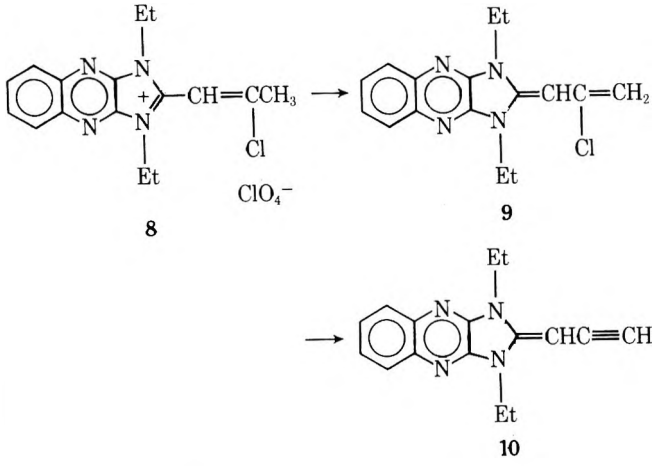
3 → **4** + **5**

We report here a new and more versatile approach, whereby dyes such as **4** and **5** may be obtained separately. One method[2] for the preparation of meso-substituted carbocyanines involves the reaction, under basic conditions, of a heterocyclic quaternary salt containing a 2-substituted propenyl group with a second quaternary salt having a suitable leaving group. Thus, reaction of the 2-chloropropenyl salt **6**[3] with the betaine **7**[4] in acetonitrile, using pyridine as condensing agent, gave the *meso*-chloro carbocyanine **1**. When triethylamine was used in place of pyridine, however, the product was the acetylenic dye **2**.[1,6]

Since **1** is not dehydrochlorinated under the conditions used to prepare **2**, it cannot be an intermediate in the formation of **2**. The reaction of 2-chloropropenyl salts with triethylamine in the absence of a second reactive quaternary salt proved to be highly illuminating. Although the reaction of **6** did not yield

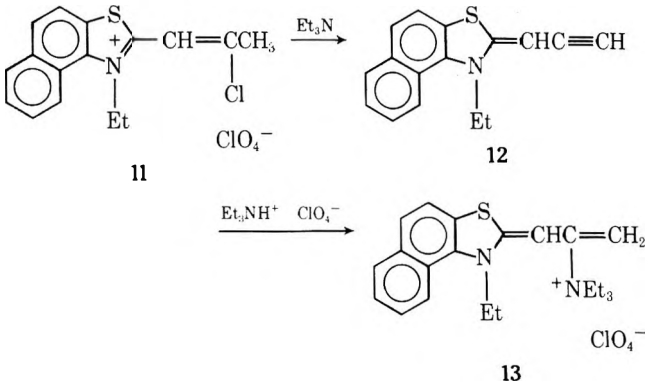


any readily isolated products, treatment of an acetonitrile solution of the corresponding derivative of imidazo[4,5-*b*]-quinoxaline, **8**, resulted in the rapid separation of the ynenamine[7] **10**, presumably via the dienamine **9**. When the



8 **9** **10**

naphtho[1,2-*d*]thiazolium salt **11**[3] was allowed to react with triethylamine under the same conditions, the initially generated ynenamine **12** underwent a subsequent addition of triethylamine hydroperchlorate across the triple bond to yield the ammonium salt **13**. Replacement of triethylamine by the

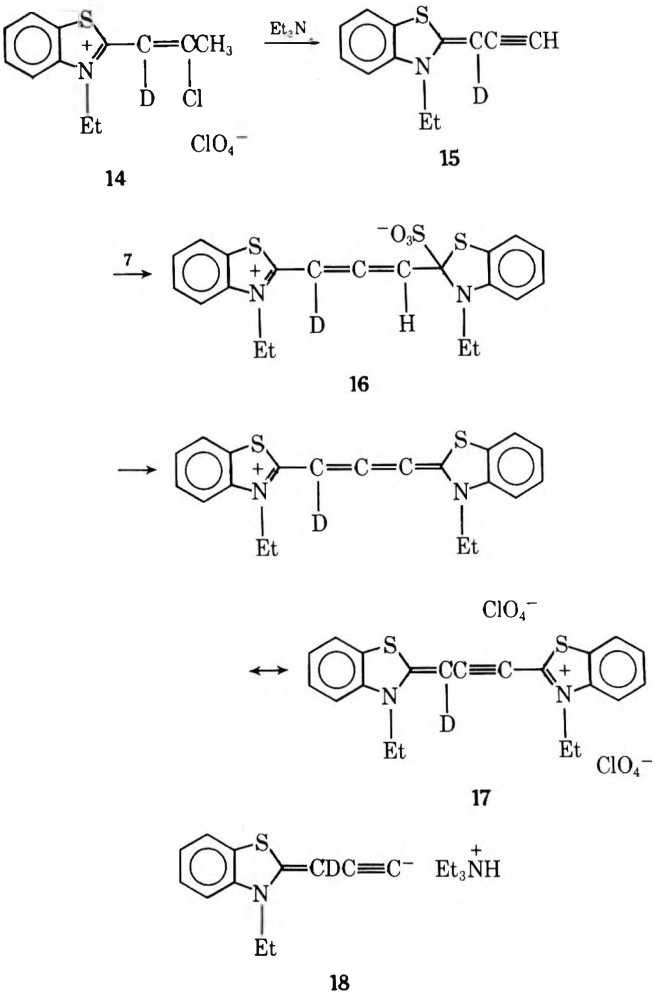


11 **12** **13**

more sterically hindered diisopropylethylamine, together with sodium hydride, resulted in termination of reaction at the ynenamine stage and **12** was isolated.

We believe that ynenamines such as **10** and **12** are the key intermediates in this synthesis of acetylenic dyes, for they readily react with **7** to give the same acetylenic dyes as are obtained from their parent 2-chloropropenyl salts, **8** and **11**.

Further insight into the mechanism of the dye-forming reaction was gained by replacement of **6** by its deuterium substituted analogue **14**. The reaction gave a dye in which deuterium was retained, consistent with a reaction sequence in which the deuterated ynenamine **15** adds to **7** to give an intermediate **16**. Since the loss of bisulfite from **16** to give **17** proceeds with retention of deuterium, this elimination must occur in a 1,2 rather than a 1,4 manner. Although a route involving the intermediacy of an acetylide ion **18** could also lead to retention of deuterium in the acetylenic dye, the addition–elimination sequence seems likely, since under comparable conditions the rate of exchange of the acetylenic hydrogen atom in **12** with D_2O proceeded much more slowly than the formation of **5** from **11**. It is interesting to note that reaction of **13** with **7** yields only **5**, though more slowly than in the reaction of **7** with either **11** or **12**, suggesting that in solution **13** may be in equilibrium with **12**. The slower reaction of **13** also confirms that **13** is formed from **12** and not vice versa.



14 **15** **16** **17** **18**

Regardless of the precise details of the mechanism by which the acetylenic dyes are formed, the retention of deuterium in **17** has important implications for the synthesis of acetylenic dyes in which the two heterocyclic nuclei are different, for it may be anticipated that the single hydrogen substituent on the conjugated chain of the dye will be adjacent to that nucleus that originally formed part of the 2-chloropropenyl salt. Accordingly, **4** and **5** were obtained from **6** and **11**, respectively. The isomeric pairs of dyes **19–30** (see Table I) were similarly obtained from the appropriate 2-chloropropenyl salts. Details of the preparations of the additional intermediates **31–38**, required for the synthesis of these dyes, are given in the Experimental Section.

Experimental Section

^{1}H NMR spectra were recorded using a Bruker HX-90 or Varian T-60 spectrophotometer. The spectra of the acetylenic dyes were obtained in Me_2SO-d_6 containing 3% pyridine-d_5 to inhibit isomerization.[8] Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer Model 257 spectrophotometer. Electronic spectra of solutions of the dyes in the concentration range of $1–2 \times 10^{-5}$ M were recorded using a Perkin-Elmer Model 450 spectrophotometer. At these concentrations, Beer's law was obeyed. No detectable isomerization occurred during the recording of NMR, IR, or electronic spectra of the dyes, with one exception noted in Table I.

All the acetylenic dyes decomposed on heating without displaying any distinct melting point. All were isomerically pure, within the limits of detection, as judged by comparisons of electronic, NMR, and IR spectra. With the exception of dye **2**, the acetylenic dyes were not recrystallized, since in some cases this leads to partial isomerization.[8] Unless otherwise noted, the dyes were dried at 60 °C.

9-Chloro-3,3′-diethylthiacarbocyanine Chloride (1). To a mixture of the chloride salt of **6**[3] (1.37 g, 0.005 mol) and **7**[9] (1.22 g, 0.005 mol) in hot acetonitrile (50 ml) was added pyridine (2.5 ml). The

mixture was heated at reflux for 30 min, with constant stirring. The crystalline dye **1**, which separated during the reaction, was collected by filtration of the hot reaction mixture and washed with acetonitrile: yield 1.06 g (47%); mp 246–248 °C dec; λ_{max}(CH_3CN) 549 nm (ϵ 18.3 × 10^4). Anal. Calcd for $C_{21}H_{20}Cl_2N_2S_2 \cdot \frac{1}{2}H_2O$: C, 56.9; H, 4.8; Cl, 15.9; N, 6.3. Found: C, 56.7; H, 5.0; Cl, 15.9; N, 6.1.

11-Chloro-1,3'-diethylnaphtho[1,2-*d*]thiazolothiacarbocyanine Chloride (3). This dye was obtained from **7**[9] and the chloride salt of **11**[3] by the method described for the preparation of dye **1**: yield 22%; mp 214–216 °C dec; λ_{max} (CH_3CN) 567 nm (ϵ 18.0 × 10^4). Anal. Calcd for $C_{25}H_{22}Cl_2N_2S_2 \cdot 1.5H_2O$: C, 58.4; H, 4.9; N, 5.5. Found: C, 58.4; H, 4.8; N, 5.6.

Dehydrochlorination of Dye 3. A mixture of **3** (0.49 g, 0.001 mol), 50% aqueous acetonitrile (5 ml), and triethylamine (0.15 g, 0.0015 mol) was heated at reflux for 1 min. To the resulting solution was added sodium perchlorate (0.2 g) dissolved in a little water and the solution slowly diluted to 15 ml with water. The dye was collected and washed successively with water, methanol, and ether, yield 0.50 g (98%). The visible, NMR, and IR spectra of the product corresponded to a mixture of dyes **4** and **5** in a ratio of approximately 2:1.

3-Ethyl-2-[(3-ethyl-2-benzothiazolinylidene)-1-propynyl]-benzothiazolium Perchlorate (2) (Method A). A mixture of the perchlorate salt of **6**[3] (1.70 g, 0.005 mol) and **7**[9] (1.22 g, 0.005 mol) in acetonitrile (25 ml) was cooled at 0–5 °C and stirred as triethylamine (1.50 g, 0.015 mol) was added in one portion. After 1 min, the reaction mixture was filtered and the filtrate diluted with ether (175 ml). Decantation of the ethereal layer followed by trituration of the viscous residue with methanol (25 ml) yielded 0.85 g (37%) of crystalline dye, which was recrystallized from ethanol. The dye was identical with that reported previously:[1] NMR δ 1.3 (t, 3), 1.6 (t, 3), 4.3 (q, 2), 4.6 (q, 2), 5.8 (s, 1), 7.1–8.5 (m, 8).

3-Ethyl-2-[(3-ethyl-2-benzothiazolinylidene)-1-propynyl-*d*]benzothiazolium Perchlorate (17). This dye was prepared from **7**[9] and **14** by method A. The crude dye had λ_{max} (CH_3CN) 513 nm (ϵ 9.9 × 10^4). The proportion of undeuterated dye was estimated as <7% by comparison of the NMR spectra of dyes **17** and **2** (singlet at δ 5.8). Attempted recrystallization of the dye from ethanol resulted in replacement of most of the deuterium by hydrogen.

2-[(5,6-Dichloro-1,3-diethyl-2-benzimidazolinylidene)-1-propynyl]-1,3-diethylimidazo[4,5-*b*]quinoxalinium Perchlorate (20) (Method B). **35** (2.30 g, 0.0055 mol), **38** (1.85 g, 0.005 mol), and acetic anhydride (0.60 g, 0.006 mol) in acetonitrile (25 ml) were stirred at 0–5 °C as triethylamine (2.5 g, 0.025 mol) was added. The initially clear solution was stirred at 0–5 °C for 15 min as dye separated. The dye was collected, washed with acetonitrile, and dried at room temperature in vacuo, yield 0.54 g (18%).

1-Ethyl-2-[(3-ethyl-2-benzothiazolinylidene)-1-propynyl]-naphtho[1,2-*d*]thiazolium perchlorate (4) was prepared from the perchlorate salt of **6**[3] and *anhydro*-1-ethyl-2-sulfonaphtho[1,2-*d*]thiazolium hydroxide[9] by method A. The dye was isolated by dilution of the reaction mixture with methanol (4 volumes): yield 20%; NMR δ 1.3 (t, 3), 1.8 (t, 3), 4.1 (q, 2), 5.1 (q, 2), 5.7 (s, 1), 7.0–8.6 (m, 10).

3-Ethyl-2-[(1-ethylnaphtho[1,2-*d*]thiazolin-2-ylidene)-1-propynyl]benzothiazolium Perchlorate (5). A. The dye was prepared from **7**[9] and **11**[3] by the procedure described for the synthesis of dye **4**: yield 46%; NMR δ 1.6 (m, 6), 4.6 (m, 4), 5.9 (s, 1), 7.3–8.7 (m, 10).

B. The above procedure was repeated using an equimolar amount of **12** in place of **11**. On addition of aqueous sodium perchlorate solution, **5** separated, yield 50%.

C. **7** (0.17 g, 0.0007 mol) and **13** (0.32 g, 0.0007 mol) were stirred with a mixture of triethylamine (0.07 g, 0.0007 mol) and acetonitrile (3 ml) at room temperature. Solution was rapidly attained and the rate of appearance of dye color was slower than in the above reactions. After 5 min, the solid dye which had separated was collected and washed with acetonitrile, yield 0.20 g (56%).

5,6-Dichloro-1,3-diethyl-2-[(1,3-diethylimidazo[4,5-*b*]quinoxalinylidene)-1-propynyl]benzimidazolium perchlorate (19) was prepared from **34** and **37** by method B: yield 20%; NMR δ 1.5 (m, 12), 4.4 (m, 8), 5.5 (s, 1), 7.5–8.6 (m, 6).

5,6-Dichloro-1,3-diethyl-2-[(3-ethyl-2-benzothiazolinylidene)-1-propynyl]benzimidazolium perchlorate (21) was prepared from the perchlorate salt of **6**[3] and **37** by method B: yield 20%; NMR δ 1.3 (t, 3), 1.5 (t, 6), 4.2 (q, 2), 4.5 (q, 4), 5.7 (s, 1), 7.1–8.0 (m, 4), 8.4 (s, 2).

2-[(5,6-Dichloro-1,3-diethyl-2-benzimidazolinylidene)-1-propynyl]-3-ethylbenzothiazolium iodide (22) was prepared from **7**[9] and **35** by method A, except that the reaction was allowed to proceed for 5 min at 25 °C. Tetraethylammonium iodide (0.64 g, 0.0025 mol) was added to the filtered reaction mixture. The solution was chilled briefly and the dye that separated was collected and washed with a little acetonitrile, then with ether: yield 40%; NMR δ 1.4 (m, 9), 4.5 (m, 6), 5.6 (s, 1), 7.3–8.7 (m, 6).

3-Ethyl-2-[(3-ethyl-2,3-dihydrothiazolo[4,5-*b*]quinolin-2-ylidene)-1-propynyl]benzothiazolium perchlorate (23) was prepared by the acid-catalyzed isomerization[8] of **24**. Thus, dye **24** (0.40 g) was dissolved in acetonitrile (100 ml) and acetic acid (2 ml) was added. After 3 h the solution was concentrated to 15 ml and chilled to yield 0.14 g (35%) of **23**: NMR δ 1.4 (t, 3), 1.7 (t, 3), 4.4 (q, 2), 4.8 (q, 2), 6.1 (s, 1), 7.3–8.8 (m, 9).

3-Ethyl-2-[(3-ethyl-2-benzothiazolinylidene)-1-propynyl]-thiazolo[4,5-*b*]quinolinium perchlorate (24) was prepared from 3-ethyl-2-methylthiothiazolo[4,5-*b*]quinolinium *p*-toluenesulfonate[10] and the perchlorate salt of **6** by method A: yield 27%; NMR δ 1.4 (t, 3), 1.7 (t, 3), 4.6 (m, 4), 6.2 (s, 1), 7.3–9.2 (m, 9).

1-Ethyl-2-[(3-ethyl-2-benzothiazolinylidene)-1-propynyl]-quinolinium perchlorate (25) was prepared from *anhydro*-1-ethyl-2-sulfoquinolinium hydroxide[9] and the perchlorate salt **6**[3] by method A; yield 23%; NMR δ 1.3 (t, 3), 1.6 (t, 3), 4.3 (q, 2), 4.9 (q, 2), 5.8 (s, 1), 7.2–8.7 (m, 10).

3-Ethyl-2-[(1-ethyl-2,3-dihydro-2-quinolinylidene)-1-propynyl]benzothiazolium perchlorate (26) was prepared from **7**[9] and **36** by method A: yield 46%; NMR δ 1.4 (m, 6), 4.5 (m, 4), 5.6 (s, 1), 7.2–8.7 (m, 10).

1-Ethyl-2-[(1,3-diethyl-2,3-dihydroimidazo[4,5-*b*]quinoxalin-2-ylidene)-1-propynyl]naphtho[1,2-*d*]thiazolium perchlorate (27) was prepared from **8** and *anhydro*-2-sulfo-1-ethylnaphtho[1,2-*d*]thiazolium hydroxide[9] by method A. The dye separated spontaneously from the reaction mixture: yield 39%; NMR δ 1.6 (m, 9), 4.5 (q, 4), 5.1 (q, 2), 5.7 (s, 1), 7.3–8.8 (m, 10).

1,3-Diethyl-2-[(1-ethylnaphtho[1,2-*d*]thiazolin-2-ylidene)-1-propynyl]imidazo[4,5-*b*]quinoxalinium perchlorate (28) was prepared from **11**[3] and **38** by method B: yield 44%; NMR δ 1.6 (m, 9), 4.5 (m, 6), 6.2 (s, 1), 7.2–8.6 (m, 10).

3-Ethyl-2-[(1,3-diethyl-2,3-dihydroimidazo[4,5-*b*]quinoxalin-2-ylidene)-1-propynyl]benzothiazolium Perchlorate (29). A. **29** was prepared from **7**[9] and **8** by method A. The dye separated spontaneously from the reaction mixture: yield 48%; NMR δ 1.5 (m, 9), 4.5 (m, 6), 5.7 (s, 1), 7.3–8.6 (m, 8).

B. The above procedure was repeated using an equimolar amount of **10** in place of **8**. On addition of aqueous sodium perchlorate solution, **29** separated, yield 57%.

1,3-Diethyl-2-[(3-ethyl-2-benzothiazolinylidene)-1-propynyl]imidazo[4,5-*b*]quinoxalinium perchlorate (30) was prepared from the perchlorate salt of **6**[3] and **38** by method B: yield 27%; NMR δ 1.4 (t, 3), 1.6 (t, 6), 4.5 (m, 6), 6.1 (s, 1), 7.3–8.6 (m, 8).

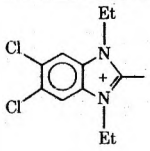
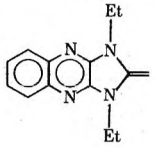
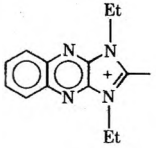
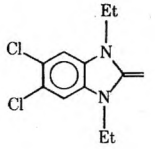
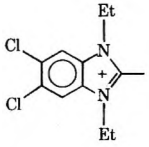
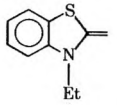
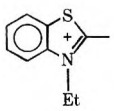
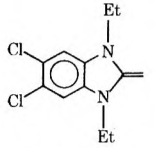
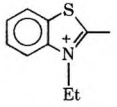
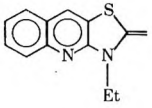
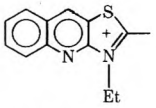
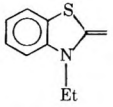
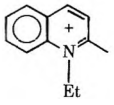
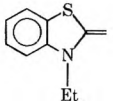
1,3-Diethyl-1,2-dihydro-2-(2-propynylidene)imidazo-[4,5-*b*]quinoxaline (10). Compound **8** (2.00 g, 0.005 mol) in acetonitrile (20 ml) was stirred as triethylamine (1.50 g, 0.015 mol) was added in one portion. After 1 min the solid that separated was collected and washed with a small volume of acetonitrile: yield 0.63 g (48%); mp (CH_3CN) ~135 °C dec; IR (KBr) 3260 (acetylenic H), 2081 cm^{-1} (C≡C); NMR (C_6D_6) δ 0.83 (t, 3), 1.32 (t, 3) 2.95 (d, 1), 3.36 (q, 2), 3.95 (d, 1), 4.36 (q, 2), 7.0–8.1 (m, 4). Anal. Calcd for $C_{16}H_{16}N_4$: C, 72.7; H, 6.1; N, 21.2. Found: C, 72.4; H, 6.2; N, 21.2.

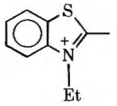
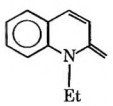
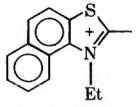
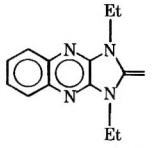
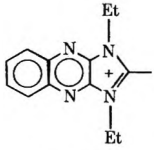
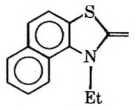
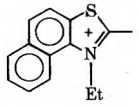
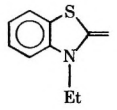
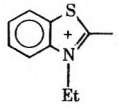
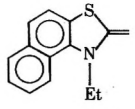
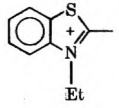
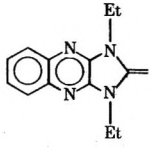
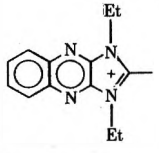
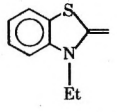
1-Ethyl-2-(2-propynylidene)naphtho[1,2-*d*]thiazoline (12). A mixture of **11**[3] (1.94 g, 0.005 mol), sodium hydride (0.6 g, 0.025 mol), and acetonitrile (25 ml) was stirred and cooled in an ice bath as diisopropylethylamine (2.5 g, 0.02 mol) was added dropwise. The mixture was filtered and solvent removed by evaporation at 30 °C, under reduced pressure. The residue was extracted with petroleum ether (bp 30–60 °C, 5 × 50 ml). The combined extracts were concentrated to 50 ml. Upon chilling, 0.28 g (22%) of **12** separated: mp (petroleum ether) ~100 °C dec; IR (KBr) 3281 (acetylenic H), 2035 cm^{-1} (C≡C); NMR (CD_3CN) δ 1.56 (t, 3), 3.61 (d, 1), 4.21 (q, 2), 4.78 (d, 1), 7.3–8.4 (m, 6). Anal. Calcd for $C_{16}H_{13}NS$: C, 76.5; H, 5.2; N, 5.6; S, 12.8. Found: C, 76.6; H, 5.4; N, 5.2; S, 12.6.

Deuteration of 12. Compound **12** (0.03 g) was dissolved in CD_3CN (0.5 ml). D_2O (0.09 g) and triethylamine (0.05 g) were added and the rate of exchange of the acetylenic hydrogen was monitored by NMR (disappearance of doublet at δ 3.68). The half-life for this process was estimated as 6 min.

Reaction of 11 with Triethylamine. A suspension of **11**[3] (0.78 g, 0.002 mol) in acetonitrile (8 ml) was stirred as triethylamine (0.60 g, 0.006 mol) was added in one portion. The solid dissolved at once. From the resulting blue-colored solution, solid soon began to separate. After 1 min, the solid was collected and washed with acetonitrile, then with ether to yield 0.26 g (30%) of **13** as a colorless solid with no distinct melting point: NMR (CF_3CO_2H) δ 1.60 (t, 9), 2.02 (t, 3), 3.89 (q, 6),

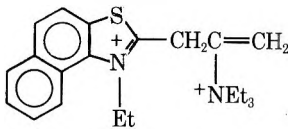
Table I. Visible Absorption Maxima of $R_1{}^+C{\equiv}CCH{=}R_2\ ClO_4{}^-$

Registry no.	Dye[a]	R_1	R_2	λ_{max} (CH_3CN), nm	$\epsilon_{max} \times 10^{-4}$	Empirical formula	Calcd	Found
61268-47-1	**19**			488	13.0	$C_{27}H_{27}Cl_3N_6O_4$	C, 53.5; H, 4.5; N, 13.9	C, 53.1; H, 4.8; N, 13.7
61268-49-3	**20**			532	>12.7[b]			C, 53.4; H, 4.6; N, 13.8
56387-15-6	**21**			468	9.2	$C_{23}H_{22}Cl_3N_3O_4S$	C, 50.9; H, 4.1; N, 7.7	C, 50.7; H, 4.1; N, 8.0
61268-50-6	**22**[c]			510	12.2	$C_{23}H_{22}Cl_2IN_3S$	C, 48.4; H, 3.9; N, 7.4	C, 48.5; H, 3.8; N, 7.2
61268-52-8	**23**			508	9.8	$C_{24}H_{20}ClN_3O_4S_2$	C, 56.1; H, 3.9; N, 8.2	C, 56.1; H, 3.9; N, 8.3
61268-54-0	**24**			546	12.3			C, 56.4; H, 4.1; N, 8.4
56387-17-8	**25**			543	7.1	$C_{23}H_{21}ClN_2O_4S$	C, 60.5; H, 4.6; N, 6.1	C, 60.8; H, 4.8; N, 6.4

56387-19-0	**26**			543	12.1			C, 60.6; H, 4.7; N, 6.3
61268-56-2	**27**			537	14.1	$C_{29}H_{26}ClN_5O_4S$	C, 60.5; H, 4.6; N, 12.2	C, 60.3; H, 4.4; N, 11.8
61268-58-4	**28**			556	11.6			C, 60.3; H, 4.6; N, 11.8
61268-60-8	**4**			526	8.4	$C_{25}H_{21}ClN_2O_4S_2$	C, 58.5; H, 4.1; N, 5.5	C, 58.8; H, 4.2; N, 5.3
61268-62-0	**5**			535	8.4			C, 58.5; H, 4.1; N, 5.4
61268-64-2	**29**			523	16.3	$C_{25}H_{24}ClN_5O_4S$	C, 57.1; H, 4.6; N, 13.3	C, 57.0; H, 4.9; N, 13.6
61268-66-4	**30**			531	12.6			C, 56.8; H, 4.6; N, 13.3

[a] Satisfactory analytical data (±0.4%) for C, H, and N were obtained for all compounds listed in this table. [b] Isomerizes too rapidly in solution for accurate determination. [c] Iodide salt.

4.91 (s, 2), 6.03 (d, 1, J = 7 Hz), 6.32 (d, 1, J = 7 Hz), 7.9–8.9 (m, 6), consistent with a protonated structure



Anal. Calcd for $C_{22}H_{29}ClN_2O_4S$: C, 58.3; H, 6.5; Cl, 7.8; N, 6.2; S, 7.1. Found: C, 58.1; H, 6.4; Cl, 8.2; N, 6.2; S, 7.3.

2-Acetonylidene-1,3-diethyl-2,3-dihydroimidazo[4,5-*b*]quinoxaline (31). A mixture of 1,3-diethyl-2-methylimidazo[4,5-*b*]quinoxalinium *p*-toluenesulfonate (20.6 g, 0.05 mol), acetic anhydride (5.6 g, 0.06 mol), and pyridine (75 ml) was heated at reflux for 15 min, cooled, and diluted to 500 ml with water. The solid was collected and washed with water. The yield of crude product was 11.9 g (84%): mp (CH_3CN) 213–214 °C; NMR ($CDCl_3$) δ 1.33 (t, 6), 2.23 (s, 3) 4.40 (q, 4), 5.10 (s, 1), 7.3–7.9 (m, 4). Anal. Calcd for $C_{16}H_{18}N_4O$: C, 68.1; H, 6.4; N, 19.9. Found: C, 67.9; H, 6.2; N, 19.8.

2-Acetonylidene-5,6-dichloro-1,3-diethylbenzimidazoline (32). A mixture of 5,6-dichloro-1,3-diethyl-2-methylbenzimidazolium iodide (38.5 g, 0.11 mol), acetic anhydride (12.0 g, 0.12 mol), 1,5-diazabicyclo[4.3.0]non-5-ene (24.8 g, 0.2 mol), and pyridine (100 ml) was heated at reflux for 15 min. After cooling, the mixture was added to 1 N NaOH (1 l.) at <10 °C. The precipitated solid was collected and washed with water. The yield of crude material was 17.5 g (58%): mp (benzene–petroleum ether) 155 °C dec; NMR ($CDCl_3$) δ 1.30 (t, 6), 2.11 (s, 3), 4.17 (q, 4), 4.72 (s, 1), 7.09 (s, 2). Anal. Calcd for $C_{14}H_{16}Cl_2N_2O$: C, 56.2; H, 5.4; N, 9.1. Found: C, 55.8; H, 5.7; N, 9.1.

2-Acetonylidene-3-ethylbenzothiazoline was prepared according to the published procedure:[11] NMR ($CDCl_3$) δ 1.33 (t, 3), 4.01 (q, 2), 5.84 (s, 1), 7.0–7.6 (m, (m, 4).

2-(Acetonylidene-*1-d*)-3-ethylbenzothiazoline (33). A solution of 2-acetonylidene-3-ethylbenzothiazoline[11] (6.6 g, 0.03 mol) in chloroform (10 ml) was shaken with deuterium oxide (5 ml) containing 1 drop of DCl (20% in D_2O) and the chloroform layer was separated. After three such treatments, the chloroform was evaporated to yield **33**, 5.6 g (8.5%). The proportion of undeuterated product was estimated as <7% by comparison of NMR spectra (singlet at δ 5.84) of this and the preceding compound.

2-(2-Chloropropenyl)-3-ethylbenzothiazolium perchlorate (6) was prepared according to the published procedure:[3] NMR (CD_3CN) δ 1.58 (t, 3), 2.74 (s, 3), 4.82 (q, 2), 7.56 (d, 1), 7.7–8.4 (m, 4).

2-(2-Chloropropenyl-*1-d*)-3-ethylbenzothiazolium Perchlorate (14). Compound **33** (1.00 g, 0.0045 mol) was added to phosphoryl chloride (5 ml) with stirring, to give a clear solution from which solid soon began to separate. After 10 min, 20 ml of benzene was added. The solid was collected, washed with benzene, and dissolved in methanol (10 ml). Addition of a solution of sodium perchlorate (1 g) in water (2 ml) gave a precipitate which was collected and washed with methanol, yield 1.10 g (72%). The proportion of undeuterated product was estimated as <7% by comparison of the NMR spectra (doublet at δ 7.56) of this and the preceding compound.

2-(2-Chloropropenyl)-1,3-diethylimidazo[4,5-*b*]quinoxalinium Perchlorate (34). Compound **31** (5.64 g, 0.02 mol) was added to phosphoryl chloride (25 ml). The mixture was stirred for 30 min, then cautiously decomposed with 600 g of an ice–water mixture. Sodium perchlorate (4.9 g, 0.04 mol) dissolved in a little water was added. The resulting precipitate was collected and washed with water, then dried at room temperature in vacuo: yield 7.13 g (88%); mp (MeOH) 196–167 °C dec. Anal. Calcd for $C_{16}H_{18}Cl_2N_4O_4$: C, 47.9; H, 4.5; Cl, 17.7; N, 14.0. Found: C, 47.5; H, 4.8; Cl, 18.0; N, 13.9.

The following two compounds were prepared similarly.

2-(2-Chloropropenyl)-5,6-dichloro-1,3-diethylbenzimidazolium perchlorate (35) was prepared from compound **32:** yield 81%; mp (MeOH) 214–216 °C dec. Anal. Calcd for $C_{14}H_{16}Cl_4N_2O_4$: C, 40.2; H, 3.8; Cl, 33.9; N, 6.7. Found: C, 39.9; H, 3.6; Cl, 34.1; N, 6.6.

2-(2-Chloropropenyl)-1-ethylquinolinium perchlorate (36) was prepared from 2-acetonylidene-1-ethyl-1*H*-quinolone:[12] yield 80%; mp (MeOH) 158–160 °C dec. Anal. Calcd for $C_{14}H_{15}Cl_2NO_4$: C, 50.6; H, 4.6; N, 4.2. Found: C, 50.4; H, 4.7; N, 4.1.

5,6-Dichloro-1,3-diethyl-2-hydroxyiminomethylbenzimidazolium Iodide (37). 5,6-Dichloro-1,3-diethyl-2-methylbenzimidazolium iodide (30.8 g, 0.08 mol) was added to a suspension of sodium hydride (0.1 mol) in acetonitrile (150 ml). The mixture was stirred until hydrogen evolution ceased, then heated to boiling and filtered. Upon cooling, 9.1 g (44%) of 5,6-dichloro-1,3-diethyl-2-methylenebenzimidazoline separated, mp (CH_3CN) 121–122 °C. This material (4.0 g, 0.016 mol) was dissolved in benzene (80 ml) and nitrosyl chloride bubbled into the solution until no more solid separated. The solid was collected and washed with benzene. For purification, the crude product was dissolved in 2 N NaOH (80 ml) containing sodium iodide (20 g). After filtration of insoluble material, the filtrates were acidified with concentrated HCl, whereupon **38** separated: yield 2.6 g (40%); mp (CH_3CN) 240 °C dec. Anal. Calcd for $C_{12}H_{14}Cl_2IN_3O$: C, 34.8; H, 3.4; N, 10.1. Found: C, 34.6; H, 3.5; N, 10.0.

1,3-Diethyl-2-hydroxyiminomethylimidazo[4,5-*b*]quinoxalinium Perchlorate (38). A solution of 1,3-diethyl-2-methylimidazo[4,5-*b*]quinoxalinium *p*-toluenesulfonate (100 g, 0.24 mol) in acetic acid (625 ml) was cooled at 15 °C as sodium nitrite (34.5 g, 0.50 mol) in water (200 ml) was added slowly. The solution was allowed to stand at room temperature for 2.5 h, then sodium perchlorate (46 g) in water (400 ml) added. After cooling to 15 °C, the solid was collected and washed with water, then with acetone: yield 67.7 g (75%); mp (MeOH–CH_3CN) 280–282 °C dec. Anal. Calcd for $C_{14}H_{16}ClN_5O_5$: C, 45.5; H, 4.4; N, 18.9. Found: C, 45.8; H, 4.4; N, 19.3.

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Registry No.—**1,** 34256-42-3; **2,** 52846-53-4; **3,** 61268-75-5; **6** Cl^-, 4126-03-3; **6** ClO_4^-, 56387-12-3; **7,** 50818-84-3; **8,** 61268-68-6; **10,** 61268-76-6; **11,** 61268-78-8; **11** Cl, 41426-06-6; **12,** 61268-79-9; **13,** 61268-81-3; **31,** 61268-82-4; **32,** 61268-83-5; **34,** 61268-68-6; **35,** 61268-85-7; **36,** 61268-87-9; **37,** 61268-88-0; **38,** 61268-90-4; *anhydro*-1-ethyl-2-sulfonaphtho[1,2-*d*]thiazolium hydroxide, 61268-91-5; 3-ethyl-2-methylthiothiazolo[4,5-*b*]quinolinium *p*-toluenesulfonate, 61268-93-7; *anhydro*-1-ethyl-2-sulfoquinolinium hydroxide, 4329-91-3; triethylamine, 121-44-8; 1,3-diethyl-2-methylimidazo[4,5-*b*]quinoxalinium *p*-toluenesulfonate, 41450-78-6; pyridine, 110-86-1; 5,6-dichloro-1,3-diethyl-2-methylbenzimidazolium iodide, 24351-12-0; 1,5-diazabicyclo[4.3.0]non-5-ene, 3001-72-7; 2-acetonylidene-3-ethylbenzothiazoline, 13861-37-5; 2-acetonylidene-1-ethyl-1*H*-quinolone, 4589-41-7; 5,6-dichloro-1,3-diethyl-2-methylenebenzimidazoline, 61268-94-8.

References and Notes

(1) J. D. Mee, *J. Am. Chem. Soc.*, **96**, 4712 (1974). This paper constitutes part 1 of the series.
(2) F. M. Hamer in "The Chemistry of Heterocyclic Compounds", Vol. 18, "The Cyanine Dyes and Related Compounds", A. Weissberger, Ed., Interscience, New York, N.Y., 1964, Chapter 6.
(3) N. N. Sveshikov, I. I. Levkoev, N. I. Shirokova, and N. A. Damir, *Dokl. Akad. Nauk SSSR*, **148**, 1091 (1963).
(4) Leaving groups other than SO_3^- may be employed. Alkylthio or –CH=NOR[5] groups are suitable, but –SPh is not, since addition of benzenethiol to the acetylenic dye occurs.[1]
(5) See ref 2, Chapter 2.
(6) Reaction of **6, 7,** and triethylamine was earlier studied under different conditions: I. I. Levkoev, N. N. Sveshnikov, and N. I. Shirokova, *Dokl. Acad. Nauk SSSR*, **153**, 350 (1963). In this case a mixture of dyes, not including **2,** was obtained.
(7) Only a few, acyclic, ynenamines have been reported previously: (a) A. A. Petrov and I. A. Maretina, *Zh. Obshch. Khim.*, **29**, 2458 (1959); (b) A. A. Petrov, I. A. Maretina, and N. A. Pogorzhel'skaya, *Zh. Org. Khim.*, **2**, 1757 (1966).
(8) J. D. Mee and D. M. Sturmer, *J. Org. Chem.*, following paper in this issue.
(9) Obtained by the general method of H. Larivé and R. Baralle, U.S. Patent 3 437 659 (1969).
(10) L. G. S. Brooker, U.S. Patent 2 255 407 (1941).
(11) L. G. S. Brooker and F. L. White, U.S. Patent 2 112 139 (1938).
(12) L. G. S. Brooker and F. L. White, U.S. Patent 2 341 357 (1944).

Acetylenic Analogues of the Cyanine Dyes. 3. Visible Absorption Properties and Relative Thermodynamic Stabilities of Isomeric Dyes

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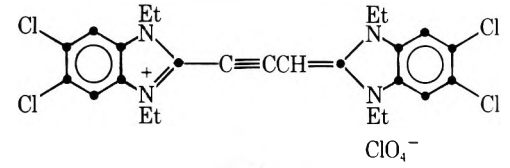
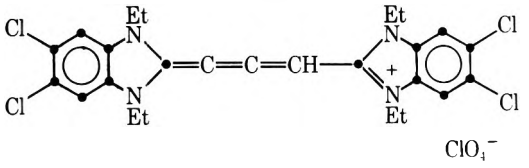
It has been found that acid-catalyzed interconversion of isomeric acetylenic dyes can occur. A discussion of the factors which influence the visible absorption properties and relative thermodynamic stabilities of pairs of isomeric dyes is presented.

Syntheses of acetylenic analogues of the cyanines have been described in earlier papers of this series.[1,2] In contrast to the cyanines, these compounds are intrinsically unsymmetrical. We report here a study of some of the effects of this asymmetry upon the visible absorption spectra and thermodynamic properties of the dyes.

Spectral Properties. Acetylenic dyes possessing two identical heterocyclic nuclei, for example **1**, have visible absorption maxima hypsochromically displaced from those of the corresponding carbocyanines by 30–40 nm. This was interpreted[1] as resulting from energetic nonequivalence of the extreme structures **1a** and **1b**.

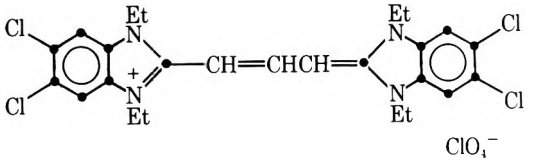


1a



1b

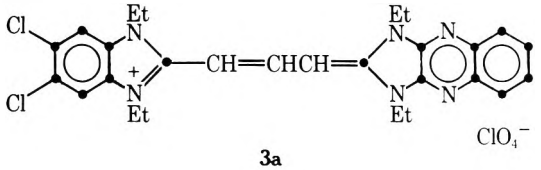
Further, comparison of the structures of **1** and its carbocyanine analogue **2** by x-ray crystallography[3] supports the



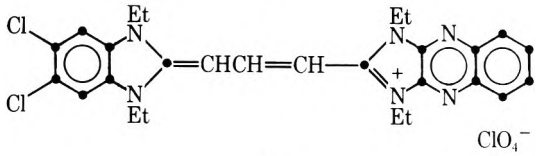
2

view that **1a** is of lower energy than **1b** and reflects the differences in geometry between these two dye classes. For convenience, extreme structures such as **1a** and **1b** are referred to as "acetylene" and "cumulene".

Acetylenic dyes containing nonidentical heterocyclic nuclei can exist in two isomeric forms, differentiated as in **19** and **20** by the position of the single hydrogen substituent on the chromophoric chain, relative to the heterocyclic nuclei. For each of the isomeric pairs shown in Table I, both dyes absorb at shorter wavelength than the unsymmetrical carbocyanine analogue (e.g., dye **3**). However, a more interesting feature of these dyes is the difference between absorption maxima of isomeric dyes. The structural factors which influence this difference may be explained as resulting from the interplay of two factors: the lower energy, other things being equal, of the acetylene rather than the cumulene extreme structure and the relative basicities of the two heterocyclic nuclei in question. Brooker[4] has established a scale of relative basicity, or ability to stabilize a positive charge, for a large number of heterocyclic nuclei. Thus in an unsymmetrical carbocyanine **3**, the extreme structure **3a**, in which the positive charge is located on the more basic benzimidazole nucleus, is of lower energy than **3b**.

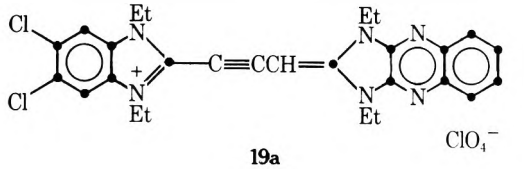


3a

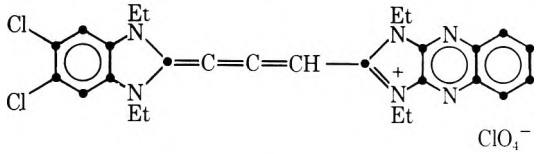


3b

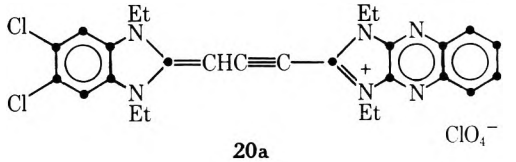
In the acetylenic analogue **19**, the tendency for the acetylenic extreme structure to be of lower energy is further reinforced by the location of the positive charge on the more basic benzimidazole nucleus. Conversely, in the isomeric dye **20**, the



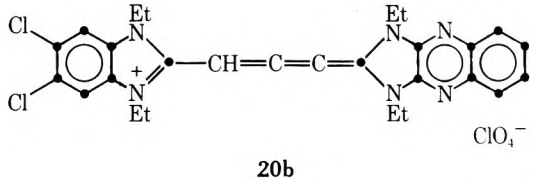
19a



19b



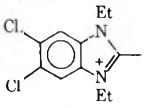
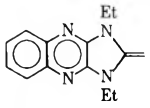
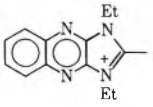
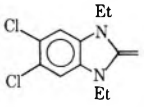
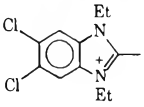
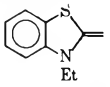
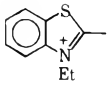
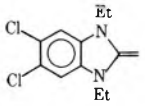
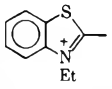
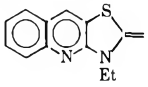
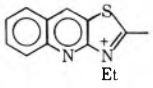
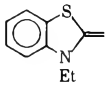
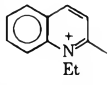
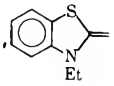
20a



20b

Table I. Isomeric Acetylenic Dyes

$\overset{+}{R}_1C{\equiv}CCH{=}R_2\ ClO_4^-$

Registry no.	Dye[a]	R_1	R_2	Rel basicity[b] R_1	Rel basicity[b] R_2	Δ basicity	λ_{max} (CH_3CN), nm	$\Delta\lambda_{max}$, nm	% of equilibrium mixture
61268-47-1	19			120	50		488		>99
						70		44	
61268-49-3	20			50	120		532		<1
56387-15-6	21			120	58		468		>98
						62		42	
61268-50-6	22[c]			58	120		510		<2
61268-52-8	23			58	24		508		>95
						34		38	
61268-54-0	24			24	58		546		<5
56387-17-8	25			80	58		543		>90
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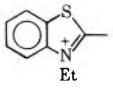
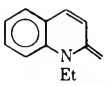
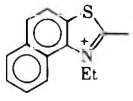
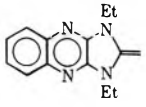
56387-19-0	26			58	80		543		<10
61268-56-2	27			70	50		537		75 ± 5
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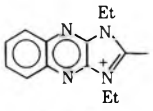
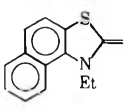
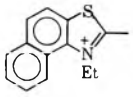
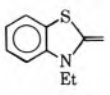
61268-58-4	28			50	70		556		25 ± 5
61268-60-8	4			70	58		526		75 ± 5
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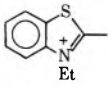
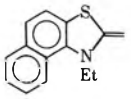
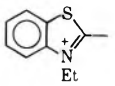
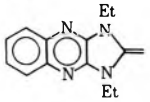
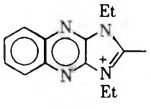
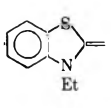
61268-62-0	5			58	70		535		25 ± 5
61268-64-2	29			58	50		523		23 ± 5
						8		8	
61268-66-4	30			50	58		531		77 ± 5

[a] For convenience, the dyes of this table are identified by the same numbers used in the preceding paper. [b] See ref 4. [c] Iodide salt.

acetylenic extreme structure has the positive charge located on the less basic imidazo[4,5-*b*]quinoxaline nucleus, and the two factors oppose one another. Thus the energy difference between the extreme structures is greater for **19** than for **20**, and the consequently greater degree of electron delocalization in **20** is responsible for the bathochromic displacement of its absorption maximum relative to that of **19**. In Table I, isomeric pairs of dyes are listed in order of decreasing difference in basicity between the two terminal nuclei. It is apparent that, in general, the dye in which the single hydrogen atom on the conjugated chain is adjacent to the more basic nucleus has an absorption maximum at longer wavelengths than that of its isomer. In addition, the greater the difference in basicity between the two nuclei, the greater is the difference between the absorption maxima of the corresponding pair of isomeric dyes. The dye pair **25** and **26** constitute an exception, for the absorption maxima of these dyes are identical, although **25** has a much broader absorption envelope. The origin of this anomalous behavior is, at present, unexplained.

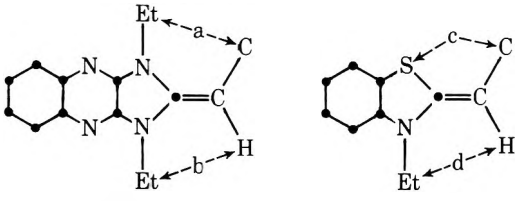
Relative Thermodynamic Stability of Isomeric Dyes. Although the addition of acids such as hydrogen chloride across the triple bond of acetylenic dyes occurs readily,[1] under suitable conditions acid-catalyzed interconversion of isomeric dyes can occur. Thus treatment of an acetonitrile solution of either isomer of a pair of acetylenic dyes with a trace of acetic acid leads to an equilibrium mixture of the two dyes. It is presumed that the equilibrium is established via a common dication formed by protonation of either isomeric dye.

$$R^+{}_1C{\equiv}CCH{=}R_2 \overset{H^+}{\rightleftharpoons} R^+{}_1CH{=}C{=}CHR^+{}_2$$

$$\overset{H^+}{\rightleftharpoons} R_1{=}CHC{\equiv}CR^+{}_2$$

The relative proportion of each isomer at equilibrium is shown in Table I. For each pair, the isomer having an absorption maximum at shorter wavelength is the thermodynamically more stable. Paralleling the arguments presented to account for the spectral absorption characteristics of the dyes, this behavior is attributed to the increased stabilization of the acetylenic extreme structure in the hypsochromic isomer. The greater the difference in basicity between the two nuclei, the more strongly is the equilibrium displaced in favor of the hypsochromic isomer.

An exception to the above is found in the dye pair **29** and **30**, in which case the equilibrium is unexpectedly displaced in favor of the bathochromic isomer **30**. A possible explanation for this behavior is as follows: planar projections[5] of isomers



29 and **30** indicate that although the four steric interactions a–d are possible, only a is significant, and this interaction occurs only in **29**. No steric interactions are indicated involving *N*-ethyl groups of either nucleus attached to the terminal sp carbon atom at the opposite end of the dye chain. It is suggested that in **29** and **30**, where the basicity difference between the two heterocyclic nuclei is small, the steric hindrance to planarity, caused by interaction a, destabilizes **29** sufficiently for **30** to predominate in the equilibrium mixture. It should be pointed out that the equilibrium ratio of **29** to **30** (23:77) corresponds to a very small energy difference (~0.9 kcal/mol) between the two isomers.

Molecular Orbital Calculations. The experimental results for acetylenic dyes correspond closely to absorption shifts and tautomer stabilities expected from Brooker's concepts about unsymmetrical dyes, the electronic properties of heterocycles, and deviations.[4] Since these concepts were based primarily on the π-electronic character of dyes without acetylenic bonds, it was of interest to use molecular orbital theory to examine the conjugated π-electron system of the present acetylenic dyes, treating them as geometrical isomers of their symmetrical carbocyanine analogues. The geometry for the acetylenic extreme structure of dye **1** is shown in Figure 1 along with that of the carbocyanine analogue **2**. The molecular orbital calculations for most of the dyes used Pariser–Parr–Pople methods,[6] modified to include σ-inductive effects.[6b,7] In addition, valence electron calculations using the CNDO/S formalism of Jaffé and co-workers[8] were carried out for model dyes. The results of these calculations and related experimental data are summarized in Table II for three classes of dyes: (A) dyes containing identical heterocycles, (B) model acetylenic and carbocyanine chromophores, and (C) isomeric dyes containing nonidentical heterocycles. The dyes containing identical heterocycles were examined with two Pariser–Parr–Pople parameter sets.[6b,7] Both provide reasonable estimates of the relative transition energies for acetylenic and carbocyanine dyes (Table IIA). Results based on the first set are in better agreement with experimental values, and these are used for the discussion below.

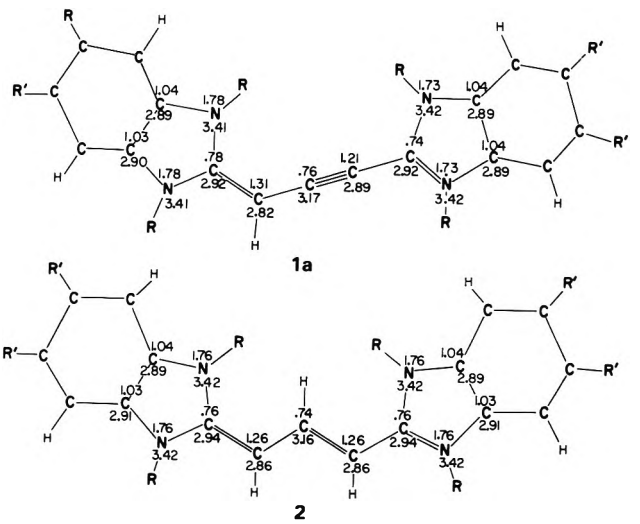


Figure 1. Acetylenic dyes and carbocyanine analogues (R = R′ = H). Charge densities [$\pi(\sigma)$] as calculated by the CNDO/S method of Jaffé and co-workers.[8] The carbocyanine analogue is predicted to absorb at significantly longer wavelength (430 nm) than the corresponding acetylenic dye (415 nm, Table IIB). Pariser–Parr–Pople calculations are summarized in Table IIA,C.

The allowed visible transition of acetylenic dyes occurs at shorter wavelength than for the corresponding carbocyanines, indicating chromophoric asymmetry as discussed in the previous sections. In the molecular orbital calculations for π electrons, introduction of this asymmetry as simple geometrical changes (bond lengths and bond angles) was sufficient to shift the predicted absorptions to shorter wavelength and localize more of the π-electron density on the heterocycle nearest the C–H carbon of the chromophore (Figure 1).

Dye **1** with the acetylenic geometry, **1a**, showed a predicted transition at 489 nm (2.53 eV), whereas the observed value is 473 nm. A "cumulene" geometry for the dye, obtained by adjusting only the sp-carbon positions to equalize all the bond lengths, gave a similar transition (488 nm).[9] The carbocyanine analogue **2** has a calculated transition at 524 nm (2.37 eV), corresponding to an observed value of 513 nm. The dyes **1**, **2**, and **6–9**, each containing identical heterocycles, exhibit a close

Table II. Spectroscopic Properties and Relative Stabilities of Acetylenic Dyes and Carbocyanine Analogues

A. Dyes with Identical Heterocyclic Nuclei

Registry no.	Dye[a]	E_T (10^{-4} ϵ)[b] obsd	Calcd by Pariser–Parr–Pople methods: Parameter set 1, $E_T(f)$[c]	Parameter set 1, π energy[d]	Set 2, $E_T(f)$[e]
52846-51-2	**1a**	2.62 (14)	2.53 (1.81)	495.86	2.30 (1.87)
61268-71-1	**1b**		2.54 (1.98)	495.62	
61268-72-2	**2**	2.42 (21)	2.37 (1.79)	494.34	2.21 (1.78)
		ΔE = 0.20 eV	ΔE = 0.16 eV		ΔE = 0.09 eV
56387-12-3	**6**	2.30 (21)	2.27 (1.96)	475.29	2.28 (2.10)
50818-84-3	**7**	2.13 (32)	2.15 (1.95)	473.79	2.20 (2.00)
		ΔE = 0.17 eV	ΔE = 0.138 eV		ΔE = 0.08 eV
61268-68-6	**8**	2.42 (9.9)	2.36 (1.72)	347.12	2.24 (1.73)
61268-69-7	**9**	2.24 (16)	2.22 (1.64)	345.71	2.14 (1.62)
		ΔE = 0.17 eV	ΔE = 0.165 eV		ΔE = 0.10 eV

B. Model Acetylenic and Carbocyanine Chromophores

Structure	Calcd quantity	Calcd values: PPP method[c]	CNDO/S method[f]
Acetylenic dye (Figure 1, R = R′ = H)	ϵ_{HF}	−9.40	−10.933 (π)
	E_T (f)	2.57 (1.70)	2.99 (1.37)
		3.68 (0.10)	3.51 (0.00001)
		3.99 (0.03)	4.15 (0.09)
Carbocyanine (Figure 1, R = R′ = H)	ϵ_{HF}	−9.37	−10.971 (π)
	E_T (f)	2.41 (1.68)	2.88 (1.29)
		3.64 (0.13)	4.09 (0.10)

C. Isomeric Dyes with Different Heterocyclic Nuclei

Dye[a]	Obsd in CH_3CN: E_T (10^{-4} ϵ),[b]	% isomer	Calcd by Pariser–Parr–Pople methods: E_T (f)[c]	π energy[d]
19	2.54 (13)	>99	2.42 (1.86)	485.71
20	2.33 (>13)	<1	2.31 (1.85)	485.57
	ΔE = 0.21 eV		ΔE = 0.11 eV	
21	2.65 (9)	>98	2.47 (1.74)	421.57
22	2.43 (12)	<2	2.42 (1.81)	421.41
	ΔE = 0.22 eV		ΔE = 0.05 eV	
29	2.37 (16)	23	2.33 (1.85)	411.22
30	2.33 (13)	77	2.26 (1.80)	411.23
	ΔE = 0.04 eV		ΔE = 0.07 eV	

[a] Dye structures: acetylenic dye 1a/1b from 1,3-diethyl-5,6-dichlorobenzimidazole and carbocyanine analogue **2**; acetylenic dye **6** from 1,3-diethylimidazo[4,5-*b*]quinoxaline and carbocyanine analogue **7**; acetylenic dye **8** from 3-ethylbenzothiazole and carbocyanine analogue **9**; tautomeric dyes (**19–22, 29, 30**) from Table I. [b] Observed transition energies (E_T, eV) and extinction coefficients (10^{-4} ϵ, l. mol^{-1} cm^{-1}) in acetonitrile (Table I and ref 1). [c] Calculated transition energies (E_T, eV) and oscillator strengths (f) for the π-electron system excluding the acetylenic bond in the plane of the molecule. The basic program (QCPE, No. 71),[6a] modified to include heteroatom inductive effects, was used with standard parameters[6c] and additional inductive effects within the chromophore.[7] [d] Total π energy in eV, as calculated by equation 2.20 in ref 12. H. A. Hammond, private communication. [e] Results using the original parameter set devised by Hammond.[6b] [f] CNDO/S method of Jaffé and co-workers.[8]

correspondence between the predicted and observed transition energies (Table IIA). In addition, transition energy *differences* between acetylenic/carbocyanine pairs of dyes are close.

Model acetylenic and carbocyanine chromophores with terminal benzimidazoles were examined by PPP and CNDO/S calculations (Table IIB and Figure 1, R = R′ = H). Calculations on acetylenic hydrocarbons have suggested weak UV transitions at longer wavelength than the allowed $\pi \rightarrow \pi^*$ transitions.[11] In dyes **1** and **2**, the CNDO/S calculations predict the lowest energy transition to be in the visible region of the spectrum with high oscillator strength, and weak transitions involving the acetylenic bond in the UV. In agreement with the π-electron calculations comparing acetylenic and carbocyanine dyes, shorter wavelength absorption for the acetylenic dye is also predicted, along with similar highest filled orbital energies and higher π-electron density on the heterocycle nearest the methine carbon in the acetylenic dye.

The isomeric acetylenic dyes (**19/20, 21/22,** and **29/30**) were examined using a fixed acetylenic geometry for all isomers (see dye 1a, Figure 1). The results of these π-electron calculations generally exhibited better agreement with spectral data than isomer stabilities (Table IIC). Calculated and observed transition energies were within 3% for dyes **20, 22, 29,** and **30** and within 6% for **19** and **21.** The dominant isomers in two dye sets (**19/20, 21/22**) were observed to be **19** and **21.** These also exhibited slightly higher total π energies,[12] but the high stability observed for these isomers is not adequately reflected in the total π energies. Dyes **29/30** are much closer in stability as shown by equivalent total π energies and a 23%/77% tautomeric mixture at equilibrium. Although it is reasonable to

suggest that the small differences in total π energy may be an artifact of the calculations, it is nevertheless interesting that the π energies qualitatively parallel the observed isomer stabilities.

The Pariser–Parr–Pople calculations used here (cyanine dye parameters, fixed acetylenic bond lengths, nonconjugated bond omitted) reproduce most of the characteristics in the visible spectra of acetylenic dyes and their carbocyanine analogues. Some π-charge localization was observed in dye **1a** similar to previous suggestions made on the basis of experimental bond lengths from an x-ray crystal structure.[3a] In addition, total π energies excluding components of the triple bond in the molecular plane provide qualitative estimates of the relative stabilities of isomeric acetylenic dyes. Thus, in both a qualitative and quantitative sense, the primary differences between acetylenic dyes and their symmetrical carbocyanine analogues can be understood as a consequence of asymmetry in the conjugated π-electron chromophore.

Experimental Section

Electronic spectra were recorded using a Perkin-Elmer Model 450 spectrophotometer.

Equilibration Experiments. Solutions of the acetylenic dyes in acetonitrile, in the concentration range of $1–2 \times 10^{-5}$ M, were used. To 3 ml of dye solution was added 1–2 drops of acetic acid. Visible absorption spectra were then recorded periodically until equilibrium was attained, giving a family of absorption curves passing through an isosbestic point (the time required to reach equilibrium varied from a few minutes to several hours). The equilibrium proportion of each acetylenic dye of a pair was readily computed using the absorption curves of the two pure isomers and that of the equilibrium mixture.

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References and Notes

(1) J. D. Mee, *J. Am. Chem. Soc.*, **96**, 4712 (1974).
(2) J. D. Mee, *J. Org. Chem.*, preceding paper in this issue.
(3) (a) D. L. Smith and H. R. Luss, *Acta Crystallogr., Sect. B*, **31**, 402 (1975); (b) D. L. Smith and H. R. Luss, *ibid.*, **28**, 2793 (1972).
(4) L. G. S. Brooker, A. L. Sklar, H. W. J. Cressman, G. H. Keyes, L. A. Smith, R. H. Sprague, E. Van Lare, G. Van Zandt, F. L. White, and W. W. Williams, *J. Am. Chem. Soc.*, **67**, 1875 (1945), and references cited therein.
(5) Similar to those used previously to explain steric effects in cyanines, e.g., see L. G. S. Brooker, F. L. White, D. W. Heseltine, G. H. Keyes, S. G. Dent, and E. J. Van Lare, *J. Photogr. Sci.*, **1**, 173 (1953).
(6) (a) Quantum-Chemistry Program Exchange (Program No. 71), Chemistry Department, Indiana University, Bloomington, Ind. 47401. (b) H. A. Hammond, *Theor. Chim. Acta*, **18**, 239 (1970). (c) Parameters and calculational methods were the same as in ref 6b except for σ-inductive effects[7] and the use of modified parameters for oxygen, nitrogen, and sulfur atoms: D. L. Beveridge and J. Hinze, *J. Am. Chem. Soc.*, **93**, 3107 (1971); J. Hinze and H. H. Jaffé, *J. Phys. Chem.*, **67**, 1501 (1963).
(7) (a) σ-inductive effects between neutral atoms was originally based on Pauling σ-electronegativity values (χ_p).[6b] Additional inductive effects between directly bonded atoms of the same type (e.g., C–C) significantly improve calculations of spectral transitions for these and other dyes. For the chromophoric carbon atoms C_α–C_β–C_α', the following χ_p values (dependent on net π charge) were used to estimate additional inductive effects between carbon atoms: C(aromatic), 2.75; C_α, 2.2–2.4; C_β, 2.7–2.9; C_α', 2.3–2.5 where C_β–C_α' were the acetylenic carbon atoms.
(8) (a) Quantum Chemistry Program Exchange (Program No. 174, CNDO/M with CNDO/2 and CNDO/S options), Chemistry Department, Indiana University, Bloomington, Ind. 47401. (b) The present calculations utilized the CNDO/S options in a more recent version of CNDO/M, kindly provided by Professor H. H. Jaffé, Chemistry Department, University of Cincinnati, Cincinnati, Ohio (see ref 8c–e) and adapted for calculations on larger molecules by J. M. McKelvey and R. A. Phillips, Eastman Kodak Co., Rochester, N.Y. 14650. (c) J. DelBene and H. H. Jaffé, *J. Chem. Phys.*, **48**, 1807, 4050 (1968); **49**, 1221 (1968); **50**, 1126 (1969). (d) R. L. Ellis, G. Kuehnlenz, and H. H. Jaffé, *Theor. Chim. Acta*, **26**, 131 (1972). (e) H. M. Chang, H. H. Jaffé, and C. A. Masmandis, *J. Phys. Chem.*, **79**, 1108, 1109 (1975).
(9) The relative orientations of the heterocycles in conformations **1a** and **1b** were identical, and only the positions of the sp carbons were modified. Carbon–carbon bond distances of the chromophore (heterocycle–CH–C–C–heterocycle) were 1.38, 1.37, 1.20, and 1.40 Å in the acetylenic dye and 1.38, 1.32, 1.32, and 1.33 Å in the cumulene dye. The absorption of a "cumulene" conformation **1b** of dye **1** was calculated as 488 nm (2.540 eV), which is close to both the observed value for dye **1** and the calculated value for the acetylenic conformation **1a**. The close correspondence between predicted absorption energies for **1a** and **1b** indicates that the calculated results are not critically dependent on the exact specification of geometry within the chromophore.
(10) S. S. Malhotra and M. C. Whiting, *J. Chem. Soc.*, 3812 (1960).
(11) H. H. Jensen, *Acta Chem. Scand.*, **25**, 235 (1971).
(12) J. A. Popie, *Trans. Faraday Soc.*, **49**, 1375 (1953), equation 2.20.

Synthesis of 6,9-Bisnormethyl-8-methoxy-12,13-epoxy-6,8,10-trichothecatriene

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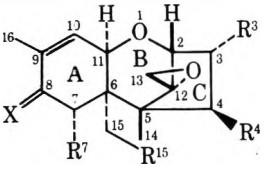
An efficient synthesis of an A-ring aromatic trichothecane analogue, 6,9-bisnormethyl-8-methoxy-12,13-epoxy-6,8,10-trichothecatriene (**11**), has been developed. The aryl allyl ether, **2**, was converted in a series of six steps to **7b** in ca. 74% overall yield. Bromination of the enolate anion of **7b**, removal of the benzyl protecting group, and cyclization (sodium hydride in ether) gave the tricyclic ketone, **9**, in very high yield. Alternatively, hydrogenolysis of **7b** followed by acetylation and bromination gave **13c**. Treatment of **13c** with DBN gave **9**. The spiro epoxide, **11**, was prepared from **9** by treatment with dimethylsulfonium methylide.

The trichothecanes are a group of sesquiterpene mycotoxins which possess the general structure **1**. Interest in this group emanates from the discovery that a number of the trichothecanes display potent activity against fungi, protozoa, viruses, and/or neoplasms. The significant mammalian toxicity which most of the trichothecanes exhibit has also been implicated as a cause of massive livestock poisoning, a result of ingestion of certain moldy foods.[1]



1

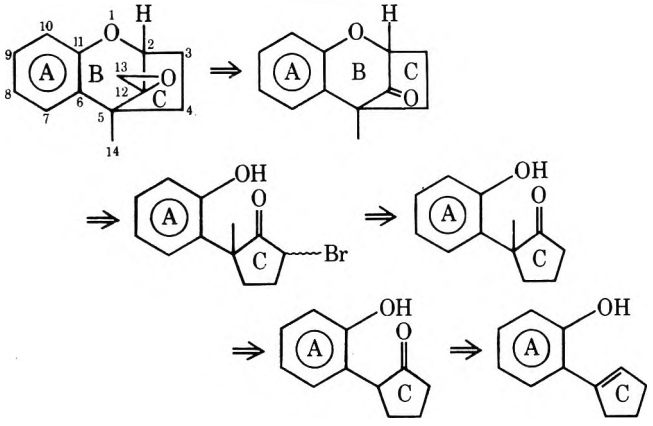
Structurally, the trichothecanes range in complexity from 12,13β-epoxytrichothec-9-ene (**1**, $R^3 = R^4 = R^7 = R^{15} = H$; X = H_2) to highly oxidized compounds such as nivalenol (**1**, $R^3 = R^4 = R^6 = R^{15} = OH$; X = O).[1] Macrocyclic lactone derivatives, bridging C-4 to C-15, are also quite common.[1] Three

trichothecane syntheses have been reported: trichodermin[2a] (1, $R^3 = R^7 = R^{15} = H$; $R^4 = OCOCH_3$; X = H_2) and 12,13β-epoxytrichothec-9-ene.[2b,3] The first two syntheses[2a,b] utilize a similar strategy insofar as the C ring is formed onto a precursor which contains the A and B rings. The most recent synthesis[3] is patterned after the proposed biosynthetic scheme for trichodermin; in this approach the bond between O-1 and C-11 is formed in a key step. All of the syntheses afford the final product in low overall yield and cannot be regarded as generally applicable for the preparation of a wide variety of compounds for thorough biological studies.

As a first step in the study of antineoplastic structure–activity requirements for the trichothecanes we examined several possible synthetic routes to this group of compounds. Our basic goal was to develop an approach which would be efficient and versatile. The versatility is required to provide synthetic approaches to a variety of trichothecanes and trichothecane analogues. We now wish to report our results in the synthesis of a trichothecane analogue which possesses an aromatic A ring.

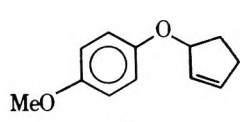
The basic strategy for the synthesis of A-ring aromatic trichothecanes is presented in Scheme I.[4] The literature

Scheme I

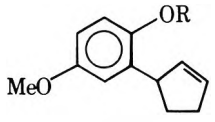


contains ample precedent for the conversion of ketones to the corresponding spiro epoxide, so the synthetic target becomes the tricyclic ketone. We chose, in our synthetic approach, to develop the tricyclic structure by an intramolecular Williamson reaction on a substrate which contained the preformed A and C rings. Thus, the first synthetic goal was to construct the 11-carbon trichothecane backbone with the A and C rings already intact. Such an approach should offer some considerable versatility in the elaboration of a variety of trichothecane analogues.

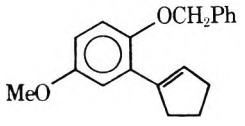
The requisite 11-carbon backbone of the A-ring aromatic trichothecane was readily assembled in two steps. Treatment of sodium *p*-methoxyphenoxide with 3-chlorocyclopentene[9] gave **2**, which, upon distillation, afforded **2** along with rearranged phenol, **3a**, in a combined yield of 70%. The thermal Claisen rearrangement of pure **2** proceeded to give **3a** in 98% yield. Attempts to isomerize the double bond in **3a**, in the



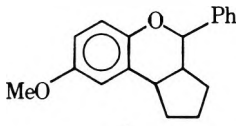
2



3a, R = H
b, R = CH_2Ph



4

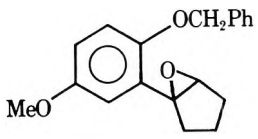


5

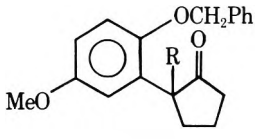
presence of the free phenol, were uniformly unsuccessful; so the phenol was converted to the benzyl ether, **3b** (96%); **3b** was smoothly converted to **4** (97%) by treatment with potassium *tert*-butoxide in Me_2SO–water.[5]

When water was omitted from the latter reaction none of the desired olefin was obtained; instead a product tentatively formulated as the chroman, **5**, was produced (90%). Support for this structure assignment was obtained when **5** was treated with hydrogen (10% Pd/C): the hydrogenolysis product, a phenol [2-(2′-benzylcyclopentyl)-4-methoxyphenol], was characterized spectroscopically.[6]

Epoxidation of **4** with *m*-chloroperbenzoic acid in a dichloromethane–aqueous sodium bicarbonate biphase system[7] gave a crystalline epoxide, **6**, in high yield (90%). The epoxide,



6

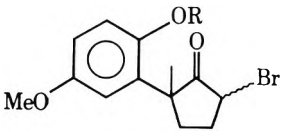


7a, R = H
b, R = Me

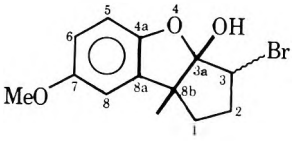
without purification, was converted to the ketone, **7a**, by treatment with boron trifluoride etherate in benzene for 1 min at 23 °C. The yield of **7a** from **4** was 89%.

The ketone, **7a**, was converted to the enolate anion by the action of sodium amide in liquid ammonia (ca. 6 h as judged by complete dissolution of starting material), then treated with excess methyl iodide to give **7b** (91%). The NMR spectrum of **7b** shows a sharp singlet at δ 1.28 for the newly introduced methyl group; absent from the NMR spectrum of **7b** was a multiplet at δ 2.90–3.42 which was assigned to the benzylic methine proton (adjacent to the carbonyl) in **7a**. Both **7a** and **7b** showed characteristic cyclopentanone IR absorption, 1745 and 1748 cm^{-1}, respectively.

Bromination of **7b** with phenyltrimethylammonium bromide perbromide (PTAB) in THF gave **8a** in only 42% yield along with *gem*-dibrominated material (ca. 25%) and unreacted starting material (ca. 25%). Pyridinium hydrobromide perbromide gave inferior results compared with PTAB. Treatment of **7b** with cupric bromide in chloroform–ethyl acetate resulted in cleavage of the benzyl group. Acetamide was added as a hydrogen bromide scavenger in an effort to avoid this cleavage; under these conditions the cupric bromide was consumed, the hydrogen bromide–acetamide complex precipitated from solution, and starting material was recovered. The preparatively useful bromination of **7b** was effected by using lithium diisopropylamide followed by bromine,[8] affording **8a** in 60% yield along with 37% of unreacted starting



8a, R = CH_2Ph
b, R = H

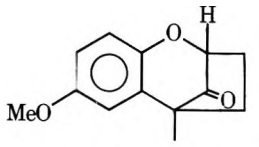


8b′

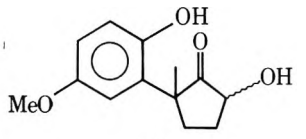
material. The separation of **8a** and **7b** was readily accomplished and the yield of **8a**, based upon recovered starting material, was 97%. No dibrominated side products were formed in this reaction when excess **7b** was used (ca. 0.68 equiv of Br_2 was used).

The benzyl group in **8a** was cleaved with anhydrous HBr in methylene chloride. The cleavage reaction proceeded to a certain point and stopped; presumably the benzyl bromide concentration reached a sufficient level such that the cleavage and rebenzylation reactions were at equilibrium. The reaction afforded **8b** in 62% yield along with 36% of recovered **8a**. Thus, the yield of **8b**, based upon the recovered starting material,

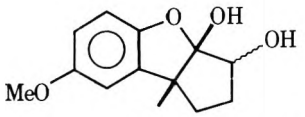
was 98%. The IR spectrum of **8b** contained no carbonyl absorption since **8b** exists as the hemiketal, **8b'**. It was possible, using medium-pressure liquid chromatography, to separate the two isomeric bromohemiketals; however, this was unnecessary since the epimeric mixture was perfectly suitable for the next step. Cyclization of **8b** with sodium hydride in anhydrous ether gave **9** in 99% yield. Considerable care had to be exercised in the handling of **9** because it showed a



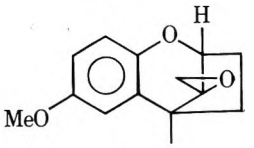
9



10



10'

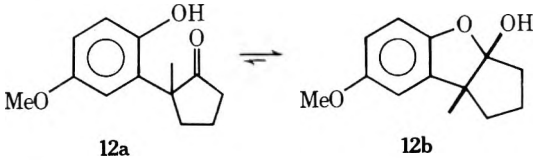


11

marked tendency to undergo hydrolytic ring opening to give **10**, particularly in the presence of acid. Both tautomeric forms of **10** could be obtained. The compound, in $CHCl_3$ solution, exists as the ketone, **10**. Dissolution of **10** in CCl_4 led to the crystallization of the less soluble hemiketal, **10'**. Spectra of **10'** could be determined in $CHCl_3$ solution provided that the spectra were recorded quickly after the solutions were prepared.

Treatment of **9** with dimethylsulfonium methylide gave the spiro epoxide, **11**, in 79% yield (based on recovered starting material). The stereochemistry of **11** is undefined. It was necessary to use an inverse addition procedure because the product spiro epoxide showed a tendency to react with the ylide to give a tertiary allylic alcohol. Formation of the tertiary allylic alcohol was quite pronounced when the ketone was added to the ylide solution. Dimsyl sodium (Me_2SO–NaH) was found to be the base of choice for generation of the ylide in this rection; when *n*-butyllithium was used a tertiary *n*-butylcarbinol was invariably formed. This latter product was observed even when excess trimethylsulfonium iodide was used and times in excess of 1 h were allowed for ylide formation.

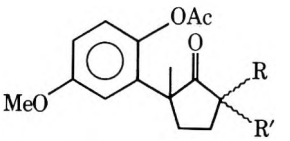
Other phenol blocking groups were examined during the course of this study. The benzyl group was removed from **7b** by hydrogenolysis (5% Pd/C); the product, **12**, existed almost exclusively as the hemiketal **12b**. The IR spectrum of **12**



12a **12b**

($CHCl_3$) showed no carbonyl absorption; however, upon the addition of a trace of triethylamine a medium intensity band appeared at 1745 cm^{-1}. Bromination of **12** with PTAB in freshly distilled anhydrous THF or with cupric bromide in chloroform–ethyl acetate yielded complex, tarry mixtures; bromination of **12** with PTAB in methylene chloride yielded 5-bromo-3a-hydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran, the product of aromatic bromination ortho to the phenolic hydroxyl.

Acetylation of **12** gave the phenyl acetate, **13a**, in high yield. Bromination of **13a** with PTAB afforded the α,α-dibromo ketone, **13b**, as the major product. Treatment of **13a** with cupric bromide in chloroform yielded **13c** as the major product (72%) with only a trace (5%) of **13b**. Treatment of **13c** with



13a, R = R' = H
b, R = R' = Br
c, R = Br; R' = H

DBN effected cleavage of the phenyl acetate and cyclization in one pot and **9** was obtained in 82% yield from **13c**.

In conclusion, the series of six steps from **2** to **7b** can be carried out in ca. 74% yield with a minimum of difficulty. Three of the remaining four steps (via **8a**) require chromatography to recover starting material for recycling but the overall yield of **11** from **2** (ten steps, via **8a**) is 55%. The synthesis is relatively simple to carry out and is versatile. The alternate synthesis of **9** from **7b** (via **12**) adds an additional step and the overall yield of **11** from **2** is reduced to 43%; however, the simplicity of the procedures involved affords some merit to this approach. Other phenols have been reacted with 3-chlorocyclopentene to give analogues of **2** which also readily undergo Claisen rearrangement; these intermediates will provide a series of compounds with a range of A-ring functionality. The intermediates **7a** and **8a** are particularly well suited for elaboration of necessary C-ring functionality; this work is in progress. Finally, this approach may also be employed for the synthesis of trichothecanes which possess an aliphatic A ring; the stereochemistry of the substituents at C-5 and C-6 (cf., **1**) can be controlled in the initial Claisen rearrangement and this work will be the subject of a forthcoming communication.

Experimental Section

NMR spectra were determined for solutions in CCl_4 (unless otherwise specified), containing ca. 1% Me_4Si as internal standard, with a Varian T-60 spectrometer. IR spectra were determined for neat samples (unless otherwise specified) with a Perkin-Elmer 237 spectrophotometer. UV data were determined for solutions in 95% ethanol (unless otherwise specified) with a Beckman DB-G spectrophotometer. Mass spectra were determined by the NIH Biomedical Technology Center at Cornell University. Melting points are uncorrected and were determined in capillary tubes with a Hoover-Thomas Unimelt apparatus. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn., and by Atlantic Microlab, Inc., Atlanta, Ga.

3-(*p*-Methoxyphenyloxy)cyclopentene (2). A solution of sodium ethoxide was prepared by gradual addition of sodium metal (23.0 g, 1.0 mol) to absolute ethanol (500 ml). The reaction mixture was allowed to cool to room temperature and *p*-methoxyphenol (124 g, 1 equiv) was added with vigorous stirring. The reaction mixture was allowed to stir for at least 1 h before being used in the subsequent reaction. The vigorously stirred suspension of sodium *p*-methoxyphenoxide in absolute ethanol was cooled to −45 °C (dry ice in chloroform–carbon tetrachloride, 1:1) and freshly prepared 3-chlorocyclopentene (102 g, 1.0 mol) was slowly added. The pH of the reaction mixture was continuously monitored (pH test paper) to ensure that the reaction remained basic. Water was added to the cooling bath and the temperature of the reaction mixture was permitted to increase to −4 °C (over ca. 1 h). (If the temperature was allowed to rise above ca. 5–7 °C, the reaction became uncontrollably exothermic with reaction temperature going over 30 °C. The reaction mixture then turned a greenish-blue color and was found to be very acidic—lower isolated yields resulted.) Anhydrous K_2CO_3 (138.2 g, 1.0 mol) was added (addition of anhydrous K_2CO_3 was made at lower temperatures only if the reaction mixture was found to have a pH of 7 or less) and the mixture was maintained below 0 °C for 5 h. The temperature was allowed to slowly increase to 15 °C after which careful monitoring of the reaction temperature was no longer essential. (Any indication of a sudden exothermic reaction required recooling of the reaction mixture to 0 °C for an additional 2 h.) The reaction mixture was stirred at room temperature for 36 h and filtered through Celite. The inorganic residue was thoroughly washed with acetone and the combined filtrate was concentrated in vacuo (below 50 °C). (It was es-

sential to monitor the pH of the filtrate and the various residues; any indication of acidity required the addition of K_2CO_3 to achieve neutralization or slight alkalinity.) The residue was dissolved in ether (1 l.), washed with 5% KOH solution (7 × 250 ml), water (1 × 250 ml), and saturated NaCl solution (1 × 500 ml), and dried (anhydrous Na_2SO_4). The ethereal solution was concentrated in vacuo and the residue was distilled in the presence of anhydrous K_2CO_3 (20% of the weight of the residue) under the lowest pressure possible. (In reactions where more than 1 mol of 3-chlorocyclopentene was employed the residue was divided according to the number of moles used and was distilled separately in the presence of anhydrous K_2CO_3.) Fluctuations in vacuum typically occurred when the pot temperature reached 160 °C; however, a gradual return to the original vacuum occurred. (In one instance where starting phenol was not removed, prolonged and continual reductions in vacuum occurred and complete destruction of product resulted.)

Distillation of the crude product gave **2** (77.8 g, 41%) and **3a** (55.7 g, 29%). 3-(*p*-Methoxyphenoxy)cyclopentene (**2**) had bp 115–120 °C (0.4 Torr); IR 969, 889, 824, 790, and 756 cm^{-1}; UV max 223 nm (ϵ 3650) and 291 (2590); NMR δ 1.87–2.57 (m, 4), 3.75 (s, 3), 5.10–5.33 (m, 1), 5.83–6.12 (m, 2), and 6.77 (s, 4).

Anl. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.79; H, 7.46.

2-(3′-Cyclopentenyl)-4-methoxyphenol (3a). A mixture of **2** (91.9 g, 0.483 mol) and anhydrous K_2CO_3 (9.2 g) was heated at 185 °C for 30 min (N_2 atmosphere) and distilled to yield 90.1 g of **3a** (98%): bp 110 °C (0.28 Torr); IR 3356 cm^{-1}; UV max 226 nm (ϵ 3760) and 271 (3310); NMR δ 1.43–2.73 (m, 4), 3.63 (s, 3), 3.79–4.32 (m, 1), 4.80 (s, 1, -OH), 5.61–6.07 (m, 2), and 6.52 (s, 3).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.96; H, 7.49.

2-(3′-Cyclopentenyl)-1-benzyloxy-4-methoxybenzene (3b). A stirred mixture of **3a** (12.38 g, 0.65 mmol), anhydrous K_2CO_3 (17.97 g, 130 mmol), and benzyl bromide (33.35, 195 mmol) in acetone (100 ml) was heated under reflux for 51 h. The cooled reaction mixture was filtered, the precipitate was washed with acetone (2 × 100 ml), and the combined acetone solution was concentrated in vacuo. The residue was dissolved in ether (500 ml) and the ethereal solution was washed with water (100 ml) and saturated NaCl solution (100 ml), dried (Na_2SO_4), and concentrated in vacuo. Anhydrous K_2CO_3 (1.3 g) was added and the residue was distilled to yield 17.5 g (96%) of **3b:** bp 163 °C (0.35 Torr); IR 1587, 917, 876, 855, 800, 735, and 696 cm^{-1}; UV max 232 nm (ϵ 4750) and 290 (3080); NMR δ 1.47–2.73 (m, 4), 3.67 (s, 3), 4.10–4.57 (m, 1), 4.98 (s, 2), 5.62–6.07 (m, 2), 6.48–6.82 (m, 3), and 7.33 (s, 5).

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.29; H, 7.21.

2-(1′-Cyclopentenyl)-1-benzyloxy-4-methoxybenzene (4). Potassium *tert*-butoxide (11.8 g, 0.11 mol) was added to Me_2SO (120 ml) with stirring; the solution was stirred for 30 min and Me_2SO was added to bring the volume to 150 ml. The mixture was treated with water (7.5 ml) and **3b** (17.56 g, 62.6 mmol), then heated at 95 °C for 1.5 h. The cooled mixture was diluted with water (1.5 l.) and extracted with ether (600 ml) in a liquid–liquid extraction apparatus. The ethereal solution was washed with water and saturated NaCl solution, dried (Na_2SO_4), and concentrated in vacuo. The residue was dried under high vacuum (P_2O_5) for 8 h and crystallized from petroleum ether to yield 16.98 g (97%) of **4:** mp 57–58 °C; IR 957, 909, 870, 851, and 694 cm^{-1}; UV max 224 nm (ϵ 10 500) and 310 (3170); NMR δ 1.63–2.93 (m, 6), 5.00 (s, 2), 6.27–6.42 (m, 1), 6.45–6.88 (m, 3), and 7.33 (s, 5).

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.40; H, 7.23.

1,2,3,3a,4,9a-Hexahydro-4-phenyl-8-methoxycyclopenta[*c*]-benzofuran (5). Potassium *tert*-butoxide (121.1 g, 1.05 mol) was added to anhydrous Me_2SO (1.4 l. with stirring); after 30 min Me_2SO was added to bring the volume to 1.5 l. and **3b** (168.0 g, 0.672 mol) was added to the stirred solution at room temperature. The mixture was heated for 1.5 h at 85 °C, cooled, diluted with water (6 l.), and extracted with ether (1.5 l.) in a liquid–liquid extraction apparatus. The ethereal solution was washed with water (3 l.) and saturated NaCl solution (500 ml), dried (Na_2SO_4), and concentrated in vacuo. The residue was crystallized from anhydrous ether to yield 151.2 g (90%) of **5:** mp 106.5–107.5 °C; IR (KBr) 999, 865, 824, 772, 748, 714, and 704 cm^{-1}; UV max 230 nm (ϵ 6240) and 293 (3620); NMR δ 1.30–2.07 (m, 6), 2.13–2.63 (m, 1), 2.80–3.16 (m, 1), 3.73 (s, 3), 4.26 (d, 1, J = 10 Hz), 6.65 (s, 3), and 7.34 (s, 5).

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.30; H, 7.19.

2-(2′-Benzylcyclopentyl)-4-methoxyphenol. A mixture of **5** (0.5 g, 1.76 mmol) and 10% Pd/C (0.5 g) in ethyl acetate (6.0 ml) was stirred under a hydrogen atmosphere for 4 days. The mixture was filtered (Celite bed) and the residue was washed with ethyl acetate (30 ml). The combined ethyl acetate solution was concentrated in vacuo and the residue was purified by TLC (silica gel–benzene) to give 2-(2′-benzylcyclopentyl)-4-methoxyphenol (97%): mp (crystallized from ether) 95–96 °C; IR 3425, 1043, 872, and 695 cm^{-1}; UV max 225 nm (ϵ 6080) and 296 (3640); UV max (NaOH in 95% ethanol) 257 nm (ϵ 2510) and 316 (5150); NMR δ 1.16–3.00 (m, 9), 3.26–3.86 [m, 4 (CH_3O, s, 3.78)], 4.80 (s, 1, OH), 6.60–6.93 (m, 3), and 7.37 (s, 5).

Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.54; H, 7.86.

1-(2′-Benzyloxy-5′-methoxyphenyl)-1,2-epoxycyclopentane (6). A stirred mixture of 4 (11.2 g, 40.0 mmol), dichloromethane (400 ml), and 0.5 M aqueous $NaHCO_3$ (120 ml) was cooled to 8 °C and slowly treated with solid *m*-chloroperbenzoic acid (85%, 8.12 g, 40.0 mmol) such that the temperature never rose above 10 °C. The cooling bath was removed and the reaction was allowed to warm to room temperature over 3.5 h (peracid consumption was monitored with potassium iodide–starch test paper). The organic phase was separated, washed with 10% aqueous Na_2SO_3 solution (120 ml), dried (Na_2SO_4), and concentrated in vacuo below 35 °C. The residue was dried over a high vacuum (P_2O_5) for 30 min and used directly in the subsequent reaction. The NMR spectrum of the crude product showed no trace of unreacted **4:** NMR δ 1.23–2.47 (m, 6), 3.33 (s, 1), 3.77 (s, 3), 5.03 (s, 2), 6.67–7.07 (m, 3), and 7.37 (s, 5).

2-(2′-Benzyloxy-5′-methoxyphenyl)cyclopentanone (7a). The crude epoxide obtained from the previous reaction was dissolved in anhydrous benzene (400 ml) and the stirred solution was treated with freshly distilled boron trifluoride etherate [2.4 ml (2.77 g), 20 mmol]. After 1 min at 23 °C the reaction was quenched with saturated aqueous Na_2CO_3 (100 ml) and stirred for 5 min. The pale yellow solution, which turned dark green upon the addition of the boron trifluoride etherate, returned to its original color ca. 1 min after the reaction was quenched. The organic phase was separated, washed with water (100 ml) and saturated NaCl solution (100 ml), dried (Na_2SO_4), and concentrated in vacuo to yield 10.5 g (94%) of **7a.** Crystallization from a small quantity of anhydrous ether yielded 9.97 g (89%) of **7a:** mp 100–101.5 °C; IR (CCl_4) 1745 cm^{-1}; UV max 217 nm (ϵ 6310), 228 (6210), and 291 (2680); NMR δ 1.55–2.60 (m, 6), 2.90–3.42 (m, 1), 3.70 (s, 3), 4.88 (s, 2), 6.48–6.88 (m, 3), and 7.33 (m, 5).

Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.86; H, 6.89.

2-Methyl-2-(2′-benzyloxy-5′-methoxyphenyl)cyclopentanone (7b). 2-(2′-Benzyloxy-5′-methoxyphenyl)cyclopentanone (**7a,** 25.85 g, 87.2 mmol) was added to a suspension of sodium amide (10.2 g, 261.6 mmol) in liquid ammonia (2.5 l.) with vigorous stirring. The reaction mixture was stirred for 6.5 h in refluxing ammonia until the initially cloudy suspension became a yellow-green transparent solution. Methyl iodide (37.15 g, 261.6 mmol) was added rapidly with stirring. The reaction mixture was stirred for an additional 2.5 h and anhydrous ether (1 l.) was added. The reaction mixture was allowed to stand without stirring until all of the liquid ammonia was distilled from the reaction (24 h). Ether was added to bring the volume to 1.25 l. and the ethereal solution was washed with water (3 × 500 ml), dried (Na_2SO_4), and concentrated in vacuo. The residue was thrice crystallized from anhydrous ether to yield 24.6 g (91.0%) of 2-methyl-2-(2′-benzyloxy-5′-methoxyphenyl)cyclopentanone (**7b**): mp 95–96 °C; IR (CCl_4) 1748 cm^{-1}; UV max 220 nm (ϵ 6780), 229 (7310), and 290 (3260); NMR δ 1.28 (s, 3), 1.47–2.43 (m, 6), 3.75 (s, 3), 4.89 (s, 2), 6.52–6.93 (m, 3), and 7.37 (s, 5).

Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.39; H, 7.17.

5-Bromo-2-methyl-2-(2′-benzyloxy-5′-methoxyphenyl)cyclopentanone (8a). Method A. 2-Methyl-(2′-benzyloxy-5′-methoxyphenyl)cyclopentanone (**7b,** 1.00 g, 3.22 mmol) was added to a stirred solution of phenyltrimethylammonium perbromide (1.30 g, 3.45 mmol) in dry tetrahydrofuran (25 ml) at room temperature. The orange reaction mixture gradually became colorless as the white phenyltrimethylammonium bromide precipitated from solution and after 2.5 h the reaction mixture was filtered and concentrated in vacuo. The residue was purified by column chromatography (silica gel, methylene chloride) to give **7b** (0.3 g, 30%), **8a** (0.53 g, 42%), and 5,5-dibromo-2-methyl-2-(2′-benzyloxy-5′-methoxyphenyl)cyclopentanone (0.39 g, 25%). **8a** had mp 91–92 °C (crystallized from ether); IR (KBr) 1757 cm^{-1}; UV max 238 nm (ϵ 4700) and 294 (3280); NMR δ 1.43 (s, 3), 1.60–2.67 (m, 4), 3.63–4.10 [m, 4 H (OCH_3, s, 3.76)], 4.82 and 5.07 (br d of d, J = 4 Hz, 2), 6.53–6.93 (m, 3), and 7.41 (s, 5); mass spectrum m/e (rel abundance) $M^+ + 2$ 390 (27), M^+ 388 (29), 299 (7), 297 (7), 218 (54), 177 (14), 162 (22), 91 (100), and 77 (6).

Anal. Calcd for $C_{20}H_{21}BrO_3$: C, 61.71; H, 5.44; Br, 20.53. Found: C, 61.70; H, 5.46; Br, 20.64.

Method B. A solution of *n*-butyllithium in hexane (8.18 ml of 1.3 M solution 106.3 mmol) was added (via syringe through a rubber injection septum) to a magnetically stirred solution of freshly distilled diisopropylamine (10.76 g, 106.3 mmol) in THF (300 ml, freshly distilled over $LiAlH_4$) maintained at −78 °C under a N_2 atmosphere. After 15 min a solution of **7b** (30.0 g, 96.65 mmol) in anhydrous THF (100 ml) was injected and the mixture was stirred at −78 °C for 30 min. At this point the white, heterogeneous mixture was treated with a 0.5 M solution of bromine in methylene chloride—the bromine solution was added rapidly until the mixture was a homogeneous, pale yellow color (131 ml, 65.6 mmol, of Br_2 was added; this corresponded to 68% of the stoichiometric requirement of Br_2). Further addition of Br_2 led to formation of dibrominated product. Immediately following the addition of bromine the cooling bath was removed and the reaction was quenched with a twofold excess of aqueous $NaHCO_3$ (17.8 g, 0.212 mmol, in 100 ml of H_2O). The cold THF layer was separated and washed with saturated NaCl solution (2 × 250 ml); the aqueous $NaHCO_3$ phase was extracted with ether (2 × 250 ml) and the ethereal solution was washed with the brine solution from the previous washing. The combined THF–ether solution was dried (Na_2SO_4) and concentrated in vacuo to yield 35.7 g of a semisolid yellow oil. Silica gel chromatography (CH_2Cl_2) afforded 22.73 g (60%) of **8a** along with 11.16 g (37%) of recovered **7b.**

3-Bromo-3a-hydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran (8b). A stirred solution of **8a** (15.8 g, 40.59 mmol) in CH_2Cl_2 (200 ml, purified through a basic alumina I column) was treated at room temperature with anhydrous HBr (via a gas dispersion tube) and maintained at a positive pressure of ca. 5 psi for 4 h. The reaction was monitored by TLC (silica gel/CH_2Cl_2) and after 4 h the reaction was at equilibrium. The mixture was concentrated in vacuo and the residue was placed under vacuum (continuous pumping at ca. 0.3 mm) for 1 h to remove the benzyl bromide. The residue was dissolved in CH_2Cl_2 and the entire process was repeated to give 16.1 g of a dark green oil. Silica gel chromatography gave 7.526 g (62%) of **8b** and 5.66 g (36%) of recovered **8a.** The epimeric mixture of **8b** had UV max 297 nm (ε 3910) and 231 (5750).

Anal. Calcd for $C_{13}H_{15}O_3Br$: C, 52.19; H, 5.05; Br, 26.71. Found: C, 52.37; H, 5.08, Br, 26.81.

The epimeric mixture was separated using medium-pressure liquid chromatography (silica gel H/CH_2Cl_2). The major isomer, ca. 60% of the mixture, was a solid and was crystallized from CH_2Cl_2: mp 78–79 °C; IR (CCl_4) 3584, 2941, 2865, 2833, 1548, 1490, 1284, 1214, 1182, 1036, 939, and 909 cm^{-1}; NMR δ 1.45 (s, 3), 1.73–2.60 (m, 4), 3.58–3.70 (br s, 1), 3.72 (s, 3), 4.37–4.62 (m, 1), and 6.47–6.72 (m, 3). The minor isomer was an oil: IR (CCl_4) 3571, 3425, 2950, 2865, 2833, 1773, 1548, 1490, 1250, 1212, 1135, 1031, 939, and 862 cm^{-1}; NMR δ 1.35 (s, 3), 1.63–2.28 (m, 4), 3.57 (s, 1), 3.73 (s, 3), 3.93–4.30 (br d of d, 1), and 6.48–6.75 (m, 3).

Synthesis of the Tricyclic Ketone, 9. Method A. A stirred suspension of NaH (98%, 0.2 g, 8.33 mmol) in anhydrous ether (15 ml), under a nitrogen atmosphere, was treated with a solution of **8b** (1.5 g, 5.014 mmol) in anhydrous ether (2 ml). After 18 h at room temperature the reaction mixture was filtered through analytical Celite and concentrated to dryness. It was absolutely essential to remove the last traces of ether from the crude product and to exclude any trace of water. The crude yellow oil was purified by silica gel chromatography (anhydrous $CHCl_3$) to yield 1.083 g (99%) of **9** as a colorless oil: IR (CCl_4) 3700–3200 (no absorption), 2941, 2865, 2760, 1770, 1613, 1585, 1488, 1385, 1198, 1042, 1022, 953, and 864 cm^{-1}; UV max 296 nm (ε 3363) and 233 (5698); NMR δ 1.32 (s, 3), 1.58–2.55 (m, 4), 3.65 (s, 3), 3.88–4.18 (d of d, 1), and 6.35–6.68 (m, 3).

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.61; H, 6.51.

Method B. DBN (0.25 g, 2.0 mmol)[10] was added to a stirred solution of 5-bromo-2-methyl-2-(2′-acetoxy-5′-methoxyphenol)cyclopentanone (**13c,** 0.673 g, 1.972 mmol) in anhydrous benzene (10 ml). The solution was stirred for 15 min at room temperature and concentrated in vacuo. The residue was purified by silica gel chromatography (CH_2Cl_2) to yield 0.353 g (82%) of **9.**

5-Hydroxy-2-methyl-2-(2′-hydroxy-5-methoxyphenyl)cyclopentanone (10) and 3,3a-Dihydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran (10′). The ketone **9** was unstable in the presence of water and underwent hydrolytic ring opening to give **10:** IR 3344, 1757 (C=O), 1070, 1036, 1018, 952, 869, 844, and 803 cm^{-1}; NMR ($CDCl_3$) δ 1.42 (s, 3), 1.50–2.70 [m, 6 (2-OH)], 3.82 (s, 3), 4.20–4.33 (m, 1), and 6.60–6.83 (m, 3). Crystallization of **10** from $CHCl_3$ (or CCl_4) afforded the hemiketal **10′:** mp 110.5–111.5 °C; IR ($CHCl_3$, taken quickly after the solution was prepared) 3333, 1079, 1071, 1036, 1010, 957, 923, 879, 853, and 806 cm^{-1}; NMR ($CDCl_3$, taken quickly after the solution was prepared) δ 1.37 (s, 3), 1.77–2.30 (m, 4), 3.20 (s, 1, –OH), 3.63 (s, 1, –OH), 3.83 (s, 3), 4.17–4.30 (m, 1), and 6.80 (s, 3); mass spectrum *m/e* (rel abundance) $M^+ - 236$ (5), 218 (100), 190 (6), 189 (3), 175 (16), 174 (1), 162 (54), 147 (8), and 91 (11).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.95; H, 6.85.

6,9-Bisnormethyl-8-methoxy-12,13-epoxy-6,8,10-trichothecatriene (11). A stirred mixture of NaH (98%, 0.11 g) in Me_2SO (10 ml, dried and distilled over CaH_2) was heated at 71 °C (N_2 atmosphere) for 7 h. The resultant gray solution, 4.58 mmol of dimethylsulfonium methylide, was cooled to room temperature, THF (10 ml, dried and distilled over $LiAlH_4$) was added, and the solution was cooled to −10 °C. Trimethylsulfonium iodide (0.935 g, 4.58 mmol) dissolved in anhydrous Me_2SO (0.5 ml) was added and the mixture was stirred for 10 min at −10 to −5 °C. The ylide solution was transferred, via a double-tipped 18 gauge 24-in. stainless steel flexible needle (both flasks were equipped with rubber septum inlets), to a stirred solution of **9** (1.0 g, 4.58 mmol) in THF (5 ml, distilled over $LiAlH_4$) which was cooled to −10 °C and kept under a purge of N_2. The inverse addition of the ylide and the washing was completed in ca. 2 min. The mixture was stirred at −5 °C for 1 h, then the temperature was allowed to rise to room temperature. The THF was removed under a stream of N_2, and the Me_2SO solution was diluted with five volumes of H_2O and extracted with ether (3 × 50 ml). The ethereal solution was washed with water (20-ml portions) until the ethereal solution was neutral. The ether was removed in vacuo, and the residue was dissolved in $CHCl_3$ (50 ml) and dried (Na_2CO_3). The solution was concentrated in vacuo to yield 0.851 g of a yellow oil which was purified by silica gel chromatography to yield 0.34 g (33%) of recovered **9** and 0.479 g (46%) of **11:** mp 89.5–90.5 °C; IR ($CHCl_3$) 3050, 2960, 2930, 2865, 2833, 2247, 1622, 1591, 1493, 1468, 1328, 1258, 1209, 1202, 1148, 1044, 1034, 979, and 811 cm^{-1}; UV max 295 nm (ε 3630) and 232 (6453); NMR ($CDCl_3$) δ 1.16 (s, 3), 1.74–2.39 (m, 4), 2.91 (d, J_{AB} = 5 Hz, 1), 3.20 (d, J_{AB} = 5 Hz, 1), 3.73 (s, 3), 4.12 (br s, 1), and 6.55–6.91 (m, 3).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.41; H, 6.95.

***cis*-3a-Hydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran (12).** A suspension of 5% Pd/C (0.60 g) in ethyl acetate (200 ml) was allowed to equilibrate over a hydrogen atmosphere for 2.5 h. A solution of 2-methyl-2-(2′-benzyloxy-5′-methoxyphenyl)cyclopentanone (**7b,** 1.24 g, 3.99 mmol) in ethyl acetate (15 ml) was added to this suspension. Hydrogen uptake ceased after 109.0 ml (4.87 mmol) was absorbed (20 h). The reaction mixture was filtered through Celite and the inorganic residue was washed with ethyl acetate (100 ml). The combined ethyl acetate solution was concentrated in vacuo. The oily residue was dried under high vacuum, and the residue crystallized slowly from the neat oil (either by scratching when chilled at 0 °C or by addition of seed crystals) to quantitatively yield *cis*-3a-hydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran (**12**): mp 54.5–57 °C; IR 3390 and 1721 cm^{-1}; UV max 228 nm (ε 3360) and 298 (3130); NMR δ 1.24 (s, 3), 1.30–2.40 (m, 6), 2.93–3.27 (m, 1, OH), 3.67 (s, 3), and 6.50 (s, 3).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.75; H, 7.35.

***cis*-5-Bromo-3a-hydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran.** Crystalline *cis*-3a-hydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran (**12,** 110.0 mg, 0.5 mmol) was added to a solution of phenyltrimethylammonium perbromide (188 mg, 0.5 mmol) in methylene chloride (7 ml) with stirring at room temperature. The orange-colored solution became colorless after 4.5 h. The reaction mixture was concentrated in vacuo at temperatures below 50 °C and the residue was extracted with hot anhydrous ether (5 × 25 ml). The ethereal solution was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by preparative TLC (silica gel–methylene chloride) to give exclusively *cis*-5-bromo-3a-hydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran: IR 3436 cm^{-1}; UV max 221 nm (ε 5850) and 304 (4060); NMR δ 1.17–2.63 [m, 9 (CH_3, s, 1.35)], 3.49 (s, 1, OH), 3.77 (s, 1), 6.57 (d, 1 J_m = 3 Hz), and 6.80 (d, 1).

Anal. Calcd for $C_{13}H_{15}BrO_2$: C, 52.16; H, 5.08, Br, 26.61. Found: C, 52.19; H, 5.05; Br, 26.71.

Method A. 2-Methyl-2-(2′-acetoxy-5′-methoxyphenyl)cyclopentanone (13a). A mixture of *cis*-3a-hydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran (**12,** 13.4

g, 60.8 mmol) and dry sodium hydride (1.6 g, 67 mmol) in anhydrous ether (125 ml) was stirred under a nitrogen atmosphere at room temperture for 1 h. The dark yellow mixture was cooled to −30 °C and acetyl chloride (9.6 g, 122 mmol) was added with vigorous stirring. Five minutes after the addition was completed the cooling bath was removed and 1% aqueous HCl (100 ml) was added. The ethereal phase was separated and the aqueous phase was washed with ether (2 × 100 ml); the combined ethereal solution was washed with saturated aqueous NaCl solution (50 ml), dried (Na_2SO_4), and concentrated under high vacuum to give an oily solid. The product was crystallized from isopropyl ether to give 13.7 g of **13a**. The mother liquor was concentrated and an additional 1.7 g of **12** was obtained. The yield of **13a** based on recovered starting material was 98%: mp 83–84 °C; IR (CCl_4) 1770 and 1742 cm^{-1}; UV max 239 nm (ϵ 3390) and 282 (2010); NMR δ 1.27 (s, 3), 1.60–2.42, [m, 9 ($COCH_3$, 3, 2.14)], and 6.47–7.06 (m, 3).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.67; H, 6.95.

Method B. A solution of **12** (7.0 g, 26.7 mmol) in pyridine (100 ml) was stirred for 30 min, acetic anhydride (20 ml, 212 mmol) was added, and the reaction mixture was stirred for 10 days at room temperature. The mixture was concentrated in vacuo and the residual pyridine was removed by azeotropic distillation with toluene. The residue was dried and crystallized from isopropyl ether to yield 6.95 g (83%) of **13a**.

5,5-Dibromo-2-methyl-2-(2′-acetoxy-5′-methoxyphenyl)cyclopentanone (13b). 2-Methyl-2-(2′-acetoxy-5′-methoxyphenyl)-cyclopentanone (**13a**, 310 mg, 1.10 mmol) was added to a solution of phenyltrimethylammonium perbromide (460 mg, 1.22 mmol) in CH_2Cl_2 (25 ml) with stirring at room temperature. The orange-colored solution became colorless after 3 h. The reaction mixture was concentrated in vacuo at temperature below 35 °C and the residue was extracted with hot anhydrous ether (5 × 25 ml). The ethereal solution was washed with water (50 ml) and saturated NaCl solution (50 ml), dried (Na_2SO_4), and concentrated in vacuo. The residue was found by NMR to contain some starting material and monobrominated product in addition to the major product, the α,α-dibrominated material. The residue was purified by preparative TLC (silica gel, methylene chloride) to give 5,5-dibromo-2-methyl-2-(2′-acetoxy-5′-methoxyphenyl)cyclopentanone (**13b**): IR 1767 cm^{-1}; UV max 232 nm (ϵ 5580) and 281 (2020); NMR δ 1.47 (s, 3), 1.85–2.52 [m, 5 ($COCH_3$, s, 2.20)], 2.70 (q, 2, $J_{4,3}$ = 6 Hz), 3.70 (s, 3), and 6.52–7.02 (m, 3).

Anal. Calcd for $C_{15}H_{16}Br_2O_4$: C, 42.88; H, 3.84; Br, 38.04. Found: C, 42.90; H, 3.85; Br, 37.94.

5-Bromo-2-methyl-2-(2′-acetoxy-5′-methoxyphenyl)cyclopentanone (13c). A mixture of $CuBr_2$ (3.13 g, 0.014 mol) and 2-methyl-2-(2′-acetoxy-5′-methoxyphenyl)cyclopentanone (**13a**, 2.10 g, 0.008 mol), in ethyl acetate (25 ml) and $CHCl_3$ (25 ml) was heated to reflux. The dark green reaction mixture changed to light amber and the black cupric bromide was converted to white cuprous bromide; after 1.5 h the reaction mixture was cooled and filtered, and the copper salt washed with ethyl acetate (100 ml). The filtrate was concentrated in vacuo (below 50 °C) and the residue was purified by column chromatography (silica gel, methylene chloride) to yield 1.73 g (72%) of 5-bromo-2-(2′-acetoxy-5′-methoxyphenyl)cyclopentanone (**13c** as a mixture of α-bromo epimers): IR 1786 cm^{-1}; UV max 230 nm (ϵ 3770) and 282 (1330); NMR δ 1.37 (minor epimer, s), 3.77 (s, 3), 4.17–4.73 (m, 1), and 6.00–7.04 (m, 3); mass spectrum *m/e* (rel abundance) M^+ + 2 342 (14), M^+ 340 (14), 300 (96), 298 (100), 219 (16), 218 (9), 201 (13), 191 (11), 177 (21), 175 (9), 165 (9), 164 (76), 162 (15), 161 (11), 149 (14), 91 (18), 55 (77), and 43 (56).

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Registry No.—**2**, 61076-47-9; **3a**, 61076-48-0; **3b**, 61076-49-1; **4**, 61076-50-4; **5**, 61076-51-5; **6**, 61076-52-6; **7a**, 61076-53-7; **7b**, 61076-54-8; **8a**, 61076-55-9; **8b′** isomer 1, 61076-56-0; **8b′** isomer 2, 61117-29-1; **9**, 61076-57-1; **10**, 61076-58-2; **10′**, 61076-59-3; **11**, 61104-49-2; **12b**, 61076-60-6; **13a**, 61076-61-7; **13b**, 61076-62-8; **13c** isomer, 61076-63-9; **13c** isomer 2, 61076-64-0; *p*-methoxyphenol, 150-76-5; 3-chlorocyclopentene, 96-40-2; benzyl bromide, 100-39-0; 2-(2′-benzylcyclopentyl)-4-methoxyphenol, 61076-65-1; *m*-chloroperbenzoic acid, 937-14-4; methyl iodide, 74-88-4; phenyltrimethylammonium perbromide, 4207-56-1; 5,5-dibromo-2-methyl-2-(2′-benzyloxy-5′-methoxyphenyl)cyclopentanone, 61076-66-2; dimethylsulfonium methylide, 6814-64-8; *cis*-5-bromo-3a-hydroxy-7-methoxy-8b-methyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran, 61076-67-3; acetyl chloride, 75-36-5; acetic anhydride, 108-24-7.

References and Notes

(1) (a) C. Tamm, *Fortschr. Chem. Org. Naturst.*, **31**, 64 (1974); (b) J. R. Bamburg, *Clin. Toxicol.*, **5**, 495 (1972); (c) J. V. Rodricks and R. M. Eppley in "Mycotoxins", I. F. H. Purchase, Ed., American Elsevier, New York, N.Y., 1974, Chapter 9; (d) E. B. Smalley and F. M. Strong, *ibid.*, Chapter 10; (e) A. Z. Joffe, *ibid.*, Chapter 12; (f) D. M. Saito and K. Ohtsubo, *ibid.*, Chapter 12; (g) S. Mizuno, *Biochim. Biophys. Acta*, **383**, 207 (1975); (h) K. E. Smith, M. Cannon, and E. Cundliffe, *FEBS Lett.*, **50**, 8 (1975); (i) A. Jimenez and D. Vasquez, *Eur. J. Biochem.*, **54**, 483 (1975).

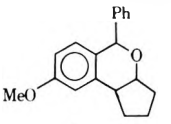
(2) (a) E. W. Colvin, S. Malcherko, and R. A. Raphael, *J. Chem. Soc., Perkin Trans. 1*, 1989 (1973); (b) Y. Fujimoto, S. Yokuru, T. Nakamura, T. Morikawa, and T. Tatsuno, *Tetrahedron Lett.*, 2523 (1974).

(3) N. Masuoka and T. Kamikawa, *Tetrahedron Lett.*, 1691 (1976).

(4) The numbering system adopted for the A-ring aromatic trichothecanes is that which is used for the naturally occurring trichothecanes.

(5) A mixture of KOH, *t*-BuOH, Me_2SO, and H_2O (apparently equivalent to the mixture of KO-*t*-Bu, Me_2SO, and water) was very much inferior in effecting the isomerization of **3b** to **4**.

(6) The isolation of 2-(2′-benzylcyclopentenyl)-4-methoxyphenol from the hydrogenolysis of **5** rules out a structural alternative to **5**, namely i. Formation of i could have been rationalized on the basis of an initial Wittig rearrangement followed by an intramolecular cyclization.



i

(7) (a) W. K. Anderson and T. Veysoglu, *J. Org. Chem.*, **38**, 2267 (1973). (b) Epoxidation of **4** with *m*-chloroperbenzoic acid in dichloromethane over solid sodium carbonate gave <50% of **6** along with a variety of epoxide ring-opened products. Similar poor results were obtained with trifluoroperacetic acid and peracetic acid oxidation of **4**.

(8) P. L. Stotter and K. A. Hill, *J. Org. Chem.*, **38**, 2576 (1973); H. O. House, M. Gall, and H. D. Olmstead, *ibid.*, **36**, 2361 (1971).

(9) R. B. Moffet, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p. 238.

(10) IR spectra of the DBN used in this experiment showed that it contained water.

Reaction of Trimethylsilyloxy-1,3-dienes with Lead(IV) Benzoate

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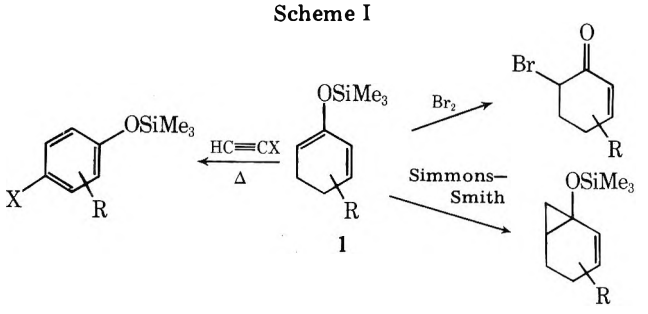
General methods for the synthesis of trimethylsilyloxy-1,3-dienes **1** are discussed. The reaction of **1** with lead(IV) benzoate (LTB), followed by treatment with fluoride ion, affords a variety of keto benzoates **4**. The structural features present in **1** determine the type of **4** which results. 1-Trimethylsilyloxy-1,3-cyclohexadienes **1d** and **1e** as well as alicyclic 2-trimethylsilyloxy-1,3-dienes **1f** and **1g** afford products arising from the 1,2 addition of benzoate to **1**. A carbonium ion mechanism involving neighboring group participation by a benzoyloxy group accounts for the 3,4-addition products occurring from the LTB reaction with **1a–c**.

Substituted trimethylsilyloxy-1,3-cyclohexadienes, **1**, react regiospecifically at the 1,2 double bond with electrophiles such as bromine[1] and the Simmons–Smith reagent.[2] Further, the diene system in **1** has proven to be a suitable component for [4 + 2] cycloaddition reactions, again with high regiospecificity.[3] Scheme I summarizes these findings.

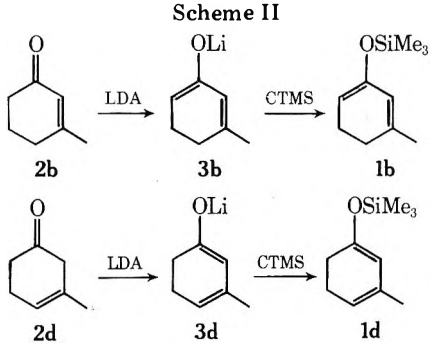
Scheme I



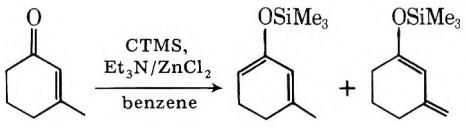
Since trimethylsilyl enol ethers react cleanly with lead(IV) benzoate to afford, upon workup, α-benzoyloxycarbonyl compounds,[4] a study was undertaken to extend this reaction with **1**. Previous to the current work, the lead(IV) carboxylate oxidation of conjugated dienes had been noted in but a few cases.[5]

In general, **1** was prepared by treatment of the appropriate ketone, **2**, with strong base (LDA), followed by quenching of the dienolate **3** with chlorotrimethylsilane (CTMS).[2a,6] Owing to the kinetic selectivity of the reactions employed, it was possible to obtain both 1- and 2-trimethylsilyloxy substitution of the 1,3-diene system. The use of β,γ-unsaturated **2** provides the former and α,β-unsaturated **2** affords the latter. This synthetic flexibility for the generation of **1** is outlined in Scheme II, and compounds **1** thus prepared are noted in Table I.

Scheme II



Production of **1** employing weak base proved to be a less general entry into the system. Standard methods for this mode of generation of **1** (CTMS/Et_3N/DMF[2a,6,7] or CTMS/Et_3N/$ZnCl_2$/benzene[3b]) afford inseparable mixtures of isomers when the enone **2** is substituted in the 3 position. Hence, the reaction of **2b** with CTMS/Et_3N in benzene, as shown in eq 1, results

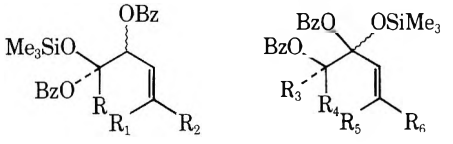


(1)

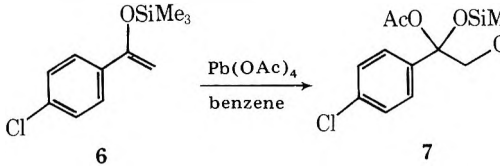
in a mixture containing both **1b** and **1h**.[2a,8] This method, however, has been used successfully in one instance to prepare the heteroannular silyloxy diene of testosterone,[2] in a specific manner. As noted in eq 1, no product of type **1d** was observed.[9] Indeed, if no 3 substitution is present, this procedure is the most convenient for the preparation of dienes of type **1a**, when large quantities are required. Compound **1g** was conveniently prepared via this route.

Mixing of **1** with an equimolar quantity of lead(IV) benzoate[10] (LTB) in methylene chloride resulted in the immediate precipitation of lead(II) benzoate. Filtration and subsequent treatment of the filtrate with triethylammonium fluoride[11] afforded the benzoates, **4**, as summarized in Table II.

The appearance of **4d–g** seems to be very much in line with literature analogy concerning the reaction of **1** with electrophiles.[1,2] Attempts to isolate intermediate dibenzoates of type **5**, by omission of the fluoride treatment, proved unsuccessful.



It had been anticipated that **5** would be present based on the known reaction of **6** with lead(IV) acetate to give **7** (eq 2).[4b]

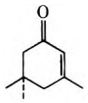
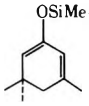
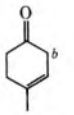
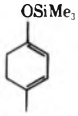
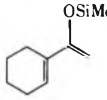
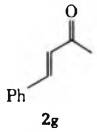
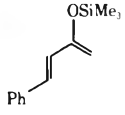


(2)

Previous attempts to isolate dibenzoates analogous to **7** from the reaction of **6** with LTB have established that the loss of trimethylsilyl benzoate is very facile,[4,12] so that failure to isolate **5** is not unexpected. Circumstantial evidence for the existence of **5** was obtained from the reaction of **1d** with LTB. In this case, the NMR spectrum of the reaction mixture, after anhydrous workup, revealed that only **4d** and trimethylsilyl benzoate were present.[13] Thus, it appears quite likely that intermediates of type **5** are involved in the production of **4d–g**.

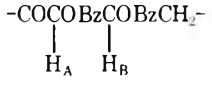
Identification of the structures for **4a** and **4a'** was forthcoming from a consideration of both NMR data and the

Table I. Physical Data for Alkyl Substituted Trimethylsilyloxy Dienes, 1[a,b]

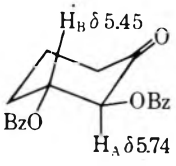
2[f]	1[g] (% yield of isolated 1)	Bp, °C (mm) [lit. bp, °C]	n^{25}D	IR (neat), cm^{-1}	NMR (CCl_4/ Me_4Si), δ	MS (15 eV), m/e (rel abundance); m*, metastable peak
 2a	 1a (80)	56–58 (6.0) [33–37 (0.01)[c]]	1.4590	1648, 1590	0.23 (s, 9 H) 2.12 (m, 4 H) 4.75 (m, 1, H) 5.70 (m, 2 H)	169 (15), 168 (M^+, 100), 167 (14), 153 (12), 75 (32), 73 (17); m* 166, 139
 2b	 1b (75)	51–53 (1.0)	1.4626	1660, 1610	0.14 (s, 9 H) 1.77 (s, 3 H) 1.9–2.2 (m, 4 H) 4.55 (m, 1 H) 5.35 (m, 1 H)	183 (17), 182 (M^+, 100), 181 (13), 167 (35), 73 (15); m* 153.5
 2c	 1c (81)	54–57 (1.5) [45–47 (0.05)[d]]	1.4509	1660, 1610	0.13 (s, 9 H) 1.97 (s, 6 H) 1.74 (s, 3 H) 1.89 (s, 2 H) 4.38 (broad s, 1 H) 5.34 (m, 1 H)	210 (M^+, 28), 196 (17), 195 (100), 179 (9); m* 164
 2d	 1d (77)	76–82 (10.0)	1.4630	1660, 1600	0.23 (s, 9 H) 1.67 (s, 3 H) 2.10 (broad s, 4 H) 4.91 (s, 1 H) 5.04 (broad s, 1 H)	183 (18), 182 (M^+, 181 (12), 167 (26), 165 (10), 73 (17); m* 180, 153.5, 136.5
 2e	 1e (77)	81–83 (9.7)	1.4633	1657, 1607	0.12 (s, 9 H) 1.70 (s, 3 H) 2.14 (m, 4 H) 4.88 (d, 1 H, J = 6 Hz) 5.40 (d, 1 H, J = 6 Hz)	183 (16), 182 (M^+, 100), 181 (12), 167 167 (30), 165 (8), 151 (7), 75 (7), 73 (22); m* 180, 153.5, 136.5
 2f	 1f (69)	85–89 (4.8) [111–115 (18)[e]]	1.4707	1640, 1590	0.18 (s, 9 H) 1.4–1.75 (m, 4 H) 1.9–2.3 (m, 4 H) 4.05 (s, 1 H) 4.22 (s, 1 H) 6.10 (m, 1 H)	197 (17), 196 (M^+ 100), 181 (88), 167 (27), 154 (32). 147 (20), 75 (24); m* 167, 121
 2g	 1g (80)	88.5–90.5 (0.25)	1.5480	1635, 1590	0.27 (s, 9 H) 4.35 (broad s, 2 H) 6.60 (AB, 2 H, J = 16 Hz) 7.06–7.46 (m, 5 H)	219 (21), 218 (M^+ 100), 217 (28), 203 (49), 127 (11), 103 (10), 75 (32), 73 (21); m* 216, 188.5

[a] Satisfactory analytical data (±0.3/ for C and H) were reported for all new compounds listed in the table. [b] See Experimental Section for specific procedures. [c] Value cited in ref 2a. [d] Value cited in ref 1. [e] Value cited in ref 3d. [f] Registry no. are, respectively, 930-68-7, 1193-18-6, 78-59-1, 31883-98-4, 5259-65-4, 932-66-1, 1896-62-4. [g] Registry no. are, respectively, 54781-19-0, 54781-27-0, 54781-28-1, 61140-45-2, 61140-46-3, 57781-35-0, 61140-47-4.

chemical behavior of the two compounds. Decoupling experiments[14] indicated the presence of a

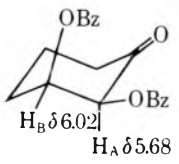


unit in both compounds. The chemical shift of H_B in **4a** compared to that of H_B in **4a'** (δ 5.45 vs. 6.02) is indicative of an axial H_B in the former and an equatorial H_B in the latter.[15] The observed coupling constants of J_{AB} = 11 Hz in **4a** and J_{AB} = 4 Hz in **4a'** lead to the conclusion that in **4a**, H_B and H_A are



J_{AB} = 11 Hz

4a



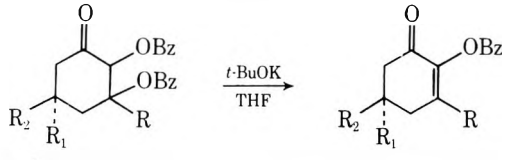
J_{AB} = 4 Hz

4a'

trans diaxial, while in **4a'**, H_B is equatorial and H_A is axial.[15] Therefore, structure **4a** is assigned to the trans dibenzoate and **4a'** to the cis dibenzoate.

Treatment of a 50:50 mixture of **4a** and **4a'** with potassium *tert*-butoxide in THF resulted in the production of **8a**, a known compound.[16] This result is consistent with the NMR data given above and the same procedure was also successful for transforming **4b** and **4c** into **8b** and **8c**, respectively (Scheme III). Although the formation of **8b** and **8c** serves to

Scheme III

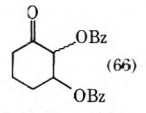
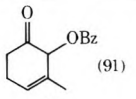
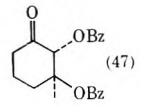
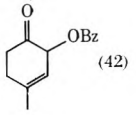
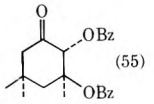
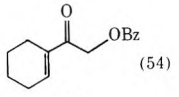
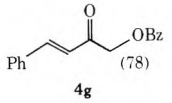


4a/4a', R, R_1, R_2 = H
b, R = Me; R_1, R_2 = H
c, R, R_1, R_2 = Me

8a, R, R_1, R_2 = H (80%)
b, R = Me; R_1, R_2 = H (65%)
c, R, R_1, R_2 = Me (63%)

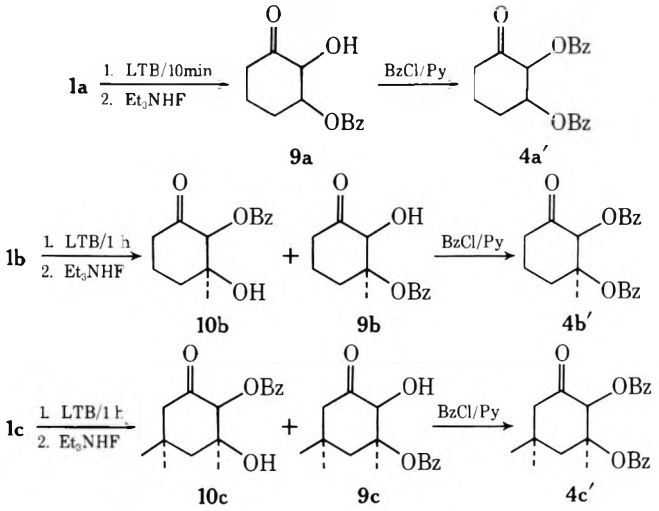
show the gross structural features of **4b** and **4c**, further evidence was deemed necessary to prove the trans stereochemistry indicated for these compounds (cf. Table II). This evidence was obtained from the reactions of **1a–c** with LTB using abbreviated reaction times. Whereas **4a** and **4a'** were produced

Table II. Reaction of 1 with Lead(IV) Benzoate Followed by Fluoride Treatment

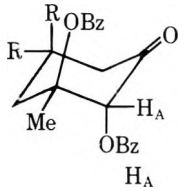
1	4 (% yield of isolated 4)	1	4 (% yield of isolated 4)
1a	 (66) 4a/4a′: trans/cis 50/50	1d	 (91) 4d
1b	 (47) 4b	1e	 (42) 4e
1c	 (55) 4c	1f	 (54) 4f
		1g	 (78) 4g

after ca. 2 h contact time with LTB, and **4b** and **4c** arose after ca. 20 h, contact time of ca. 10 min with **1a** and 1 h with 1b and **1c** led to the results summarized in Scheme IV.

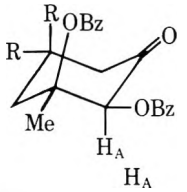
Scheme IV



The spectral properties of **9a**[14] are consistent with the proposed structure, and further proof of the cis stereochemistry in **9a** was obtained by transforming it into the previously characterized **4a′** via treatment with benzoyl chloride in pyridine. Analogous behavior by **1b** and **1c** led to the production of **9b** and **9c**, respectively, which, in turn, were transformed into the corresponding cis dibenzoates **4b′** and **4c′**. Comparison of the NMR spectra of **4b** and **4c** with those of **4b′** and **4c′** strengthens the proposed assignments. In each pair of isomers the proton designated H_A in the cis isomer



4b, R = H δ 6.06
c, R = Me δ 5.87

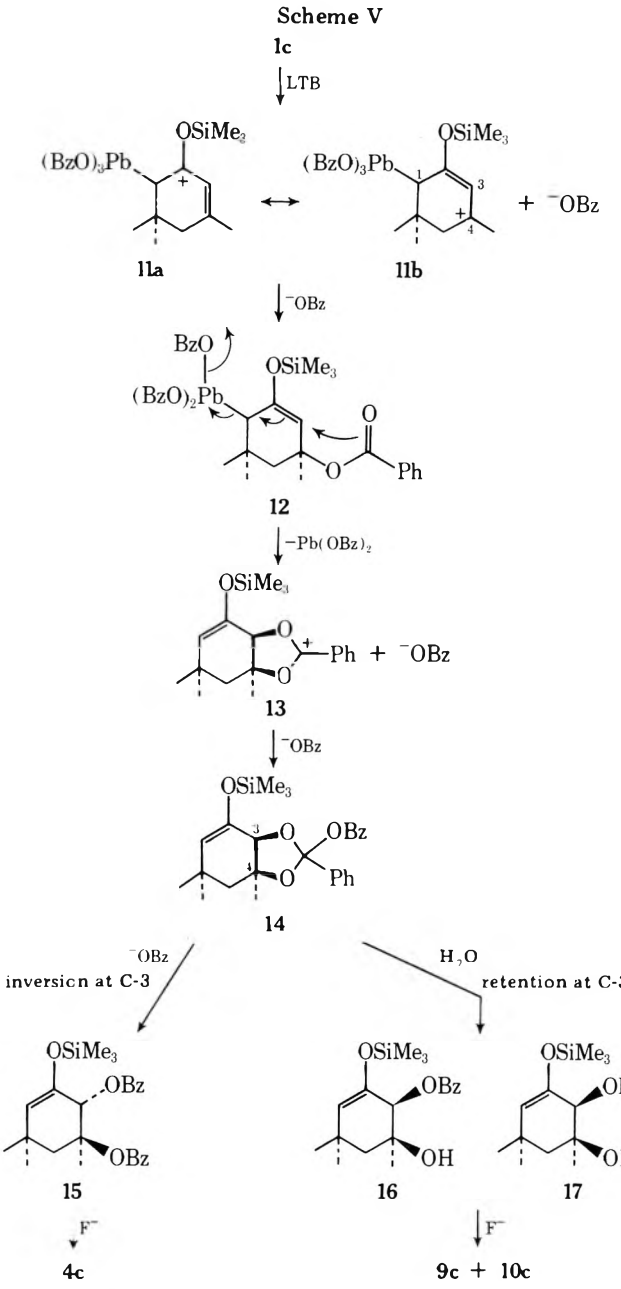


4b′, R = H δ 5.32
c′, R = Me δ 5.34

occurs at higher field, as would be expected for the structures as described.

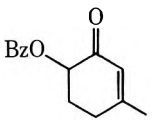
A mechanistic interpretation for the above findings is presented in Scheme V using, as an example, the transformations of **1c**.

Scheme V



Attack of LTB at the electron-rich 1,2 double bond of **1c** affords **11**, analogous to the normal behavior shown by **1** toward electrophiles. Trapping of **11** by benzoate addition at C-4 via either an intra- or intermolecular process gives **12**. Expulsion of lead(II) benzoate from **12** with neighboring group participation leads to **14** via the carbocation **13**. Prolonged time in the reaction medium (dry solvent) then affords **15** with inversion most likely occurring at the allylic center, C-3. Subsequent reaction of **15** with fluoride ion at silicon gives the trans dibenzoate **4c**. On the other hand, short reaction time prevents the inversion mechanism from functioning and **14** is intercepted by water,[17] thereby affording **16** and **17**. These, in turn, are transformed into **9c** and **10c** upon fluoride treatment. The proposed mechanism finds direct analogy from that postulated for the reaction of cyclopentadiene with LTB.[5a] It is of interest that the data presented in ref 5b do not pre-

clude 1,4-addition leading eventually to 3,4-substituted products as indicated in the present work. A small amount of **18** (ca. 5%) isolated from the reaction of **1b** with LTB implies



18

that, at least in this case, **11** can be channeled into a 1,2-addition product to a small extent. This compound could arise either from 1,2-addition or from 1,4-addition followed by loss of benzoic acid to afford **18**.[18]

Appearance of both **4a** and **4a'** from the reaction of **1a** with LTB may argue for decomposition of **14** via both an inversion process at C-3 to produce **4a** and a concerted six-center rearrangement with retention at C-3 leading to **4a'**. The latter process would be severely restricted in **14** generated from **1b** and **1c** owing to nonbonded interactions caused by the C-4 methyl substituent. In fact, no cis dibenzoates (i.e., **4b'** and **4c'**) were discovered in the reactions of **1b** and **1c** with LTB. The possibility of equilibration between **4a** and **4a'** was ruled out when pure **4a'** remained unchanged after treatment with Et_3NHF for 10 h.

Direct proof for the intermediacy of **15** and **16** was obtained by isolation of the two compounds. Treatment of **1c** with LTB for 20 h followed by aqueous workup gave **15**, which was quantitatively converted into **4c** upon treatment with Et_3NHF. Reaction of **1c** with LTB for 10 min followed by addition of methanol gave **16**. When **16** was treated with Et_3NHF, **10c** was obtained as the sole reaction product.

Experimental Section

General. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton magnetic resonance (NMR) spectra were recorded at 60 MHz on a Varian Anaspect EM 360 spectrometer using tetramethylsilane as internal standard. Infrared spectra were obtained on a Perkin-Elmer 621 grating infrared spectrometer. Low-resolution mass spectral data was obtained with an Hitachi Perkin-Elmer RMU-6E instrument (15 eV) equipped with a direct inlet system. Elemental microanalyses were determined employing a Perkin-Elmer 240 Elemental Analyzer. Indices of refraction were measured on a Bausch and Lomb Abbe-type refractometer utilizing the D line of sodium at a temperature of 25 °C. For all column chromatography, silica gel Woelm 0.032–0.063 mm (ICN Pharmaceuticals GmbH & Co.) was used. TLC analyses utilized silica gel 7GF (Baker). The lead tetrabenzoate was prepared from commercial lead tetraacetate (90%, Alfa-Ventron) by the method of Hurd and Austin,[10] mp 186–187 °C dec. The triethylammonium fluoride was obtained as a white solid (very hygroscopic) by the procedure of Hunig.[11] Anhydrous magnesium sulfate was employed as drying agent.

Preparation of Trimethylsilyloxy Dienes 1a–f. The procedure employed was essentially the same as that outlined by Conia for the synthesis of **1a–c**.[2a] To 100 ml of tetrahydrofuran[19] (distilled from $LiAlH_4$) at −18 °C (ice/methanol) was added 5.0 g (49.4 mmol) of diisopropylamine followed by 20.6 ml of *n*-butyllithium (2.45 M in hexane, Alfa-Ventron). After 10 min, 45 mmol of enone **2** was added over 10 min. For the preparation of **1d, 1e,** and **1f** the enone was dissolved in ca. 10 ml of tetrahydrofuran and the reaction run at −78 °C. After 10 min, 12 ml (94 mmol) of chlorotrimethylsilane was added rapidly. The reaction mixture was warmed to room temperature and allowed to stir for 2 h and then diluted with 200 ml of pentane. Extraction with 150 ml of cold (ca. 5 °C) aqueous sodium bicarbonate, drying, filtration, and removal of solvent in vacuo gave crude **1a–f**. Distillation at reduced pressure afforded pure **1a–f**. The physical data for **1a–f** are presented in Table I.

***trans*-1-Phenyl-3-trimethylsilyloxybutadiene (1g).** The method of Danishefsky was applied.[3b] To a suspension of 0.20 g (1.5 mmol) of zinc chloride in 15 ml of triethylamine was added 7.3 g (50 mmol) of **2g** in 15 ml of dry benzene followed by 13 ml (100 mmol) of chlorotrimethylsilane. After stirring for 15 h at 40 °C, the reaction mixture was cooled and added to 100 ml of ether. Filtration and removal of solvent in vacuo gave crude **1g**. Distillation at reduced pressure afforded pure **1g**. The physical constants are listed in Table I.

3-Methyl-3-cyclohexen-1-one (2d). To 600 ml of ammonia (distilled from sodium) was added 250 ml of ether (distilled from $LiAlH_4$) containing 24.4 g (200 mmol) of *m*-methylanisole. Then 250 ml of *tert*-buttyl alcohol (distilled from calcium hydride) was added rapidly with stirring, and 7.0 g (1.0 mol) of lithium (in small pieces) was added in portions over 20 min. This mixture was allowed to stir under ammonia reflux for 2 h. The excess Li/NH_3 was then destroyed with solid ammonium chloride and the ammonia allowed to evaporate under an atmosphere of nitrogen (fume hood). Pentane (500 ml) was added and gentle heat was applied (water bath) to drive off any residual ammonia. The reaction mixture was then partitioned between an additional 300 ml of pentane and 500 ml of water. The pentane layer was then extracted with water until no change in volume of the water extract was noted. The pentane layer was dried and concentrated in vacuo. The crude enol ether was dissolved in 400 ml of methanol/water (3:1) containing 800 mg of oxalic acid dihydrate and allowed to stir for ca. 1 h. This mixture was diluted with 500 ml of water and extracted several times with methylene chloride. The methylene chloride extracts were combined and washed once with 100 ml of water, dried, filtered, and concentrated in vacuo. Distillation at reduced pressure gave 13.3 g (60%) of **2d,** bp 65.5–66.0 °C (13 mm) [lit.[20] bp 61–62 °C (14 mm)].

4-Methyl-3-cyclohexen-1-one (2e). The method cited for the preparation of **2d** was applied to *p*-methylanisole and afforded 14.3 g (65%) of pure **2e,** bp 68–70 °C (14 mm) [lit.[21] bp 74 °C (17 mm)].

Lead Tetrabenzoate Oxidations. General Procedure. To a solution of 1.52 g (2.2 mmol) of LTB in 40 ml of methylene chloride (stored over calcium chloride) cooled to −18 °C (ice/methanol) was added a solution of 2.0 mmol of trimethylsilyloxydiene **1** in 2 ml of methylene chloride (nitrogen atmosphere). After 5 min at −18 °C, the reaction mixture was stirred for 1 h at room temperature (deviations from the standard 1 h are noted in the specific instances below). The slurry was then filtered to remove lead dibenzoate and the filtrate treated with triethylammonium fluoride (725 mg, 6.0 mmol). After stirring under nitrogen for 2–8 h, the reaction mixture was diluted with 60 ml of methylene chloride and washed successively with 20 ml of 50% aqueous sodium carbonate, 20 ml of 1.5 M hydrochloric acid, and 20 ml of aqueous sodium bicarbonate. The organic solution was dried and filtered. Removal of solvent in vacuo yielded crude products which were purified by the specific methods noted below.

***trans*-2,3-Dibenzoyloxycyclohexanone (4a) and *cis*-2,3-Dibenzoyloxycyclohexanone (4a').** From 2.0 mmol of **1a** was obtained LTB reaction time) 443 mg (66%) of trans/cis **4a/4a'**. Separation was effected by fractional crystallization from ether/petroleum ether (bp 30–60 °C).

Compound 4a (32% isolated): mp 128–129 °C; IR (KBr) 1740, 1720, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.8 (m, 6 H), 5.22–5.85 (complex m, 2 H, CH_BOBzCH_AOBz) (irradiation in the methylene region reduces the multiplet to an AB pattern, δ, 5.74, d (sharp) and 5.45 d (broad), J = 11 Hz), 7.2–8.2 (m, 10 H); mass spectrum *m/e* (rel abundance) 338 (M^+, <1), 310 (7), 216 (16), 122 (19), 106 (10), 105 (100).

Anal. Calcd for $C_{20}H_{18}O_5$: C, 71.00; H, 5.36. Found: C, 70.86; H, 5.33.

Compound 4a' (29% isolated): mp 130–131 °C; IR (KBr) 1745, 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.8–2.8 (m, 6 H), 5.68 (d, 1 H, J = 4 Hz), 6.02 (m, 1 H) (irradiation at ca. δ 6.02 collapses the δ 5.68 signal into a singlet, while irradiation in the methylene region collapses the δ 6.02 signal into a doublet, J = 4 Hz), 7.2–8.2 (m, 10 H); mass spectrum *m/e* (rel abundance) 338 (M^+, 3), 310 (12), 216 (12), 122 (16), 106 (10), 105 (100).

Anal. Calcd for $C_{20}H_{18}O_5$: C, 71.00; H, 5.36. Found: C, 71.26; H, 5.34.

Attempted Equilibration of 4a/4a'. A solution of 120 mg (0.36 mmol) of **4a'** in 25 ml of methylene chloride containing 0.25 g (2 mmol) of triethylammonium fluoride was stirred under nitrogen for 10 h. NMR analysis of the crude product after normal LTB reaction workup conditions revealed the presence of only **4a'**.

***trans*-2,3-Dibenzoyloxy-3-methylcyclohexanone (4b) and 6-Benzoyloxy-3-methyl-2-cyclohexen-1-one (18).** From 2.0 mmol of **1b** was obtained (20 h LTB reaction time), after column chromatography ($CHCl_3$), 218 mg (31%) of **4b** and 25 mg (5%) of **18**. With methylene chloride distilled form P_2O_5, 47% of **4b** was obtained.

Compound 4b: mp 117.5–118.0 °C; IR (KBr) 1740 (sh), 1720 (sh), 1702 cm^{-1}; NMR ($CDCl_3$) δ 1.73 (s, 3 H), 1.8–3.0 (m, 6 H), 6.06 (s, 1 H), 7.1–8.3 (m, 10 H); mass spectrum *m/e* (rel abundance) 252 (M^+, <1), 324 (7), 230 (65), 122 (13), 106 (10), 105 (100), 98 (11).

Anal. Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.76; H, 5.72.

Compound 18: mp 92–93 °C; IR (KBr) 1722, 1678, 1630 cm^{-1}; NMR ($CDCl_3$) δ 2.0 (s, 3 H), 2.2–2.6 (m, 4 H), 5.49 (d of d, 1 H, J = 7, 11 Hz), 5.93 (broad s, 1 H), 7.2–8.2 (m, 5 H); mass spectrum *m/e* (rel abundance) 230 (M^+, 6), , 125 (43), 109 (13), 108 (100), 105 (43), 97 (13), 82 (37).

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.85; H, 6.06.

***trans*-2,3-Dibenzoyloxy-3,5,5-trimethylcyclohexanone (4c).** From 2.0 mmol of **1c** was obtained (20 h reaction time), after column chromatography ($CHCl_3$), 417 mg (55%) of **4c,** as a colorless oil: IR (neat) 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.07 (s, 3 H), 1.10 (s, 3 H), 1.86 (s, 3 H), 2.47 (s, 2 H), 2.48 (d, 1 H, J = 14 Hz), 2.79 (d, 1 H, J = 14 Hz), 5.87 (s, 1 H), 7.2–8.2 (m, 10 H); mass spectrum *m/e* (rel abundance) 258 (27), 122 (16), 106 (10), 105 (100).

Anal. Calcd for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found: C, 72.90; H, 6.17.

2-Benzoyloxy-3-methyl-3-cyclohexen-1-one (4d). From 2.0 mmol of **1d** was obtained, after removal of solvent, 418 mg (91%) of essentially pure **4d** (NMR, TLC). Column chromatography ($CHCl_3$) afforded an analytical sample: IR (neat) 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.80 (s, 3 H), 2.35–2.73 (m, 4 H), 5.77 (broad s, 1 H), 5.90 (broad s, 1 H), 7.2–8.2 (m, 5 H); mass spectrum *m/e* (rel abundance) 230 (M^+, 6), 108 (12), 106 (10), 105 (100), metastable 47.

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.28; H, 6.11.

2-Benzoyloxy-4-methyl-3-cyclohexen-1-one (4e). From 2.0 mmol of **1e** was obtained 194 mg (42%) of **4e:** mp 68.5–69.5 °C (ether/petroleum ether); IR (KBr) 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.81 (s, 3 H), 2.3–2.7 (m, 4 H), 5.50 (m, 1 H), 5.92 (m, 1 H), 7.2–8.2 (m, 5 H); mass spectrum *m/e* (rel abundance) 230 (M^+, 5), 122 (14), 108 (26), 106 (10), 105 (100).

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.87; H, 6.12.

1-Benzoyloxy-3,4-tetramethylene-3-buten-2-one (4f). From 2.0 mmol of **1f** was obtained 262 mg (54%) of **4f:** mp 97.5–98.5 °C (ether/petroleum ether); IR (KBr) 1720, 1675, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.5–1.8 (m, 4 H), 2.00–2.42 (m, 4 H), 5.27 (s, 2 H), 6.93 (m, 1 H), 7.2–8.2 (m, 5 H); mass spectrum *m/e* (rel abundance) 244 (M^+, 5), 122 (15), 110 (10), 109 (100), 105 (50), 81 (10), metastable 60.

Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.69; H, 6.54.

***trans*-1-Benzoyloxy-4-phenyl-3-buten-2-one (4g).** From 2.0 mmol of **1g** was obtained 413 mg (78%) of **4g:** mp 120–121 °C (ether); IR (KBr) 1725, 1700 cm^{-1}; NMR ($CDCl_3$) δ 5.17 (s, 2 H), 6.83 (d, 1 H, J = 16 Hz). 7.20 (d, 1 H, J = 16 Hz), 7.2–8.2 (m, 10 H); mass spectrum *m/e* (rel abundance) 266 (M^+, 9), 144 (28), 127 (10), 126 (100), 105 (48).

Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.58; H, 5.58.

***cis*-3-Benzoyloxy-2-hydroxycyclohexanone (9a).** From 2.0 mmol of **1a** was obtained (solvent not dried and LTB reaction time of 10 min) 70 mg (15%) of **9a,** by fractional crystallization (ether/petroleum ether): mp 120.5–121.5 °C; IR (KBr) 3480, 1710 cm^{-1} (broad); NMR ($CDCl_3$) δ 1.75–2.76 (m, 6 H), 3.79 (d, 1 H, J = 4 Hz, –OH), 4.38 (d of d, 1 H, J = 4, 4 Hz), 5.76 (m, 1 H), 7.2–8.2 (m, 5 H); mass spectrum *m/e* (rel abundance) 234 (M^+, 18), 206 (10), 122 (72), 112 (70), 106 (10), 105 (100), 83 (15), 82 (10).

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.65; H, 5.98.

***cis*-2-Benzoyloxy-3-hydroxy-3-methylcyclohexanone (10b) and *cis*-3-Benzoyloxy-2-hydroxy-3-methylcyclohexanone (9b).** From 2.0 mmol of **1b** was obtained 70 mg (14%) of **10b** and 60 mg (12%) of **9b,** by fractional crystallization (ether/petroleum ether) from the crude reaction mixture.

Compound 10b: mp 147–148 °C; IR (KBr) 3510, 1730, 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.38 (s, 3 H), 1.8–2.7 (m, ? H), 5.34 (s, 1 H), 7.2–8.2 (m, 5 H); mass spectrum *m/e* (rel abundance) 248 (M^+, 8), 126 (30), 106 (10), 105 (100).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.60; H, 6.41.

Compound 9b: mp 112–113 °C; IR (KBr) 3460, 1720 (sh), 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.83 (s, 3 H), 1.6–3.2 (m, 6 H), 3.83 (d, 1 H, J = 12 Hz, –OH), 4.06 (d, 1 H, J = 12 Hz), 7.2–8.2 (m, 5 H); mass spectrum *m/e* (rel abundance) 248 (M^+, 11), 126 (78), 122 (36), 106 (10), 105 (100), 98 (13).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.45; H, 6.51.

***cis*-2-Benzoyloxy-3-hydroxy-3,5,5-trimethylcyclohexanone (10c) and *cis*-3-Benzoyloxy-2-hydroxy-3,5,5-trimethylcyclohexanone (9c).** From 2.0 mmol of **1c** was obtained 100 mg (18%) of **10c** and 90 mg (16%) of **9c,** by fractional crystallization from the crude reaction mixture (ether/petroleum ether).

Compound 10c: mp 164.5–165.0 °C; IR (KBr), 3510, 1733. 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (s, 3 H), 1.07 (s, 3 H), 1.33 (s, 3 H), 1.93 (s, 2 H), 2.25 (d, 1 H, J = 14 Hz), 2.55 (d, 1 H, J = 14 Hz), 2.44 (s, 1 H, –OH). 5.33 (s, 1 H), 7.2–8.2 (m, 5 H); mass spectrum *m/e* (rel abundance) 276 (M^+, 11), 155 (9), 154 (69), 106 (10), 105 (100), metastable 86.5.

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.73; H, 7.47.

Compound 9c: mp 133–134 °C; IR (Kbr) 3460, 1725 (sh). 1715 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (s, 3 H), 1.12 (s, 3 H), 1.85 (s, 3 H), 1.85 (d, 1 H, J = 16 Hz), 2.44 (s, 2 H), 3.06 (d, 1 H, J = 16 Hz), 3.82 (d, 1 H, J = 7 Hz, –OH), 4.10 (d, 1 H, J = 7 Hz), 7.2–8.2 (m, 5 H); mass spectrum *m/e* (rel abundance) 276 (M^+, 3), 155 (10), 154 (100), 139 (11).

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, /.30. Found: C, 69.76; H, 7.49.

2-Benzoyloxy-2-cyclohexen-1-one (8a). To 200 ml of dry diethyl ether (containing 10% tetrahydrofuran) was added 300 mg (0.89 mmol) of **4a/4a'** followed by 200 mg (1.8 mmol) of potassium *tert*-butoxide. After refluxing overnight, under nitrogen, the reaction mixture was diluted with 100 ml of ether and washed with water (2 × 20 ml). After drying and removal of solvent in vacuo, crystallization from ether/hexane yielded 150 mg (80%) of **8a:** mp 89–90 °C (lit.[16] mp 86.5–87.0 °C); IR (KBr) 1728, 1683 cm^{-1}; NMR ($CDCl_3$) δ 1.8–2.8 (m, 6 H), 6.67 (t, 1 H, J = 4 Hz), 7.2–8.2 (m, 5 H); mass spectrum *m/e* (rel abundance) 216 (M^+, 12), 106 (10), 105 (100), metastable 51.

Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.60. Found: C, 72.47; H, 5.52.

2-Benzoyloxy-3-methyl-2-cyclohexen-1-one (8b). To 20 ml of dry tetrahydrofuran, through which dry nitrogen had been bubbled for ca. 30 min, was added 119 mg (0.34 mmol) of **4b** followed by 56 mg (0.50 mmol) of potassium *tert*-butoxide. After stirring under nitrogen for 1.5 h at room temperature, the reaction mixture was diluted with 100 ml of ether and washed with water (3 × 20 ml). The water washings were combined and extracted with 30 ml of ether. The ether extracts were combined, dried, and concentrated in vacuo affording 51 mg (65%) of **8b** as a colorless oil. Molecular distillation at 120 °C (0.2 mm) gave an analytical sample: IR (neat) 1733, 1680, 1650 cm^{-1} (sh); NMR ($CDCl_3$) δ 2.0–2.8 (m, 6 H), 1.93 (s, 3 H), 7.2–8.2 (m, 5 H); mass spectrum *m/e* (rel abundance) 230 (M^+, 62), 106 (10), 105 (100).

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.89; H, 6.37.

2-Benzoyloxy-3,5,5-trimethyl-2-cyclohexen-1-one (8c). To 20 ml of dry tetrahydrofuran, through which dry nitrogen had been bubbled for ca. 30 min, was added 183 mg (0.48 mmol) of **4c** followed by 112 mg (1.0 mmol) of potassium *tert*-butoxide. After 30 min of stirring at room temperature under nitrogen, the reaction mixture was diluted with 100 ml of ether and washed with water (3 × 20 ml). The water extracts were combined and extracted with 30 ml of ether. The ether extracts were combined, dried, filtered, and concentrated in vacuo. Crystallization of the crude product from ether/hexane afforded 78 mg (63%) of **8c:** mp 70.0–70.5 °C; IR (KBr) 1730, 1682, 1660 cm^{-1}; NMR)cdcl$_3$) δ 1.13 (s, 6 H), 1.86 (s, 3 H), 2.42 (s, 4 H), 7.4–8.3 (m, 5 H); mass spectrum *m/e* (rel abundance) 258 (M^+, 33), 106 (10), 105 (100).

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.66; H, 7.07.

Benzoylation of Alcohols 9a, 9b, and 9c. General Procedure. To 40–60 mg of alcohol was added 2 ml of pyridine and 40 mg of benzoyl chloride. After 30 h at room temperature, the reaction mixture was added to 15 ml of 10% hydrochloric acid. Extraction with ether (3 × 20 ml), washing with 15 ml of 1.5 N hydrochloric acid and 15 ml of aqueous sodium bicarbonate, drying, and removal of solvent in vacuo gave crude dibenzoate. Column chromatography or crystallization provided pure dibenzoate.

***cis*-2,3-Dibenzoyloxy-3-methylcyclohexanone (4b').** From 45 mg (0.18 mmol) of **9b** was obtained, after column chromatography (hexane/ethyl acetate, 8:1), 51 mg (81%) of **4b'** as a colorless oil: IR (neat) 1720, 1710 cm^{-1} (sh); NMR ($CDCl_3$) δ 1.7–2.7 (m, 5 H), 1.85 (s, 3 H), 3.0–3.4 (m, 1 H), 5.32 (s, 1 H), 7.2–8.2 (m, 10 H); mass spectrum *m/e* (rel abundance) 352 (M^+, 1), 324 (8), 230 (55), 122 (15), 106 (10), 105 (100).

Anal. Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.65; H, 5.89.

***cis*-2,3-Dibenzoyloxycyclohexanone (4a').** From 50 mg (0.21 mmol) of **9a** was obtained, after crystallization from ether, 42 mg (59%) of **4a',** mp 130–131 °C. The **4a'** so produced was spectrally identical (IR, NMR) with the **4a'** obtained from LTB treatment of

1a, and further, no depression of melting point (mmp 130–131 °C) was noted upon admixture.

***cis*-2,3-Dibenzoyloxy-3,5,5-trimethylcyclohexanone (4c').** From 37.5 mg (0.136 mmol) of **9c** (50 mg of a 75:25 mixture of **9c** and **10c**) was obtained, after column chromatography ($CHCl_3$), 20 mg (53%) of **4c'**: mp 125–126 °C (ether/petroleum ether); IR (KBr) 1740, 1715 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (s, 2 H), 1.15 (s, 3 H), 1.85 (s, 3 H), 1.95 (d, 1 H, J = 14 Hz), 2.33 (d, 1 H, j = 14 Hz), 2.62 (d, 1 H, J = 14 Hz), 3.22 (d, 1 H, J = 14 Hz), 5.34 (s, 1 H), 7.8–8.2 (m, 10 H); mass spectrum *m/e* (rel abundance) 380 (M^+, 2), 352 (10), 322 (12), 258 (55), 154 (22), 126 (10), 122 (10), 106 (10), 105 (100), metastables 175, 42.5.

Anal. Calcd for $C_{23}H_{24}O_5$: C, ?2.61; H, 6.36. Found: C, 72.61; H, 6.42.

***trans*-5,6-Dibenzoyloxy-3,3,5-trimethyl-1-trimethylsilyloxycyclohexene (15).** To 1.52 g (2.2 mmol) of LTB in 40 ml of dry methylene chloride (distilled from P_2O_5) was added 420 mg (2.0 mmol) of **1c** at room temperature. After 20 h of stirring under nitrogen, the reaction mixture was diluted with 50 ml of methylene chloride and washed with 50 ml of water and 50 ml of aqueous sodium bicarbonate. Drying and removal of solvent in vacuo gave crude **15**. Column chromatography (hexane/ethyl acetate, 7:1) gave 140 mg (15%) (hydrolysis noted upon chromatography) of analytically pure **15**: IR (neat) 1720, 1675 cm^{-1}; NMR ($CDCl_3$) δ 0.16 (s, 9 H), 1.07 (s, 3 H), 1.18 (s, 3 H), 1.72 (s, 3 H), 1.98 (d, 1 H, J = 14 Hz), 2.58 (d, 1 H, J = 14 Hz), 5.00 (s, 1 H), 5.91 (s, 1 H), 7.2–8.2 (m, 10 H); mass spectrum *m/e* (rel abundance) 330 (10), 315 (5), 235 (12), 234 (19), 219 (31), 211 (14), 137 (17), 136 (31), 110 (10), 109 (100), 105 (21), metastable 301.

Anal. Calcd for $C_{26}H_{32}O_5Si$: C, 68.99; H, 7.13. Found: C, 69.15; H, 7.22.

Hydrolysis of 15. To 120 mg (0.27 mmol) of **15** in 15 ml of methylene chloride was added 0.25 g (2 mmol) of triethylammonium fluoride. After 1 h at room temperature, the reaction mixture was diluted with 30 ml of methylene chloride, washed with 20 ml of aqueous sodium bicarbonate, dried, and concentrated in vacuo, affording 100 mg (99%) of **4c**, spectrally (IR, NMR) identical with that obtained via LTB treatment of **1c**.

***cis*-6-Benzoyloxy-5-hydroxy-3,3,5-trimethyl-1-trimethylsilyloxycyclohexene (16).** To 1.52 g (2.2 mmol) of LTB in 40 ml of methylene chloride was added 420 mg (2.0 mmol) of **1c** at −18 °C. After 10 min of stirring at room temperature under nitrogen, 2.5 ml of anhydrous methanol was added and the mixture allowed to stir overnight. The reaction mixture was then diluted with 50 ml of methylene chloride and washed with 50 ml of water followed by 50 ml of aqueous sodium bicarbonate. Drying and removal of solvent in vacuo gave crude **16** as a colorless oil. Column chromatography (hexane/ethyl acetate, 7:1) afforded 313 mg (45%) of pure **16**: IR (neat) 3500, 1720, 1665 cm^{-1}; NMR ($CDCl_3$) δ 0.10 (s, 9 H), 1.08 (s, 3 H), 1.22 (s, 3 H), 1.33 (s, 3 H), 1.53 (d, 1 H, J = 14 Hz), 1.90 (d, 1 H, J = 14 Hz), 2.22 (s, 1 H, –OH), 4.86 (s, 1 H), 5.43 (s, 1 H), 7.2–8.2 (m, 5 H); mass spectrum *m/e* (rel abundance) 348 (M^+, 5), 333 (7), 330 (41), 315 (40), 226 (14), 225 (22), 216 (38), 169 (100), 105 (74), metastables 301, 154, 147, 128, 35.

Anal. Calcd for $C_{19}H_{28}O_4Si$: C, 65.48; H, 8.10. Found: C, 65.53; H, 8.23.

Hydrolysis of 16. The same proceduce cited for the hydrolysis of **15** was applied to **16**, affording a 64% yield of pure **10c**. The **10c** so produced had a melting point of 164–165 °C which showed no depression upon admixture (mmp 164–165 °C) with **10c** produced from LTB treatment of **1c**. Further, the spectral properties (IR and NMR) of the **10c** produced by both methods were identical.

Acknowledgments. The authors gratefully acknowledge the Research Council of the University of Idaho for partial support of this work. The authors would also like to acknowledge Mr. D. Harsch for obtaining the C and H analyses reported.

Registry No.—**4a**, 61140-48-5; **4a'**, 61140-49-6; **4b**, 61140-50-9; **4b'**, 61140-51-0; **4c**, 61140-52-1; **4c'**, 61140-53-2; **4d**, 61140-54-3; **4e**, 61140-55-4; **4f**, 61140-56-5; **4g**, 61140-57-6; **8a**, 4884-82-6; **8b**, 61140-58-7; **8c**, 61140-59-8; **9a**, 61140-60-1; **9b**, 61140-61-2; **9c**, 61140-62-3; **10b**, 61140-63-4; **10c**, 61140-64-5; **15**, 61140-65-6; **16**, 61140-66-7; **18**, 61140-67-8; *m*-methylanisole, 100-84-5; *p*-methylanisole, 104-93-8; benzoyl chloride, 98-88-4; lead(IV) benzoate, 7717-48-8.

References and Notes

(1) L. Blanco, P. Amice, and J. M. Conia, *Synthesis*, 194 (1976).
(2) (a) C. Girard and J. M. Conia, *Tetrahedron Lett.*, 3327 (1974); (b) J. M. Conia and C. Girard, *ibid.*, 2767 (1973).
(3) (a) G. M. Rubottom and D. S. Krueger, *Tetrahedron Lett.*, in press; (b) S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **95**, 7807 (1974); (c) M. E. Jung and C. A. McCombs, *Tetrahedron Lett.*, 2935 (1976); (d) C. Symmes, Jr., and L. D. Quinn, *J. Org. Chem.*, **41**, 238 (1976).
(4) (a) G. M. Rubottom, J. M. Gruber, and G. M. Mong, *J. Org. Chem.*, **41**, 1673 (1976); (b) G. M. Rubottom, J. M. Gruber, and K. Kincaid, *Synth. Commun.*, **6**, 59 (1976).
(5) (a) F. V. Brutcher, Jr., and F. J. Vara, *J. Am. Chem. Soc.*, **78**, 5695 (1956); (b) R. Criegee, *Justus Liebigs Ann. Chem.*, **481**, 263 (1930); (c) R. Criegee and H. Beuker, *ibid.*, **541**, 218 (1939).
(6) This method is an extention of the method developed by H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
(7) C. Girard, P. Amice, J. P. Barnier, and J. M. Conia, *Tetrahedron Lett.*, 3329 (1974).
(8) NMR analysis of distilled product.
(9) This phenomenon seems to be general; see ref 1, 3a, 3b, and 7.
(10) C. D. Hurd and P. R. Austin, *J. Am. Chem. Soc.*, **53**, 1543 (1931).
(11) S. Hunig and G. Wehner, *Synthesis*, 180 (1975).
(12) This reaction is analogous to the loss of acetic anhydride to afford α-acetoxy ketones when enol acetates are treated with lead(IV) acetate: (a) R. Criegee, *Angew. Chem.*, **70**, 173 (1958); (b) W. S. Johnson, B. Gastambide, and R. Pappo, *J. Am. Chem. Soc.*, **79**, 1991 (1957).
(13) Comparison of the spectra of pure **4d** and pure trimethylsilyl benzoate with that of the reaction mixture indicated that no other components were present.
(14) See Experimental Section.
(15) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, Chapter 3.
(16) F. G. Bordwell and K. M. Wellman, *J. Org. Chem.*, **31**, 351 (1966).
(17) The water present in trace amounts in the reaction solvent, as well as the water used in workup procedures, effects the transformation described.
(18) Products analogous to **17** have been observed when enones are treated with lead(IV) acetate (LTA); see (a) W. Oppolzer and K. K. Muhalanabis, *Tetrahedron Lett.*, 3411 (1975); (b) T. Sone, S. Terashima, and S. Yamada, *Synthesis*, 725 (1974); (c) Y. Fukuyama and T. Tokoroyama, *Tetrahedron Lett.*, 4869 (1973); (d) L. F. Fieser and M. A. Romero, *J. Am. Chem. Soc.*, **75**, 4716 (1953); (e) S. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **27**, 948 (1944). This transformation apparently involves the intermediacy of enol derivatives of LTA; see (f) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, p 537; (g) R. Criegee in "Oxidations in Organic Chemistry", Part A, K. B. Wiberg, Ed., Academic Press, New York, N.Y., 1965, p 277.
(19) Subsequent to the preparation of most of compounds **1**, it was discovered that DME affords **1** of higher purity upon distillation. Therefore, the use of this solvent is to be recommended.
(20) R. M. Acheson, *J. Chem. Soc.*, 4232 (1956).
(21) A. J. Birch, *J. Chem. Soc.*, 593 (1946).

Addition of *tert*-Butyl Hypohalites to 3,4-Dihydro-2*H*-pyran and Its 2-Alkoxy and 2-Alkoxy-6-methyl Derivatives in Hydroxylic Solvents[1]

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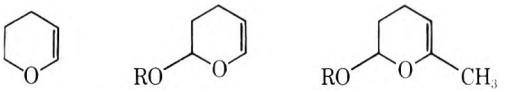
Electrophilic addition of *tert*-butyl hypochlorite and hypobromite to 3,4-dihydro-2*H*-pyran (**1**) in alcohol and organic acid solvents yielded cis/trans mixtures of the 1,2-addition products 3-halo-2-alkoxytetrahydropyrans (**4a–k**). Addition of these reagents to 2-alkoxy-3,4-dihydro-2*H*-pyrans (**2a** and **2b**) in the corresponding alcohol solvents yielded cis/trans mixtures of the 1,2-addition products 3-halo-2,6-dialkoxytetrahydropyrans (**5a–d**). In contrast, additions to 2-alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans (**3a** and **3b**) yielded cis/trans mixtures of the 1,2-addition products 3-halo-2,6-dialkoxy-2-methyltetrahydropyrans (**6a–d**) and the 1,4-addition products 3-halo-6,6-dialkoxy-2-hexanone (**7a–d**). The important influence of the axial 2-alkoxy group and the 6-methyl group on the course of these reactions is discussed, as well as the stereochemistry of the products and the mechanisms of the reactions.

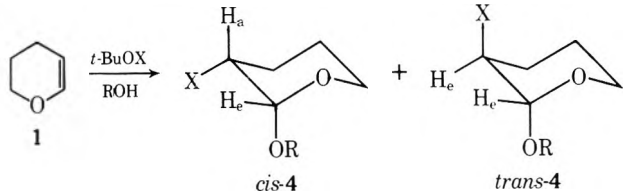
A comparison of electrophilic additions to 2-alkoxy-3,4-dihydro-2*H*-pyrans (**2**) vis-à-vis the unsubstituted compound 3,4-dihydro-2*H*-pyran (**1**) indicates the instrumental role of the 2-alkoxy group on the outcome of the reaction.[3] In addition, it is becoming apparent that the introduction of an alkyl group at the C-6 position, such as with the 2-alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans (**3**), substantially enhances the reactivity of the dihydropyran ring system.[3a,b,4] We now wish to describe the electrophilic addition of *tert*-butyl hypohalite reagents[5] to these dihydropyrans **1–3** in hydroxylic



1 **2** **3**

solvents that demonstrates the unique synergistic effect of the 6-alkyl group coupled with the 2-alkoxy group on the course of the reaction.

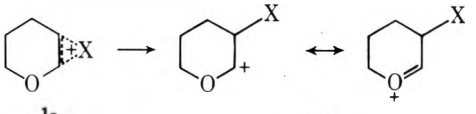
Addition of *tert*-butyl hypohalites (hypochlorite and hypobromite) to the unsubstituted 3,4-dihydro-2*H*-pyran (**1**) in hydroxylic solvents (alcohols and acids) yielded cis/trans mixtures of the corresponding 1,2-addition products **4a–k** (see



1 *cis*-**4** *trans*-**4**

Table I). Analysis of the product mixtures by 100-MHz NMR spectroscopy confirmed the configurations (and predominant conformations) for the cis- and trans-addition products. The alkoxy group at the newly developed anomeric center (C-2) is axial as is predicted by the anomeric effect[6,7] and confirmed by NMR analysis since the vicinal coupling constants are small (J_{ea} = 3.0–3.5 Hz, cis isomer, and J_{ee} = 3.2–4.9 Hz, trans isomer). The cis and trans isomers are resolvable on GLC analysis and distinguishable by NMR analysis[6,8] since the equatorial anomeric proton (C-2) for the cis diastereomer is always shifted further downfield than that of the trans and its coupling constant is usually smaller ($J_{ea} < J_{ee}$).

The mechanism of 1,2-additions of *tert*-butyl hypohalites to olefins is known to involve the electrophilic addition of X^+ to the double bond followed by the nucleophilic solvent.[5c,9] Halogen addition to 3,4-dihydro-2*H*-pyran has been discussed previously in detail,[6,8c] so we will only reiterate here that all products, especially when X is Cl, are derived principally from the oxocarbonium ion **1b.**



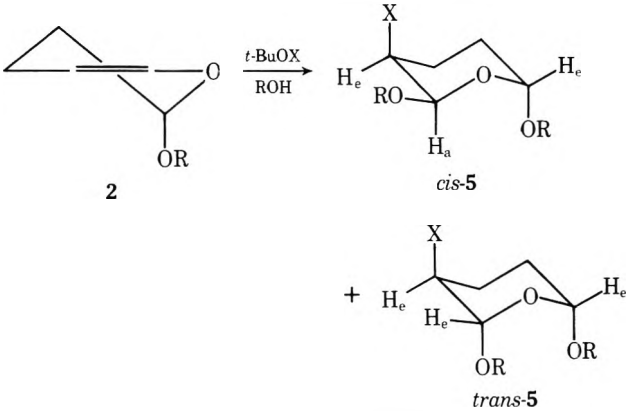
1a **1b**

For all of the alkyl alcohol solvents the ratio of cis:trans products was ca. 15:85 with *tert*-butyl hypochlorite. However, with the other nucleophilic solvents such as benzyl alcohol and the organic acids, which perhaps can more effectively stabilize the oxocarbonium ion **1b,** there was an appreciable increase in the formation of the cis isomer. Attempts to use other protic solvents such as alkylamines failed, presumably because of the competing N-chlorination of the solvent.[10]

Addition of *tert*-butyl hypobromite to 3,4-dihydro-2*H*-pyran (**1**) yielded similar results[11] as those with *tert*-butyl hypochlorite; however, it is necessary to add traces of a free-radical inhibitor such as dihydroquinone to minimize competing side reactions. There is also more trans isomer formed with *tert*-butyl hypobromite, reflecting the increased importance of the intermediate halonium ion **1a** when X is Br.

Although the addition of *tert*-butyl hypohalites to acyclic vinyl ethers in alcohol solvents has been evaluated,[5c,9c] we have found using the conditions described in the Experimental Section marked improvements in the isolated yields.[12]

Addition of the *tert*-butyl hypohalites to the 2-alkoxy-3,4-dihydro-2*H*-pyrans **2a** and **2b** in the respective alcohol solvent yielded the corresponding 1,2-addition products **5a–d**



2 *cis*-**5** *trans*-**5**

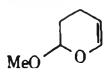
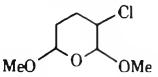
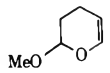
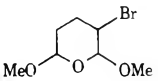
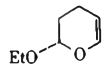
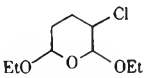
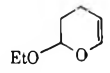
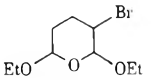
(see Table II). In these examples, however, the diastereomeric mixture is ca. a 50:50 cis:trans mixture with *tert*-butyl hypo-

Table I. *tert*-Butyl Hypohalite Addition to 3,4-Dihydro-2*H*-pyran

Hypohalite/solvent	Product	Cis/trans[a]	Isolated yield,[b] %
t-BuOCl/CH_3OH[c]	3-Chloro-2-methoxytetrahydropyran (4a)	15/85	72
t-BuOCl/C_2H_5OH[c]	3-Chloro-2-ethoxytetrahydropyran (4b)	15/85	67
t-BuOCl/*n*-C_3H_7OH[c]	3-Chloro-2-*n*-propoxytetrahydropyran (4c)	15/85	64
t-BuOCl/*i*-C_3H_7OH[c]	3-Chloro-2-isopropoxytetrahydropyran (4d)	15/85	50
t-BuOCl/*n*-C_4H_9OH[c]	3-Chloro-2-*n*-butoxytetrahydropyran (4e)	15/85	69
t-BuOBr/*n*-C_4H_9OH[d]	3-Bromo-2-*n*-butoxytetrahydropyran (4f)	10/90	75[i]
t-BuOCl/*sec*-C_4H_9OH[e]	3-Chloro-2-*sec*-butoxytetrahydropyran (4g)	20/80	60
t-BuOCl/*t*-C_4H_9OH[f]	3-Chloro-2-*tert*-butoxytetrahydropyran (4h)	15/85	35
t-BuOCl/$C_6H_5CH_2OH$[e]	3-Chloro-2-benzyloxytetrahydropyran (4i)	33/67	70
t-BuOCl/CH_3CO_2H[g]	3-Chloro-2-acetoxytetrahydropyran (4j)	32/68	85
t-BuOCl/$C_2H_5CO_2H$[h]	3-Chloro-2-propionoxytetrahydropyran (4k)	45/55	80

[a] Determined by GLC analysis and confirmed by 100-MHz NMR spectroscopy. [b] Isolated yield after distillation. [c] Reaction conditions are described in Experimental Section for 4e. [d] Reaction conditions are described in Experimental Section for 4f. [e] Same reaction conditions as 4e except temperature (0 °C). [f] Same reaction conditions as 4e except temperature (20 °C). [g] Reaction conditions are described in Experimental Section for 4j. [h] Same reaction conditions as 4j except temperature (0 °C). [i] Isolated yield after column chromatography.

Table II. *tert*-Butyl Hypohalite Addition to 2-Alkoxy-3,4-dihydro-2*H*-pyrans

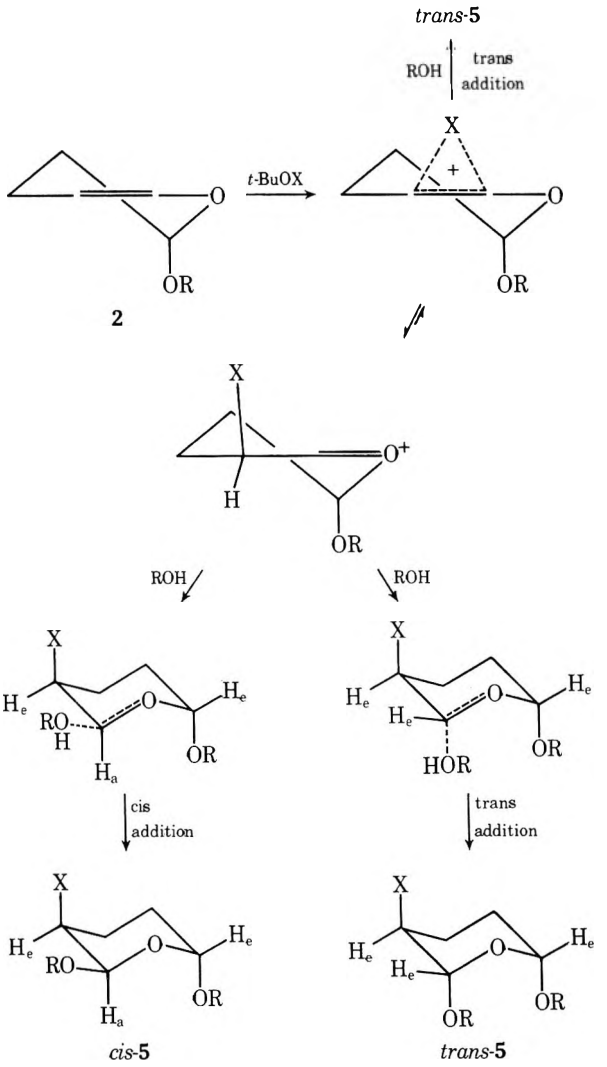
Dihydropyran	Hypohalite/solvent	Product	Isolated yield,[a] %
 2a	*t*-BuOCl/MeOH[b]	 5a	61
 2a	*t*-BuOBr/MeOH[c]	 5b	63
 2b	*t*-BuOCl/EtOH[b]	 5c	76
 2b	*t*-BuOBr/EtOH[c]	 5d	74

[a] Isolated by column chromatography. [b] Reaction conditions are described in the Experimental Section for 5a. [c] Reaction conditions are described in the Experimental Section for 5b.

chlorite and slightly less (ca. 40:60) with *tert*-butyl hypobromite. The starting 2-alkoxy-3,4-dihydro-2*H*-pyrans (**2a** and **2b**, as well as **3a** and **3b**), as has been previously reported,[13] exist predominantly (greater than 90%, NMR analysis) in the conformation where the C-2 anomeric proton is equatorial (alkoxy group is axial). This stereochemistry about the original anomeric center, as indicated by 100-MHz NMR spectroscopy, was preserved in the products (now C-6 in *cis*- and *trans*-**5**). The signal for the anomeric C-6 proton in each diastereomer was a superficial triplet ($J_{ea} \approx J_{ee}$ = 3.0–4.0 Hz) as expected for an equatorial proton at this position. The stereochemistry about the newly developed anomeric center at C-2, however, was clearly two diastereomers with the two different proton signals as doublets with small coupling constants (5.7–7.0 Hz) indicating an axial proton in one and equatorial proton in the other coupled to the adjacent equatorial (J_{ae} and J_{ee}) proton at C-3. These results are depicted in Scheme I.

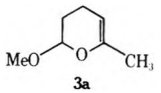
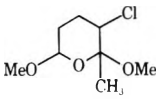
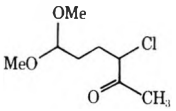
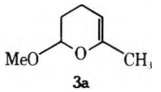
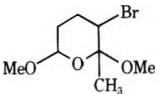
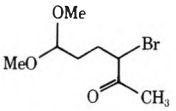
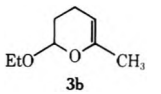
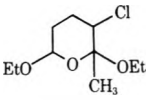
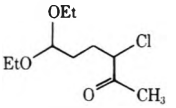
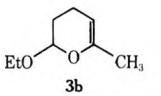
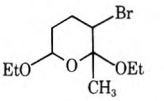
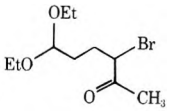
The presence of the bulky axial alkoxy group at C-2 would result in a preferential trans addition of the halogen to the dihydropyran **2**. Subsequent addition of alcohol to the intermediate oxocarbonium ion would be affected by the axial alkoxy group as well. Trans-diaxial addition creates a rather serious 1,3 interaction between alkoxy groups thus making the cis-equatorial addition much more competitive. With *tert*-butyl hypobromite some trans product would arise from the intermediate bromonium ion.

Scheme I

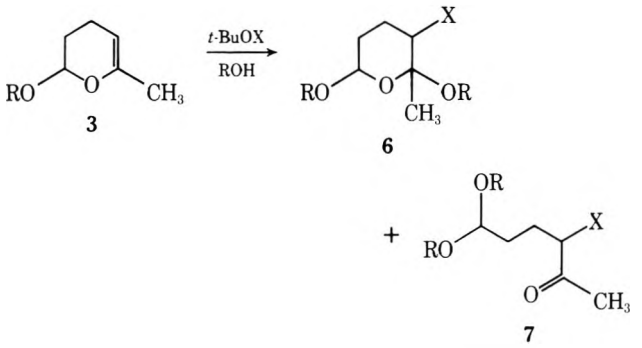


In contrast to these results with 3,4-dihydro-2*H*-pyran (**1**) and its 2-alkoxy derivatives **2a** and **2b**, addition of the *tert*-butyl hypohalites in alcohol to the 2-alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans **3a** and **3b** yielded mixtures of products **6a–d** and **7a–d** that are derived from 1,2- and 1,4-addition, respectively (see Table III). The 1,2-addition products **6a–d** were mixtures of cis and trans isomers. The ratio and the

Table III. *tert*-Butyl Hypohalite Addition to 2-Alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans

Dihydropyran	Hypohalite/solvent	Products: 1,2-Addition (yield)[a]	Products: 1,4-Addition (yield)[a]
 **3a**	*t*-BuOCl/MeOH[b]	 **6a** (39%)	 **7a** (40%)
 **3a**	*t*-BuOBr/MeOH[c]	 **6b** (62%)	 **7b** (21%)
 **3b**	*t*-BuOCl/EtOH[b]	 **6c** (36%)	 **7c** (53%)
 **3b**	*t*-BuOBr/EtOH[c]	 **6d** (47%)	 **7d** (39%)

[a] Isolated by column chromatography. [b] Reaction conditions are described in the Experimental Section for the addition of *tert*-butyl hypochlorite to 2-methoxy-6-methyl-3,4-dihydro-2*H*-pyran (3a). [c] Reaction conditions are described in the Experimental Section for the addition of *tert*-butyl hypobromite to 2-methoxy-6-methyl-3,4-dihydro-2*H*-pyran (3a).



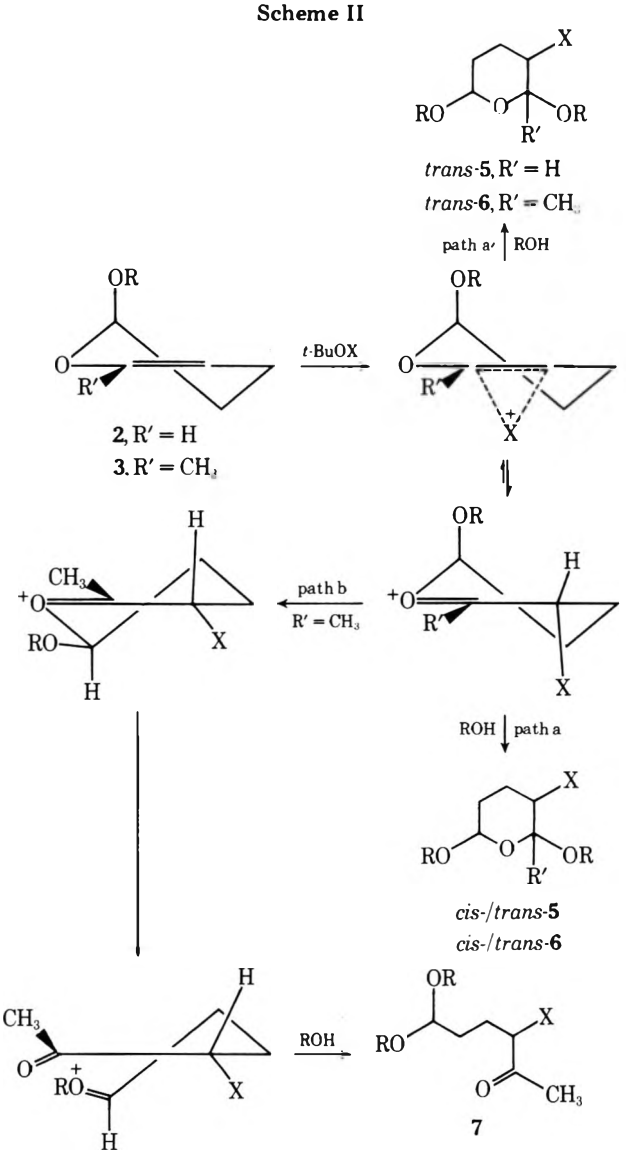
stereochemistry of the products were similar to those obtained with the 2-alkoxy-3,4-dihydro-2*H*-pyrans (**2a** and **2b**). That is, the stereochemistry about the original anomeric center was preserved and the cis and trans isomers are diastereomers at the new anomeric center.

The ratio of the 1,2- vs. 1,4-addition products in the reaction of *tert*-butyl hypochlorite with dihydropyrans **3a** and **3b** was found not to be significantly affected by the temperature of the reaction. For example, with **3a** the ratio of 1,2- to 1,4-addition was ca. 50:50 for −50, −15, and 20 °C. For **3b**, this ratio was the same at the low temperature and ca. 40:60 at −15 and 20 °C. At temperatures below −15 °C competing side products derived from free-radical reactions[5d,9d] became important. One such product that was characterized was the allylic chlorinated product 2-alkoxy-6-chloromethyl-3,4-dihydro-2*H*-pyran (**8**).[14]

The addition of *tert*-butyl hypobromite to these pyrans **3a** and **3b**, however, had to be performed at −60 °C to prevent serious competition from free-radical reactions. Even the use of free-radical inhibitors or exclusion of light did not effectively suppress these reactions. The ratio of 1,2- vs. 1,4-additions at this temperature was ca. 75:25 for **3a** and 60:40 for **3b**.

We interpret these results and the differences between the addition of *tert*-butyl hypohalites to 2-alkoxy-3,4-dihydro-2*H*-pyrans (**2a** and **2b**) and 2-alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans (**3a** and **3b**) in the following manner (see Scheme II). As was discussed earlier, the presence of the bulky axial

Scheme II



alkoxy group at the anomeric carbon would result in the preferential formation of the trans halonium ion and subsequently the oxocarbonium ion. When X is chlorine, path a, via the oxocarbonium ion, would dominate as the route to cis and trans 1,2-addition products. When X is bromine, path a′, via the bromonium ion intermediate, would become competitive yielding trans 1,2-addition products. However, when R′ is a group that can stabilize the oxocarbonium ion intermediate, such as methyl, a new course (path b) becomes important. This stabilization evidently allows time for the conformational change that enables participation (synchronous assistance)[15] of the 2-alkoxy group that ultimately yields the 1,4-addition product **7**.

Although the sine qua non for the formation of the 1,4-addition product from these dihydropyran systems is the presence of the 6-methyl group, it is the unique synergistic effect of the 6-alkyl group coupled with the 2-alkoxy group that diverts the normal course of the addition reaction.

Experimental Section[13]

General Comments. The 2-alkoxy-3,4-dihydro-2*H*-pyrans (**2a, 2b**) and the 2-alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans (**3a, 3b**) were prepared by a method previously described.[17] Pyran **1** and **2b** are available from Aldrich Chemical Co. The *tert*-butyl hypochlorite and *tert*-butyl hypobromite were prepared,[5a,c] dried over $CaCl_2$, and stored in the dark below 0 °C until use. All solvents were reagent grade. All reactions were performed in dry glassware under a static nitrogen atmosphere. The reaction temperature was monitored with an internal thermometer. Gas chromatography (GLC) analyses were performed on 120 × 0.4 cm (i.d.) glass columns packed with 5% Carbowax 20M supported on 60–80 mesh Chromosorb W (AW, DMCS). Distillations were accomplished with short-path or Kügelrohr apparatus; all boiling points are uncorrected. Column chromatography was performed on 60–100 mesh Floridin magnesium silicate (Florisil) columns by eluting with petroleum ether and petroleum ether–Et_2O. The assigned structure of each product (or mixture) was consistent with the spectral data and composition analysis (±0.4% for C, H, X). The latter (**4a–k, 5a–d, 6a–d, 7a–d**) were submitted to the Editor. Significant data on all new compounds are included in the Experimental Section. A representative selection of experiments is described to illustrate these reactions.

3-Chloro-2-*n*-butoxytetrahydropyran (4e). To a stirred and cooled (−50 °C) solution of 3,4-dihydro-2*H*-pyran (**1**, 2.91 g, 34.6 mmol) in 1-butanol (35 ml) was slowly added (ca. 10 min) 3.80 g (35.0 mmol) of *tert*-butyl hypochlorite, during which time the exothermic reaction caused the temperature to rise to −40 °C. After 5 min the cooling bath (dry ice–ethanol) was removed and the reaction mixture allowed to warm to 0 °C and then partitioned between ice–water and petroleum ether. The organic layer was separated, washed with water (four times) and brine, and then dried ($MgSO_4$). Removal of solvent in vacuo afforded 6.37 g of a pale yellow oil. Analysis (GLC) of the oil indicated a 15:85 mixture of cis and trans isomers of **4e** that after distillation (bp 103–108 °C, 14 mm) and column chromatography afforded 4.51 g (66%) of **4e** as a colorless oil: bp 106–108 °C (14 mm); IR (film) 2970, 2940, 2880, 1460, 1440, 1200, 1135, 1095, 1070, 1030, 870, 730 cm^{-1}; NMR (100 MHz, CCl_4) δ 4.62 (0.17 H, d, J = 3.2 Hz, equatorial anomeric proton, cis isomer), 4.46 (0.83 H, d, J = 3.5 Hz, equatorial anomeric proton, trans isomer), 4.02–3.25 (5 H, m), 2.45–1.20 (8 H, complex m), 0.93 (3 H, perturbed t, J = 7.0 Hz); mass spectrum m/e (rel intensity) 194 (M^+, 4), 192 (M^+, 13), 138 (3), 136 (8), 121 (13), 119 (31), 92 (12), 90 (40), 83 (15), 64 (9), 62 (32), 57 (57), 55 (100), 41 (71), 29 (76).

3-Bromo-2-*n*-butoxytetrahydropyran (4f). To a stirred and cooled (−50 °C) solution of 3,4-dihydro-2*H*-pyran (**1**, 316 mg, 3.76 mmol) and dihydroquinone (1–2 mg, free-radical inhibitor) in 1-butanol (7 ml) was slowly added (ca. 10 min) 688 mg (4.50 mmol) of *tert*-butyl hypobromite, during which time the exothermic reaction caused the temperature to rise to −40 °C. After 5 min, the cooling bath (dry ice–ethanol) was removed and the reaction mixture allowed to warm to 0 °C. Normal workup, as described above for **4e**, afforded a pale orange oil. Analysis (GLC) of the orange oil indicated a 10:90 mixture of cis and trans isomers of **4f** that after column chromatography afforded 715 mg (77%) of **4f** as a colorless oil: IR (film) 2970, 2940, 2880, 1460, 1440, 1200, 1130, 1090, 1070, 1025, 870, 730 cm^{-1}; NMR (100 MHz, CCl_4) δ 4.60 (0.10 H, d, J = 3.1 Hz, equatorial anomeric proton, cis isomer), 4.49 (0.90 H, d, J = 3.6 Hz, equatorial anomeric proton, trans isomer), 4.07–3.25 (5 H, complex m), 2.55–2.15 (1 H, m), 2.15–1.70 (2 H, m), 1.70–1.20 (5 H, m), 0.93 (3 H, perturbed t, J = 7.0 Hz); mass spectrum m/e (rel intensity) 238 (M^+, 29), 236 (M^+, 30), 182 (5), 180 (5), 165 (48), 163 (49), 136 (65), 134 (67), 108 (26), 106 (26), 83 (16), 73 (17), 57 (57), 55 (100), 41 (33), 29 (34).

3-Chloro-2-acetoxytetrahydropyran (4j). To a stirred and cooled (10 °C) solution of 3,4-dihydro-2*H*-pyran (**1**, 3.36 g, 40.0 mmol) in glacial acetic acid (35 ml) was slowly added (ca. 10 min) 4.44 g (40.9 mmol) of *tert*-butyl hypochlorite, during which time the exothermic reaction caused the temperature to rise to 20 °C. After 10 min the reaction mixture was worked up, as described above for **4e**, and afforded 6.59 g of a pale yellow oil. Analysis (GLC) of the oil indicated a 32:68 mixture of cis and trans isomers of **4j** that after distillation afforded 5.95 g (85%) of **4j** as a colorless oil: bp 126–128 °C (18 mm); IR (film) 2970, 2900, 2870, 1755, 1440, 1230, 1140, 1120, 1070, 1040, 1020, 950, 870, 770, 740 cm^{-1}; NMR (100 MHz, CCl_4) δ 5.98 (0.32 H, d, J = 3.2 Hz, equatorial anomeric proton, cis isomer), 5.63 (0.68 H, d, J = 4.9 Hz, equatorial anomeric proton, trans isomer), 4.13–3.48 (3 H, m), 2.50–1.30 (4 H, m), on which is superimposed two singlets at 2.09 (0.96 H, s, cis isomer) and 2.05 (2.04 H, s, trans isomer); mass spectrum m/e (rel intensity) 180 (M^+, 1), 178 (M^+, 5), 138 (4), 136 (18), 121 (10), 119 (44), 92 (8), 90 (25), 83 (22), 64 (10), 62 (33), 55 (100), 43 (53), 41 (75), 39 (65), 29 (32), 27 (46).

3-Chloro-2,6-dimethoxytetrahydropyran (5a). To a stirred and cooled (−55 °C) solution of 2-methoxy-3,4-dihydro-2*H*-pyran (**2a**, 1.25 g, 11.0 mmol) in methanol (30 ml) was slowly added (ca. 5 min) 1.30 g (12.0 mmol) of *tert*-butyl hypochlorite, during which time the exothermic reaction caused the temperature to rise to −50 °C. After 5 min the cooling bath (dry ice–2-propanol) was removed and the reaction mixture allowed to warm to 0 °C. Normal workup, as described above for **4e**, afforded 1.30 g of a yellow oil. Analysis (GLC) of the oil indicated one major peak, which on subsequent NMR analysis suggested ca. 50:50 mixture of diastereomers of **5a**, that after column chromatography afforded 1.21 g (61%) of **5a** as a pale yellow oil: IR (film) 2980, 2950, 2850, 1450, 1390, 1220, 1200, 1160, 1120, 1060, 1010, 940, 910, 790 cm^{-1}; NMR (100 MHz, CCl_4) δ 4.71 (0.5 H, t, J = 3.5 Hz, equatorial anomeric proton at C-6), 4.56 (0.5 H, d, J = 6.0 Hz, anomeric proton at C-2), 4.48 (0.5 H, t, J = 3.5 Hz, equatorial anomeric proton at C-6), 4.33 (0.5 H, d, J = 5.7 Hz, anomeric proton at C-2), 3.83–3.50 (1 H, m), 3.46 (1.5 H, s), 3.43 (1.5 H, s), 3.41 (1.5 H, s), 3.39 (1.5 H, s), 2.42–1.45 (4 H, m); mass spectrum m/e (rel intensity) 181 (1), 179 (2), 151 (4), 149 (12), 122 (6), 120 (18), 107 (4), 105 (11), 94 (14), 92 (39), 75 (15), 71 (24), 58 (100), 43 (11), 41 (15).

3-Bromo-2,6-dimethoxytetrahydropyran (5b). To a stirred and cooled (−60 °C) solution of 2-methoxy-3,4-dihydro-2*H*-pyran (**2a**, 660 mg, 5.79 mmol) in methanol (15 ml) was slowly added (ca. 5 min) 1.07 g (7.0 mmol) of *tert*-butyl hypobromite, during which time the exothermic reaction caused the temperature to rise to −55 °C. After 5 min the cooling bath (dry ice–2-propanol) was removed and the reaction mixture allowed to warm to 0 °C. Normal workup, as described above for **4e**, afforded 1.23 g of a yellow oil. Analysis (GLC) of the oil indicated one major peak, which on subsequent NMR analysis indicated ca. 40:60 mixture of diastereomers of **5b**, that after column chromatography afforded 1.00 g (76%) of **5b** as a pale yellow oil: IR (film) 2970, 2935, 2910, 2820, 1440, 1375, 1225, 1170, 1120, 1050, 1010, 950, 730 cm^{-1}; NMR (60 MHz, CCl_4) δ 4.79–4.36 (2 H, overlapping triplets and doublets, equatorial anomeric protons at C-6 and anomeric protons at C-2), 3.94–3.61 (1 H, m), 3.46 (1.2 H, s), 3.42 (1.8 H, s), 3.40 (1.8 H, s), 3.37 (1.2 H, s), 2.42–1.15 (4 H, m); mass spectrum m/e (rel intensity) 225 (1), 223 (1), 195 (15), 193 (15), 166 (30), 164 (32), 151 (10), 149 (10), 138 (22), 136 (22), 118 (10), 113 (7), 85 (40), 71 (26), 58 (100), 45 (11), 43 (13), 41 (15).

Reaction of 2-Methoxy-6-methyl-3,4-dihydro-2*H*-pyran (3a) with *tert*-Butyl Hypochlorite. To a stirred solution (20 °C) of 2-methoxy-6-methyl-3,4-dihydro-2*H*-pyran (**3a**, 5.78 g, 45.2 mmol) in methanol (57 ml) was slowly added (ca. 20 min) 5.00 g (47.0 mmol) of *tert*-butyl hypochlorite, during which time the exothermic reaction caused the temperature to rise to 25 °C. After 10 min the reaction mixture was worked up, as described above for **4e**, and afforded 8.11 g of a yellow oil. Analysis (GLC) of the oil indicated a 49:51 mixture of 1,2-addition product **6a** and 1,4-addition product **7a**. Careful column chromatography afforded 3.42 g (39%) of **6a** (NMR analysis indicated ca. 33:67 mixture of diastereomers that are partially resolved by GLC) as a pale yellow oil and 3.56 g (40%) of **7a** as a colorless, viscous oil.

3-Chloro-2,6-dimethoxy-2-methyltetrahydropyran (6a). IR (film) 2970, 2920, 2810, 1450, 1380, 1220, 1210, 1185, 1115, 1065, 1015, 990, 980, 960, 900, 865, 810 cm^{-1}; NMR (100 MHz, CCl_4) δ 4.56 (1 H, t, J = 3.8 Hz, equatorial anomeric proton), 4.00–3.85 (1 H, m, two overlapping triplets, J = ca. 4 Hz), 3.41 (3 H, s), 3.30 (1 H, s), 3.28 (2

H, s), 2.72–2.30 (1 H, m), 2.30–1.50 (3 H, complex m), 1.41 (1 H, s), 1.36 (2 H, s); mass spectrum *m/e* (rel intensity) 195 (0.25), 193 (0.75), 181 (0.5), 179 (1.5), 165 (2.7), 163 (8), 127 (2.6), 122 (1.7), 121 (2.5), 120 (6), 119 (7), 108 (8), 106 (25), 91 (12), 71 (41), 58 (100), 43 (31), 41 (14).

3-Chloro-6,6-dimethoxy-2-hexanone (7a). IR (film) 2950, 2840, 1722, 1440, 1390, 1360, 1125, 1070, 915 cm^{-1}; NMR (100 MHz, CCl_4) δ two overlapping triplets at 4.38 (1 H, t, J = 5.5 Hz) and 4.17 (1 H, t, J = 7.3 Hz), 3.24 (6 H, s), 2.24 (3 H, s), 2.00–1.55 (4 H, complex m); mass spectrum *m/e* (rel intensity) 195 (0.1), 193 (0.3), 165 (2), 163 (6), 127 (4), 85 (2), 75 (100), 71 (86), 58 (48), 47 (13), 43 (49), 41 (18), 31 (12).

Reaction of 2-Methoxy-6-methyl-3,4-dihydro-2*H*-pyran (3a) with *tert*-Butyl Hypobromite. To a stirred and cooled (−60 °C) solution of 2-methoxy-6-methyl-3,4-dihydro-2*H*-pyran (**3a**, 358 mg, 2.80 mmol) in methanol (8 ml) was slowly added (ca. 5 min) 536 mg (3.40 mmol) of *tert*-butyl hypobromite, during which time the exothermic reaction caused the temperature to rise to −55 °C. After 5 min the cooling bath (dry ice–2-propanol) was removed and the reaction mixture allowed to warm to 0 °C. Normal workup, as described above for **4e**, afforded 647 mg of a yellow oil. Analysis (GLC) of the oil indicated a 76:24 mixture of 1,2-addition product **6b** and 1,4-addition product **7b**. Careful column chromatography afforded 418 mg (62%) of **6b** (NMR analysis indicated ca. 40:60 mixture of diastereomers) as a pale yellow oil and 138 mg (21%) of **7b** as a colorless, viscous oil.

3-Bromo-2,6-dimethoxy-2-methyltetrahydropyran (6b). IR (film) 2970, 2925, 2810, 1440, 1370, 1210, 1165, 1100, 1055, 1010, 970, 955, 890, 860 cm^{-1}; NMR (60 MHz, CCl_4) δ 4.55 (1 H, t, J = 4 Hz, equatorial anomeric proton), 4.15–3.88 (1 H, m, two overlapping triplets), 3.40 (3 H, s), 3.30 (1.2 H, s), 3.29 (1.8 H, s), 2.84–2.20 (1 H, complex m), 2.20–1.54 (3 H, complex m), 1.46 (1.2 H, s), 1.44 (1.8 H, s); mass spectrum *m/e* (rel intensity) 239 (1), 237 (1), 209 (5), 207 (5), 180 (2), 178 (2), 166 (5), 165 (2), 164 (5), 163 (2), 152 (6), 150 (6), 99 (11), 85 (11), 71 (30), 58 (100), 43 (22).

3-Bromo-6,6-dimethoxy-2-hexanone (7b). IR (film) 2935, 2825, 1715, 1435, 1355, 1120, 1060 cm^{-1}; NMR (100 MHz, CCl_4) δ two overlapping triplets centered at 4.34 (1 H, t, J = 6 Hz) and 4.32 (1 H, t, J = 7 Hz), 3.26 (6 H, s), 2.31 (3 H, s), 2.22–1.82 (2 H, m), 1.82–1.50 (2 H, m); mass spectrum *m/e* (rel intensity) 209 (14), 207 (18), 166 (3), 164 (3), 127 (73), 95 (11), 84 (16), 75 (100), 71 (73), 58 (36), 43 (68), 32 (73), 31 (100).

3-Chloro-2-methoxytetrahydropyran (4a). Bp 73–75 °C (14 mm); NMR (100 MHz, CCl_4) δ 4.52 (0.15 H, d, J = 3.0 Hz, equatorial anomeric proton, cis isomer), 4.38 (0.85 H, d, J = 3.2 Hz, equatorial anomeric proton, trans isomer), 3.93–3.39 (3 H, m), 3.40 (0.45 H, s, cis isomer), 3.36 (2.55 H, s, trans isomer), 2.40–1.05 (4 H, m); mass spectrum *m/e* (rel intensity) 152 (M^+, 2), 150 (M^+, 5), 124 (3), 122 (10), 121 (6), 119 (26), 92 (24), 90 (50), 87 (24), 75 (12), 64 (30), 62 (91), 61 (91), 55 (100), 41 (18), 39 (17).

3-Chloro-2-ethoxytetrahydropyran (4b). Bp 120–122 °C (17 mm); NMR (100 MHz, CCl_4) δ 4.61 (0.15 H, d, J = 3.2 Hz, equatorial anomeric proton, cis isomer), 4.45 (0.85 H, d, J = 3.5 Hz, equatorial anomeric proton, trans isomer), 3.93–3.58 (3 H, m), 3.58–3.28 (2 H, m), 2.49–2.08 (1 H, m), 2.08–1.58 (2 H, m), 1.58–1.09 (1 H, m), two overlapping triplets at 1.25 (0.45 H, t, J = 7.1 Hz, cis isomer) and 1.20 (2.55 H, t, J = 7.1 Hz, trans isomer); mass spectrum *m/e* (rel intensity) 166 (M^+, 2), 164 (M^+, 7), 138 (1), 136 (4), 121 (6), 119 (24), 101 (14), 92 (8), 90 (26), 83 (13), 75 (58), 64 (16), 62 (53), 57 (18), 55 (100), 47 (55), 41 (36), 39 (35), 29 (51), 27 (66).

3-Chloro-2-*n*-propoxytetrahydropyran (4c). Bp 113–115 °C (30 mm); NMR (100 MHz, CCl_4) δ 4.58 (0.15 H, d, J = 3.0 Hz, equatorial anomeric proton, cis isomer), 4.42 (0.85 H, d, J = 3.4 Hz, equatorial anomeric proton, trans isomer), 3.95–3.19 (5 H, complex m), 2.45–1.20 (4 H, complex m) on which is superimposed a hextet at 1.59 (2 H, hextet, J = 7.1 Hz), and two overlapping triplets at 0.98 (0.45 H, t, J = 7.1 Hz) and 0.94 (2.55 H, t, J = 7.1 Hz); mass spectrum *m/e* (rel intensity) 180 (M^+, 21) 178 (M^+, 60), 152 (2), 150 (7), 138 (5), 136 (15), 121 (32), 119 (95), 92 (26), 90 (75), 89 (45), 83 (15), 64 (14), 62 (41), 55 (100), 43 (67), 41 (17).

3-Chloro-2-isopropoxytetrahydropyran (4d). Bp 94–95 °C (20 mm); NMR (100 MHz, CCl_4) δ 4.71 (0.15 H, d, J = 3.5 Hz, equatorial anomeric proton, cis isomer), 4.52 (0.85 H, d, J = 3.7 Hz, equatorial anomeric proton, trans isomer), 4.02–3.60 (3 H, m), 3.58–3.27 (1 H, m), 2.47–2.05 (1 H, m), 2.05–1.59 (2 H, m), 1.59–1.25 (1 H, m), two anisochronous methyl signals at 1.18 (3 H, d, J = 6.2 Hz) and 1.12 (3 H, d, J = 6.2 Hz); mass spectrum *m/e* (rel intensity) 134 (2), 132 (7), 121 (6), 119 (18), 100 (7), 83 (7), 64 (2), 62 (7), 55 (23), 43 (100), 31 (17), 29 (14).

3-Chloro-2-*sec*-butoxytetrahydropyran (4g). Bp 125–127 °C (30 mm); NMR (100 MHz, CCl_4) δ doublets centered at 4.86 and 4.69 (0.1 H, d, J = ca. 3 Hz, equatorial anomeric protons, two cis diastereomers), doublets centered at 4.49 and 4.46 (0.9 H, d, J = 3.6 Hz, equatorial anomeric protons, two trans diastereomers), 3.95–3.30 (4 H, m), 2.45–2.05 (1 H, m), 2.05–1.65 (2 H, m), 1.65–1.25 (3 H, m), two sets of overlapping doublets centered at 1.20 and 1.18 (0.3 H, J = ca. 7 and 6 Hz, two cis diastereomers) and 1.16 and 1.09 (2.7 H, d, J = 6.0 and 6.5 Hz, two trans diastereomers), and at least two overlapping triplets centered at 0.92 and 0.89 (3 H, J = 7.0 Hz); mass spectrum *m/e* (rel intensity) 194 (M^+, 3), 192 (M^+, 10), 179 (0.5), 177 (1.5), 165 (1), 163 (4), 138 (17), 136 (46), 121 (27), 119 (100), 92 (28), 90 (80), 83 (14), 64 (9), 62 (26), 57 (66), 55 (90), 41 (40), 29 (43).

3-Chloro-2-*tert*-butoxytetrahydropyran (4h). Bp 118–122 °C (10 mm); NMR (100 MHz, CCl_4) δ 4.89 (0.15 H, d, J = 3.3 Hz, equatorial anomeric proton, cis isomer), 4.60 (0.85 H, d, J = 4.3 Hz, equatorial anomeric proton, trans isomer), 4.00–3.25 (3 H, m), 2.46–2.06 (1 H, m), 2.06–1.60 (2 H, m), 1.60–1.30 (1 H, m), 1.24 (1.35 H, s, cis isomer), 1.22 (7.65 H, s, trans isomer); mass spectrum *m/e* (rel intensity) 194 (M^+, 0.2), 192 (M^+, 0.8), 179 (0.5), 177 (2), 139 (2), 137 (6), 121 (7), 119 (23), 92 (2), 90 (6), 83 (11), 57 (100), 55 (17), 41 (13).

3-Chloro-2-benzyloxytetrahydropyran (4i). Bp 120–123 °C (1 mm); NMR (100 MHz, CCl_4) δ 7.24 (5 H, apparent s), two overlapping AB systems of the anisochronous benzylic protons centered at 4.70 (0.33 H, d, J = 12.2 Hz) and 4.46 (0.33 H, d, J = 12.2 Hz) for the cis isomer and at 4.68 (0.67 H, d, J = 12.2 Hz) and 4.42 (0.67 H, d, J = 12.2 Hz) for the trans isomer that are superimposed on the equatorial anomeric protons centered at 4.69 (0.33 H, d, J = 3.2 Hz, cis isomer) and 4.53 (0.67 H, d, J = 3.4 Hz, trans isomer), 3.95–3.61 (2 H, m), 3.61–3.30 (1 H, m), 2.48–1.20 (4 H, m); mass spectrum *m/e* (rel intensity) 228 (M^+, 0.4), 226 (M^+, 1.2), 190 (3), 144 (12), 91 (100), 77 (4), 65 (12), 55 (10), 41 (6), 39 (13).

3-Chloro-2-propionoxytetrahydropyran (4k). Bp 126–130 °C (14 mm); IR (film) 1752 cm^{-1}; NMR (100 MHz, CCl_4) δ 6.00 (0.45 H, d, J = 3.0 Hz, equatorial anomeric proton, cis isomer), 5.63 (0.55 H, d, J = 4.9 Hz, equatorial anomeric proton, trans isomer), 4.08–3.43 (3 H, complex m), two overlapping quartets at 2.38 (0.9 H, q, J = 7.3 Hz) and 2.33 (1.1 H, q, J = 7.3 Hz), 2.20–1.40 (4 H, m), two overlapping triplets at 1.18 (1.35 H, t, J = 7.3 Hz, cis isomer) and 1.14 (1.65 H, t, J = 7.3 Hz, trans isomer); mass spectrum *m/e* (rel intensity) 121 (11), 119 (32), 100 (4), 83 (6), 77 (4), 57 (100), 55 (22), 43 (4), 41 (7), 39 (8), 29 (32), 28 (43), 27 (14).

3-Chloro-2,6-diethoxytetrahydropyran (5c). NMR (100 MHz, CCl_4) δ 4.80 (0.6 H, t, J = 3.8 Hz, equatorial anomeric proton at C-6), 4.64 (0.6 H, d, J = 7.0 Hz, anomeric proton at C-2), 4.54 (0.4 H, t, J = ca. 3 Hz, equatorial anomeric proton at C-6), 4.38 (0.4 H, d, J = 6.2 Hz, anomeric proton at C-2), 4.02–3.32 (5 H, complex m), 2.50–1.90 (2 H, m), 1.90–1.40 (2 H, m), two overlapping triplets at 1.21 (4.8 H, t, J = 7.0 Hz) and 1.17 (1.2 H, t, J = 7.1 Hz); mass spectrum *m/e* (rel intensity) 209 (0.3), 207 (1), 165 (3), 163 (9), 137 (2), 136 (2), 135 (6), 134 (7), 108 (8), 106 (26), 99 (8), 93 (2), 91 (8), 85 (8), 80 (5), 78 (15), 72 (100), 57 (17), 47 (13), 45 (8), 44 (50), 43 (23), 41 (16), 29 (28).

3-Bromo-2,6-diethoxytetrahydropyran (5d). NMR (60 MHz, CCl_4) δ two overlapping triplets at 4.85 (0.9 H, t, J = 3.2 Hz, equatorial anomeric proton at C-6) and 4.75 (0.1 H, t, J = ca. 4 Hz, equatorial anomeric proton at C-6) on which is superimposed a doublet at 4.75 (0.9 H, d, J = 6.6 Hz, anomeric proton at C-2), 4.44 (0.1 H, d, J = 6.6 Hz, anomeric proton at C-2), 4.20–3.14 (5 H, complex m), 2.44–2.00 (2 H, m), 1.95–1.52 (2 H, m), two overlapping triplets at 1.25 (0.3 H, t, J = 7.0 Hz) and 1.22 (5.7 H, t, J = 7.2 Hz); mass spectrum *m/e* (rel intensity) 253 (1), 251 (1), 209 (5), 207 (7), 180 (14), 178 (15), 152 (6), 150 (6), 124 (5), 122 (4), 99 (20), 85 (5), 72 (100), 57 (9), 44 (27), 43 (10), 41 (11), 29 (15).

3-Chloro-2,6-diethoxy-2-methyltetrahydropyran (6c). NMR (100 MHz, CCl_4) δ 4.65 (0.5 H, t, J = 3.0 Hz, equatorial anomeric proton), 4.56 (0.5 H, t, J = 3.2 Hz, equatorial anomeric proton), 4.03–3.20 (5 H, m) that includes a quartet at 3.53 (q, J = 7.0 Hz), 2.50–2.22 (1 H, m), 2.22–1.43 (3 H, m), 1.40 (3 H, s), two overlapping triplets at 1.18 (3 H, t, J = 7.0 Hz) and 1.16 (3 H, t, J = 7.0 Hz); mass spectrum *m/e* (rel intensity) 223 (1), 221 (3), 179 (8), 177 (24), 150 (2), 148 (8), 136 (6), 134 (18), 122 (19), 120 (54), 92 (21), 85 (32), 72 (100), 57 (16), 45 (27), 44 (64), 42 (17), 29 (21), 27 (13).

3-Chloro-6,6-diethoxy-2-hexanone (7c). IR (film) 1725 cm^{-1}; NMR (100 MHz, CCl_4) δ 4.42 (1 H, t, J = 4.7 Hz), 4.17 (1 H, q, J = 7.7 and 5.9 Hz), 3.53 (4 H, q, J = 7.0 Hz), 2.26 (3 H, s), 2.02–1.37 (4 H, m), 1.15 (6 H, t, J = 7.0 Hz); mass spectrum *m/e* (rel intensity) 179 (9), 177 (27), 103 (100), 85 (82), 75 (46), 72 (33), 57 (33), 47 (73), 44 (33), 43 (90), 29 (45), 27 (23).

3-Bromo-2,6-diethoxy-2-methyltetrahydropyran (6d). NMR (60 MHz, CCl_4) δ two overlapping triplets at 4.64 (0.6 H, t, J = ca. 5 Hz) and 4.59 (0.4 H, t, J = ca. 4 Hz), 4.20–3.10 (5 H, complex m) that

includes a quartet at 3.58 (q, J = 7 Hz), 2.75–2.20 (1 H, m), 2.20–1.57 (3 H, m), 1.48 (1.2 H, s), 1.46 (1.8 H, s), 1.19 (6 H, t, J = 7 Hz); mass spectrum m/e (rel intensity) 267 (1), 265 (1), 253 (1), 251 (1), 223 (12), 221 (12), 180 (10), 178 (10), 166 (10), 164 (8), 141 (15), 113 (12), 85 (26), 72 (100), 57 (18), 43 (49), 29 (16).

3-Bromo-6,6-diethoxy-2-hexanone (7d). IR (film) 1718 cm^{-1}; NMR (60 MHz, CCl_4) δ two overlapping triplets at 4.38 (1 H, t, J = 5 Hz) and 4.32 (1 H, t, J = 7 Hz), 3.88–3.08 (4 H, m), 2.30 (3 H, s), 2.24–1.38 (4 H, complex m), 1.18 (6 H, t, J = 7 Hz); mass spectrum m/e (rel intensity) 268 (M^+, 1), 266 (M^+, 1), 223 (30), 221 (32), 180 (3), 178 (3), 166 (2), 164 (2), 151 (3), 149 (3), 113 (11), 103 (100), 85 (58), 75 (28), 72 (28), 57 (17), 47 (26), 43 (47), 29 (12).

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Registry No.—**1**, 110-87-2; **2a**, 4454-05-1; **2b**, 103-75-3; **3a**, 28194-35-6; **3b**, 52438-71-8; *cis*-**4a**, 6559-29-1; *trans*-**4a**, 6559-30-4; *cis*-**4b**, 6559-31-5; *trans*-**4b**, 6559-32-6; *cis*-**4c**, 61092-36-2; *trans*-**4c**, 61092-37-3; *cis*-**4d**, 61092-38-4; *trans*-**4d**, 61092-39-5; *cis*-**4e**, 61092-40-8; *trans*-**4e**, 61092-41-9; *cis*-**4f**, 55162-86-2; *trans*-**4f**, 61092-42-0; *cis*-(*R**)-**4g**, 61092-43-1; *cis*-(*S**)-**4g**, 61092-44-2; *trans*-(*R**)-**4g**, 61092-45-3; *trans*-(*S**)-**4g**, 61092-46-4; *cis*-**4h**, 61092-47-5; *trans*-**4h**, 61092-48-6; *cis*-**4i**, 61092-49-7; *trans*-**4i**, 61092-50-0; *cis*-**4j**, 14750-43-7; *trans*-**4j**, 14750-42-6; *cis*-**4k**, 61092-51-1; *trans*-**4k**, 61092-52-2; *cis*-**5a**, 61092-53-3; *trans*-**5a**, 61092-54-4; *cis*-**5b**, 38017-14-0; *trans*-**5b**, 61092-55-5; *cis*-**5c**, 61092-56-6; *trans*-**5c**, 61092-57-7; *cis*-**5d**, 61092-58-8; *trans*-**5d**, 61092-59-9; *cis*-**6a**, 61092-60-2; *trans*-**6a**, 61092-61-3; *cis*-**6b**, 61092-62-4; *trans*-**6b**, 61092-63-5; *cis*-**6c**, 61092-64-6; *trans*-**6c**, 61092-65-7; *cis*-**6d**, 61092-66-8; *trans*-**6d**, 61092-67-9; **7a**, 61092-68-0; **7b**, 61092-69-1; **7c**, 61092-70-4; **7d**, 61092-71-5; **8c**, 61092-72-6; *t*-BuOCl, 507-40-4; *t*-BuOBr, 1611-82-1; 2-chloro-1,1-dibutoxyethane, 17437-27-3; butyl vinyl ether, 111-34-2.

References and Notes

(1) Part 5 in the series "The Chemistry of 2-Alkoxy-3,4-dihydro-2*H*-pyrans". For part 4 see A. J. Duggan and S. S. Hall, *J. Org. Chem.*, **40**, 2238 (1975).

(2) Taken in part from the Ph.D. Thesis of A.J.D. that was submitted to the Graduate School, Rutgers University, Oct 1974.

(3) (a) S. S. Hall and A. J. Duggan, *J. Org. Chem.*, **39**, 3432 (1974); (b) S. S. Hall and H. C. Chernoff, *Chem. Ind. (London)*, 896 (1970); (c) F. Sweet and R. K. Brown, *Can. J. Chem.*, **45**, 1007 (1967); (d) J. E. Franz, D. M. Dietrick, A. Henshall, and C. Osouch, *J. Org. Chem.*, **31**, 2847 (1966); (e) J. K. Williams, D. W. Wiley, and B. C. McKusick, *J. Am. Chem. Soc.*, **84**, 2210 (1962).

(4) (a) Unpublished observations in our laboratory, S. S. Hall, A. J. Duggan, and M. Mackaravitz, on the relative reactivity of tetracyanoethylene with pyrans **2** and **3**; (b) A competitive rate study, using *tert*-butyl hypochlorite in methanol, designed to measure the effect of substituents on the reactivity of the 3,4-dihydro-2*H*-pyran ring system will be published.

(5) (a) M. J. Mintz and C. Walling, *Org. Synth.*, **49**, 9 (1969); (b) F. D. Chattaway and O. G. Backeberg, *J. Chem. Soc.*, 2999 (1923); (c) J.-M. Geneste and A. Kergomard, *Bull. Soc. Chim. Fr.*, 470 (1963); (d) C. Walling and A. Padwa, *J. Org. Chem.*, **27**, 2976 (1962); (e) C. Walling and R. T. Clark, *J. Org. Chem.*, **39**, 1962 (1974).

(6) R. U. Lemieux and B. Fraser-Reid, *Can. J. Chem.*, **43**, 1460 (1965).

(7) (a) J. T. Edward, *Chem. Ind (London)*, 1102 (1955); (b) R. U. Lemieux and N. J. Chü, Abstracts, 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 1958, p 31N.

(8) (a) F. Sweet and R. K. Brown, *Can. J. Chem.*, **44**, 1571 (1966); (b) *ibid.*, **46**, 2283 (1968); (c) L. D. Hall and J. F. Manville, *ibid.*, **47**, 361 (1969); (d) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

(9) (a) A. Bresson, G. Dauphin, J.-M. Geneste, A. Kergomard, and A. Lacourt, *Bull. Soc. Chim. Fr.*, 2432 (1970); (b) C. F. Irwin and G. F. Hennion, *J. Am. Chem. Soc.*, **63**, 858 (1941); (c) K. Weissermel and M. Lederer, *Chem. Ber.*, **96**, 77 (1963); (d) W. Oroshnik and R. A. Mallory, *J. Am. Chem. Soc.*, **72**, 4608 (1950); (e) G. E. Heasley, V. M. McCully, R. T. Wiegman, V. L. Heasley, and R. A. Skidgel, *J. Org. Chem.*, **41**, 644 (1976).

(10) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, p 91, and references cited therein.

(11) Since many of the corresponding bromine derivatives of Table I have been prepared with *N*-bromophthalimide in hydroxylic solvents [E. M. Gaydou, *Tetrahedron Lett.*, 4055 (1972)] only a few reactions using *tert*-butyl hypobromite were pursued.

(12) 2-Chloro-1,1-di-*n*-butoxyethane from *n*-butyl vinyl ether and *tert*-butyl hypochlorite in 1-butanol at −15 °C as a colorless oil after distillation (90% yield): bp 120 °C (15 mm); NMR (100 MHz, CCl_4) δ 4.49 (1 H, t, J = 5.6 Hz), 3.48 (4 H, q, J = 6.3 Hz) on which is superimposed a doublet at 3.38 (2 H, d, J = 5.6 Hz), 2.46–1.18 (8 H, m), 0.92 (6 H, perturbed t, J = ca. 7 Hz); mass spectrum m/e (rel intensity) 159 (4), 137 (3), 136 (3), 135 (10), 134 (9), 103 (9), 80 (6), 78 (18) 57 (100), 56 (38), 43 (19), 41 (65), 29 (55).

(13) (a) A. J. Duggan and S. S. Hall, *J. Org. Chem.*, **40**, 2238 (1975); (b) Vu Moc Thuy and P. Maitte, *Bull. Soc. Chim. Fr.*, 4423 (1970); (c) N. M. Shetchmann, E. A. Victorama, E. A. Karakhanov, N. Kvorostakina, and N. S. Zefirov, *Dokl. Akad. Nauk SSSR, Ser. Khim.*, **196**, 367 (1971); (d) G. Descotes, J.-C. Martin, and N. Mathicolonis, *Bull. Soc. Chim. Fr.*, 1077 (1972).

(14) 2-Ethoxy-6-chloromethyl-3,4-dihydro-2*H*-pyran (**8c**): IR (film) 1655 cm^{-1}; NMR (100 MHz, CCl_4) δ 4.97–4.86 (1 H, m), 4.54 (1 H, t, J = 3.3 Hz), 4.46 (2 H, s), 3.80 (1 H, d of q, J = 9.8 and 7.3 Hz), 3.46 (1 H, d of q, J = 9.8 and 7.3), 2.55–2.13 (2 H, m), 2.04–1.50 (2 H, m), 1.16 (3 H, t, J = 7.3 Hz); mass spectrum m/e (rel intensity) 178 (M^+, 3), 176 (M^+, 9), 141 (30), 140 (30), 133 (7), 131 (21), 95 (47), 85 (70), 72 (100), 57 (92), 45 (17), 43 (99), 31 (41), 29 (64), 27 (35).

(15) C. A. Grob, *Angew. Chem., Int. Ed. Engl.*, **8**, 535 (1969), and references cited therein.

(16) The IR spectra were determined with a Perkin-Elmer Model 237B and a Beckman Model IR-10 infrared recording spectrophotometers. The NMR spectra were determined at 60 MHz with a Varian Associates Model T-60 and at 100 MHz with a Varian Associates Model HA-100 NMR spectrometers. The chemical shifts are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with a Consolidated Electronics Corp. Model 110-21B mass spectrometer. Gas chromatographic analyses (GLC) were performed on a Hewlett-Packard Model 7610A high-efficiency chromatograph with a flame detector.

(17) (a) R. I. Longely, Jr., and W. S. Emerson, *J. Am. Chem. Soc.*, **72**, 3079 (1950); (b) C. W. Smith, D. G. Norton, and S. A. Ballard, *ibid.*, **73**, 5267 (1951); (c) K. Ryoji, O. Hiroski, A. Nakamura, and K. Fukuda, Japanese Patent 7 368 573 (1973); German Patent 2 163 515 (1973).

An Electrochemical and Spectrophotometric Study of the Reduction of Some 9-Substituted Fluorenes in Dimethylformamide[1]

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Electrochemical and spectrophotometric results for the electrode reduction in DMF of the nonalternant hydrocarbon fluorene substituted at one 9 position by a methyl, phenyl, or benzyl group indicate that the radical anion originally produced decomposes to the fluorenyl anion and hydrogen. In the presence of proton donor the parent species is regenerated. If the second 9 position is substituted by a benzyl group the radical anion again yields the fluorenyl carbanion, which, in the presence of proton donor, yields the singly substituted fluorene. Fluorene substituted at the 9 position by two phenyl groups, two methyl groups, or a phenyl and a methyl group does not cleave any of these substituents. Rather in at least one case it appears as if C_{11}–C_{12} bond cleavage occurs instead. In none of these cases does a normal ECE type mechanism seem to occur.

The electrochemical reduction of alternant aromatic hydrocarbons has been shown to proceed by the so-called electrochemical–chemical–electrochemical (ECE) mechanism in electrochemically inert protic media.[2-7] The anion radical produced at the electrode abstracts a proton from the donor, with the subsequent reduction of the neutral radical. Another chemical step then follows this second electrochemical reduction. In aprotic media the anion radical must abstract protons from solvent, supporting electrolyte, another hydrocarbon molecule, or impurity, or return to starting material. Polarographically, most alternant aromatic hydrocarbons display two one-electron waves in aprotic media, and one two-electron wave, at more positive reduction potentials, in the presence of proton donors.

However, the situation for nonalternant aromatic hydrocarbons is not so clear. A few systems have been studied, with varying results. The type of molecule which has received most attention is that in which a bridge methylene is present between two parts of a benzenoid system. The bridge methylene contributes to the aromaticity of the ring system through hyperconjugative effects, and hence these compounds are considered nonalternant. Further, the methylene hydrogens are found to be weakly acidic (pK_a = 20–25).[8-10] Janata et al. studied the electrochemical reduction of 4,5-methylenephenanthrene and found that the usual ECE process occurred in the presence of proton donors, and even to a small extend in aprotic media where self-protonation took place.[10] It was found that 9,10-dihydro-4,5-methylenephenanthrene was a product in both situations, and that 4,5-methylenephenanthrene behaved as a typical alternant aromatic hydrocarbon. For this system a second wave was observed at more negative potentials under both proton-donor and aprotic conditions. This was attributed to reduction of the 9,10-dihydro-4,5-methylenephenanthrene, a fluorene derivative. Study of the nonalternant hydrocarbon fluorene (RH_2) itself by Jezorek et al. revealed behavior quite different from that of 4,5-methylenephenanthrene or other alternant hydrocarbons. This was true under both aprotic and proton-donor conditions.[11,12] It was found that the reduction of the protonated radical (RH_3·) did not occur. That is, after the initial electrochemical and chemical steps, the mechanism was different from those previously studied. In the presence of proton donors, in fact, both polarographic and constant-potential electrolysis yielded an n value of 3, rather than the usual 2. Jezorek et al. proposed a mechanism in which loss of a 9-hydrogen atom was a product-determining step. When similar experiments were done on fluoranthene these anomalous results were not obtained, thus implicating the 9 position in the mechanism of the three-electron reduction of fluorene.[12]

In order to better understand the electrochemical behavior of nonalternant hydrocarbons, a series of 9-substituted fluorenes was examined in this study under both proton-donor and aprotic conditions. The aprotic experiments were expected to answer the question of whether parent hydrocarbon participated in self-protonation of the radical anion, as was postulated for fluorene.[12] The 9-substituted fluorenes are expected to be more acidic than fluorene itself.[13] Some 9,9-disubstituted fluorenes were also studied, and for these, of course, there are no hydrogens in the 9 position and parent participation is not possible. These 9-substituted and 9,9-disubstituted fluorenes were also studied under proton-donor conditions to see if anomalous results such as were found for fluorene would be obtained.

The species included in this investigation are 9-methylfluorene (9-MF), 9-phenylfluorene (9-PF), 9-benzylfluorene (9-BF), 9,9-dibenzylfluorene (DBF), 9-phenyl-9-benzylfluorene (PBF), 9-benzyl-9-methylfluorene (BMF), 9,9-diphenylfluorene (DPF), 9-phenyl-9-methylfluorene (PMF), and 9,9-dimethylfluorene (DiMF).

Results and Discussion

This discussion will be broken into three parts because the nonalternant fluorene derivatives investigated in this study were found to display three distinct types of electrode reduction behavior. Those fluorenes substituted at only one of the two 9 positions exhibited one identifiable mechanism; those substituted at one 9 position by a benzyl group and at the other by some other moiety were found to have a second type of mechanism; and those disubstituted fluorenes in which neither 9 substituent was a benzyl group displayed yet a third type.

The Monosubstituted Fluorenes. A. Aprotic Conditions. All of the monosubstituted fluorenes exhibited a one-wave polarogram under aprotic conditions in dimethylformamide (DMF), and a diffusion limited current, i_d, linearly dependent on the square root of the height of the mercury column, $h^{1/2}$, suggesting a diffusion controlled process.[14] The quantity $E_{3/4} - E_{1/4}$ (the potential at $i = \frac{3}{4}i_d$ and $\frac{1}{4}i_d$, respectively) was determined for each polarogram and found to be 0.060 ± 0.005 V, suggesting a reversible one-electron process.[15] Cyclic voltammograms at about 0.2 and 2 V/s scan rates were taken for all three fluorene derivatives, with 9-MF showing an oxidation peak upon potential scan reversal at both scan rates, and 9-PF exhibiting evidence of an oxidation

Table I. Electrochemical and Spectral Data for the Substituted Fluorenes in DMF under Aprotic Conditions[a]

Substrate	$-E_{1/2}$, V[b]	CV oxidation wave[c] 0.2 V/s	CV oxidation wave[c] 2.0 V/s	λ_{max} for anion(s), nm[d]	Radical anion	Coulometric n value
9-BF	3.30	No	No	382	No	1
9-PF	3.16	No	Yes	372, 410 (sh), 490	No	1
9-MF	3.28	Yes	Yes	383	No	1
DBF	3.26	No	No	390–410, 490	No	2
PBF	3.09	No	No	390, 500	No	2
BMF	3.23	No	No	330, 350, 385	No	2
DPF	3.18	Yes	Yes		Yes, blue	
DiMF	3.39	Yes	Yes		Yes, blue	
PMF	3.22				Yes, blue	

[a] All substrates exhibited linear i_d vs. $h^{1/2}$, one wave polarograms with n values of 1, and an $E_{3/4} - E_{1/4}$ of 0.060 ± 0.005 V. [b] Vs. $Ag/AgClO_4$ (satd). [c] Cyclic voltammetric. [d] Produced coulometrically in special flow cell.

peak at the faster scan rate but not the slower. The 9-BF showed no evidence of an oxidation wave.

Controlled potential electrolysis at a mercury pool electrode in a specially designed flow cell allowed the UV–visible spectrum of the electrolysis products to be obtained during the reduction process.[16] Observed peaks were at 382 nm for 9-BF, 372, 410 (shoulder), and 490 nm for 9-PF, and at 383 nm for 9-MF (Table I). These peak positions correspond fairly closely to those reported by Bowden and Cockerill[13] in other solvents for the anions of the respective substrates. Addition of an excess of D_2O to the electrolysis solution produced a quantitative yield of the starting material 40–80% deuterated at the 9 position as determined by NMR spectroscopy. Constant potential electrolysis in an ordinary H-type cell carried out on the plateau of the polarographic wave gave an n value of about 1.0 for all three hydrocarbons as determined by integration of the current–time (i–t) curve. The same n value was obtained in the flow-cell experiments using 0.001 M substrate. The colored carbanion could be seen forming at the electrode for all three species. As these anions are sensitive to air,[12] conventional workup techniques could not be employed. At the conclusion of the electrolysis water was added to the electrolyzed solution and the product extracted with hexane. Evaporation of the hexane gave the 9-substituted substrate in quantitative yield. A summary of the electrochemical and spectral data for the three 9-substituted fluorenes is given in Table I.

B. Proton-Donor Conditions. The three monosubstituted fluorene derivatives exhibited similar behavior upon electrolysis in the presence of proton donor, just as they had under aprotic conditions. No change in $E_{1/2}$ was observed when polarograms were performed in hydroquinone media, but acute maxima were observed when the proton donor concentration was about 0.01 M and higher. The polarographic limiting current increased anywhere from 7- to 13-fold compared to the aprotic value and depending on the substrate used, when the proton donor concentration was increased from zero to about 0.1 M. The increase in i_d for these compounds was very small up to about 0.001 M hydroquinone. From this point up to the highest concentration of proton donor studied, 0.1 M, i_d increased rapidly in an exponential-like fashion. This description of the i_d vs. hydroquinone concentration curve holds for all the species reported in this study with only quantitative differences, the reasons for which are not clear.

Constant potential electrolysis in hydroquininone media did not produce an exponentially decreasing current. Instead a constant value much higher than background was observed. Extensive gas evolution at the cathode was obtained, and workup of the reaction mixture yielded only substrate as product. Constant potential electrolysis in the presence of hydroquinone of 9-PF and 9-BF deuterated at the 9 position was carried out under the same conditions as were used for the nondeuterated compounds. Again the only product was starting material in each case. Analysis of the products by NMR spectroscopy revealed that about 60% replacement of deuterium by proton had occurred. It should be pointed out that when 50% replacement of deuterium by proton has occurred, the probability of deuterated and nondeuterated fluorenes being reduced at the electrode is the same. Because the electrolysis current did not go to zero with time in 0.02 M hydroquinone media, an n value could not be calculated. It should be noted that results for both the macrocoulometry and flow-cell coulometry experiments were identical. While psuedo-first-order kinetics probably did not hold in the macrocoulometry situation as the hydroquinone excess over substrate was only twofold, a situation much closer to first order existed in the flow-cell experiments where a 20-fold or more excess of proton donor was used.

Based on the aprotic and hydroquinone media electrolysis experiments an overall mechanism for 9-BF, 9-PF, and 9-MF can be proposed.

$$ARH + e^- \rightleftarrows ARH\cdot^- \quad (1)$$

$$ARH\cdot^- \rightarrow AR^- + \tfrac{1}{2}H_2 \quad (2)$$

where R = benzyl, phenyl, or methyl.
In the presence of proton donor:

$$AR^- + HX \rightarrow ARH + X^- \quad (3)$$

The cyclic voltammetric experiments demonstrate that the radical anions are not especially stable, even though at faster scan rates, and for 9-MF, evidence of reversibility at the electrode is obtained. It would appear, however, that the anions are relatively stable compared to the radical anions, as the carbanions fulfill the $4n + 2$ rule of aromatic resonance stabilization.[17] The overall mechanism then appears to be one of cyclic regeneration of substrate, rather than the possible ECE pathway, that is, reactions 2 and 3 rather than 4.

$$ARH\cdot^- \xrightarrow{HX} \text{neutral radical} \rightarrow \text{further reduction} \quad (4)$$

The first of the two possible pathways for decomposition of the radical anions, 2 and 3, catalytic hydrogen reduction, apparently predominates for all three singly substituted fluorenes under the conditions of this study.

9,9-Disubstituted Fluorenes Containing the Benzyl Group. A. Aprotic Conditions. Just as for the singly substituted fluorenes described above the doubly substituted, benzyl-containing fluorenes were found to have one-wave polarograms under aprotic conditions in DMF. In addition, they exhibited an i_d linearly dependent on $h^{1/2}$, and an $E_{3/4} - E_{1/4}$ of 0.060 ± 0.005 V. Cyclic voltammograms at scan rates

of about 0.2 and 2 V/s showed no evidence of an oxidation wave with potential reversal. This indicates an overall irreversible process, at least under these experimental conditions. Constant potential electrolysis on the plateau of the polarographic wave, performed in the special flow cell, produced colored reaction products with broad absorption spectra. These spectra appeared to be a composite of a mixture of product species, one of which may have been the benzyl anion,[18-20] another the anion of the fluorene fragment. In addition there may have been present some species produced by reaction of these carbanions with traces of oxygen.[12] The electrochemical and spectrophotometric data are summarized in Table I. When water was added to the electrolyzed solution in either the flow cell or regular H cell, the mixture extracted with hexane, and the hexane evaporated, only singly substituted fluorene was obtained; a benzyl group was lost in all three cases. Integration of the i–t curve under aprotic conditions in both the coulometric–spectrophotometric and massive electrolysis experiments yielded an n value of approximately 2 for each of the three doubly substituted, benzyl-containing fluorenes. This result was unexpected because the polarographic limiting current was about the same as that for fluorene itself, a known one-electron reduction. As the diffusion coefficients for these substituted fluorenes are expected to be about the same as for fluorene, it follows that reduction of the substituted fluorenes should also be a one-electron process. It is a fact, however, that constant potential electrolysis at a mercury pool, where reaction products can accumulate and where the solution is stirred, is a different experiment than polarography, where the dropping-mercury electrode is being constantly renewed with fresh mercury and the solution is unstirred.[14]

B. Proton Donor Conditions. Polarography performed on the disubstituted, benzyl-containing fluorenes in the presence of varying concentrations of hydroquinone was not accompanied by a significant shift in $E_{1/2}$ with increased proton donor concentration as required for an ECE type mechanism. However, i_d was threefold higher for DBF and ninefold for PBF and BMF at 0.1 M hydroquinone as compared to the aprotic values. Constant potential electrolysis in the presence of hydroquinone showed behavior for DBF similar to that of 9-BF; for PBF similar to 9-PF; and for BMF similar to 9-MF. Extraction of the electrolyzed mixture with hexane yielded only the monosubstituted fluorene species mentioned above, a benzyl group having been lost in each case. Based upon the n value obtained coulometrically and the monosubstituted products recovered from the hexane extraction, it would appear that cleavage of a benzyl radical occurs upon addition of one electron to the disubstituted, benzyl-containing fluorenes, but that this cleavage is sufficiently slow or otherwise different so as to not influence the polarographic behavior. Indications are that even in the presence of proton donor the rate of cleavage is fast compared to protonation (ECE pathway) or that even if protonation does occur, the neutral radical is not further reduced and subsequent cleavage still occurs. Coulometric n values in the presence of hydroquinone were impossible to calculate as, after a time, the current leveled out at a value much higher than background.

As the monosubstituted fluorene fragment was recovered in all cases there is no question that benzyl-group cleavage occurs. In order to explain the n value of 2 it would seem reasonable to postulate that the benzyl fragment is further reduced to the anion,[21] and reacts with solvent and/or impurities to form toluene. However, attempts to identify toluene in the reaction mixture were not fruitful, nor were efforts to identify bibenzyl (formation of which, however, cannot explain an n value of 2). Therefore, the total mechanistic picture remains unclear. Benzyl cleavage is certain, however, as is formation of the monosubstituted fluorene fragment *via* protonation of the carbanion.

It should be noted that the monosubstituted fluorene fragment is itself electroactive, and at the higher proton donor concentrations, i_d increases markedly, as was seen for the three monosubstituted fluorenes discussed earlier. Therefore, the electrolysis current, leveling off at a value much higher than background in the presence of proton donor, can be considered to be a composite of the reduction of the disubstituted fluorenes, and monosubstituted fluorene fragment, and possibly of the benzyl fragment. The fluorene fragment facilitates catalytic hydrogen ion reduction, as explained in the section on monosubstituted fluorenes, and results in large current increases as the proton donor concentration is increased.

That it is a benzyl radical that splits off the parent fluorene molecule rather than a phenyl or methyl group can be ascribed to the fact that the benzyl radical is resonance stabilized to a greater extent than either the CH_2· or C_6H_5· radicals. Kerr[22] and Benson[23] have shown that the homolytic dissociation energy of the H_3C–H bond in methane and the C_6H_5–H bond in benzene is about 104 kcal/mol for both but for the $C_6H_5CH_2$–H bond of toluene is only about 85 kcal/mol. It thus appears as if the benzyl radical is about 19 kcal/mol more stable than the methyl and phenyl radicals.

It is interesting to note that while carbon–carbon bond cleavage is not uncommon for alkali metal reduction of disubstituted fluorenes[24,25] or for electrochemical oxidations,[26] it is a very unusual process for electrochemical reductions. It is possible that the very stable cyclopentadienyl-type structure of the fluorene anion makes it a good leaving group, not unlike a halide-anion leaving group in the electrochemical reduction of organic halogen compounds.[27]

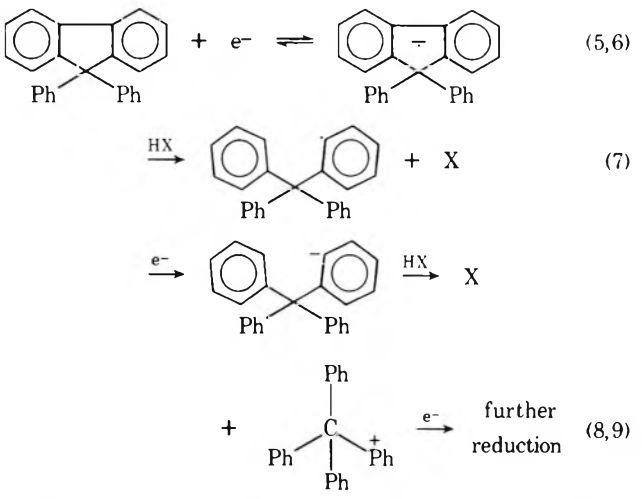
Disubstituted Fluorenes Not Containing a Benzyl Group. A. Aprotic Conditions. Just as for the six fluorenes described previously, DPF, PMF, and DiMF gave one-wave polarograms under aprotic conditions in DMF solvent, and exhibited an i_d linearly dependent on $h^{1/2}$ and an $E_{3/4} - E_{1/4}$ of 0.060 ± 0.005 V. Cyclic voltammograms of DPF and DiMF at scan rates of about 0.2 and 2.0 V/s possessed oxidation peaks in all cases, and potential differences between the cathodic and anodic peaks of 56 and 60 mV, respectively. This is close to the Nernstian value of 59 mV expected for a reversible one-electron process. The electrochemical and spectral data are summarized in Table I.

Constant potential electrolysis on the plateau of the polarographic wave produced the blue anion radicals of the substrates for all three fluorene compounds. No breakdown of these anion radicals to the yellow-red carbanions could be detected even after several hours standing under the nitrogen atmosphere. It appears that the anion radicals of these three species are much more stable than those discussed earlier.

Addition of water to the electrolyzed DPF solution, extraction with hexane, and evaporation of the hexane yielded a white solid with three components as shown by thin layer chromatography on alumina, with hexane developer. However, 9-PF was not one of the products as may have been suggested by the reactions of the disubstituted fluorenes discussed earlier or by the metalation studies of Janzen and coworkers.[25] For PMF and DiMF a similar extraction procedure yielded a colorless oil as product. Gas chromatographic analysis of the oil from DiMF on a Carbowax 20M column at 180 °C showed four components, none of which was 9-MF. Thin layer chromatographic analysis, with hexane developer, of the oil from PMF electrolysis showed no 9-PF or 9-MF. None of the products were identified further as these analyses and the long-term stability of the radical anions indicates that the cleavage of 9 substituents observed for the benzyl-substituted fluorenes does not occur in these three cases.

B. Proton Donor Conditions. Polarography of these three

disubstituted fluorenes in the presence of increasing concentrations of hydroquinone resulted in an increase of i_d and a positive shift in $E_{1/2}$, as expected for an ECE mechanism. In 0.10 M hydroquinone the i_d was about 12, 6, and 6 times larger than under aprotic conditions for DPF, DiMF, and PMF, respectively. Shifts in $E_{1/2}$ were about 9, 7, and 8 mV respectively, quite small compared to the usual ECE situation of perhaps 50–100-mV shifts. Also, acute maxima were observed at proton donor concentrations above 5×10^{-2} *M*. Extraction with hexane of the solutions from exhaustive electrolysis of the three fluorene derivatives gave the same products as are discussed above. Again, in the presence of proton donor, it appears as if loss of a 9 substituent does not occur. Apparently only the 9-benzyl group, of the series of substituents studied, is a good leaving group. Reaction products were not identified individually because it was clear that cleavage at the 9 position did not occur. An exception to this was the solid product resulting from DPF electrolysis. This solid had a very high melting point, about 230 °C, and its UV spectrum exhibited a peak near 222 nm and a broad, less intense, band centered around 270 nm, virtually identical with the spectrum of tetraphenylmethane.[28] The mass spectrum exhibited two peaks of roughly equivalent intensity with *m/e* values of 322 and 320. A possible mechanism can be postulated as follows. The radical anion of DPF can undergo a reaction with proton donor at C_{11} or C_{12} (equivalent positions) resulting in cleavage of the C_{11}–C_{12} bond and the production of tetraphenylmethane (mol wt 320). Subsequent reduction and protonation of a double bond would result in a product of molecular weight 322. Major peaks for both of these species were observed in the mass spectrum, as indicated above.



This mechanism is still speculative, as not enough corroborating evidence is on hand, but it does appear as if C_{11}–C_{12} bond cleavage occurs, unlike the situation for the other fluorene derivatives studied.

Conclusions

Of the fluorene derivatives reported in this investigation the singly substituted species most resemble fluorene itself in mechanism. Both fluorene and the singly substituted derivatives are thought to release a hydrogen atom after the first reduction step[12] rather than being protonated and further reduced as in a normal ECE sequence. Also, the three carbanions produced all react with oxygen, as does fluorenyl carbanion, to produce fluorenone.[12]

The doubly substituted derivatives, of course, cannot release a hydrogen atom, but do either cleave a benzyl group from the 9 position or apparently undergo cleavage of the five-membered ring system itself. For some reason, not understood at this time, these nonalternant hydrocarbons do not follow the usual ECE reaction pathway to a dihydro reduction product, but rather shed 9-position substituents or (apparently) cleave the C_{11}–C_{12} bond. Continued investigations are underway in our laboratory to attempt to understand the reasons for this unusual behavior.

Experimental Section

Instrumental. All electrochemical measuremnts were carried out using a Princeton Applied Research Model 173 potentiostat, Model 176 current-to-voltage converter with digital readout, and Model 178 electrometer probe. Reproducibility of potential settings was about ±2 mV. The ramp voltage for polarography was generated using a circuit described by Means.[29] An Exact Model 126b VCF sweep generator was used to obtain triangular waves of the desired frequency for cyclic voltammetry. Recording of some of the electrochemical experiments was done on an Electro Instruments Model 500 X–Y recorder. Cyclic voltammograms were recorded and stored on a Tektronix Model 5103N oscilloscope, and photographs taken with a C-5 oscilloscope camera. Cyclic voltammetry experiments utilized a Metrohm Model E 410 hanging-mercury-drop electrode.

Exhaustive, controlled potential, massive electrolysis experiments were carried out using a conventional H-type cell equipped with a fine-porosity, sintered-glass frit separating cathode and anode compartments. The mercury-pool cathode was continuously stirred by a magnetic stirrer to expose fresh metal surface during electrolysis. Simultaneous coulometric–spectrophotometric experiments were carried out using a special flow cell designed by Janata and Mark.[16] This cell, designed for the cell compartment of the Cary 14 spectrophotometer, allowed the spectra of electrode reaction products to be observed during the electrolysis.

The reference electrode used was constructed from two 2-cm lengths of 4-mm glass tubing separated by a 2-cm length of Corning Glass Works porous cane (thirsty glass). All three pieces were then covered by heat-shrinkable polyethylene tubing. A second piece of polyethylene tubing was sealed to one of the pieces of glass tubing, and this compartment filled with 0.1 M tetra-*n*-butylammonium perchlorate (TBAP) in DMF, and the end closed off with a 1 cm piece of porous cane. This compartment served as the salt bridge. The top compartment contained a saturated solution of $AgClO_4$ in 0.1 M TBAP–DMF solution. A length of polished silver wire was immersed in this solution as the electrical contact element. This electrode was equilibrated for at least 24 h before use, and all air bubbles were removed. These electrodes were found to be stable for several weeks.

Chemicals and Solutions. TBAP (G. F. Smith) was dissolved in a minimum of acetone and the solution filtered; it was then precipitated by adding distilled water, filtered, and washed twice with distilled water. This product was dissolved again in acetone, precipitated with ethyl ether, filtered, washed three times with ethyl ether, and dried in a vauum oven at 100 °C for 6 h. This procedure completely removed iodide impurity. DMF (Burdick and Jackson, Distilled in Glass) was dried by the method of Moe.[30] Dimethylamine impurity produced was removed by degassing under vacuum for 2 h. Purified solvent was stored over activated Linde Type 5A molecular sieves for at least 72 h before use. The D_2O used was the usual high purity, commercially available grade. If Karl Fischer titration showed the water content of the stock DMF to be less than 0.015%, the solvent was used directly without purification after storing over sieves as above. Background currents of all solvent–0.1 M TBAP solutions were less than about 0.2 μA at the point of solvent breakdown, about −3.6 V.

All electrochemical solutions were 0.1 M in TBAP. The concentration of electroactive species was about 0.001 M for polarographic, cyclic voltammetric, and coulometric–spectrophotometric experiments, and 0.01 M for exhaustive electrolysis studies. Solutions for protic electrolysis were about 0.02 M in hydroquinone.

Polarographic and cyclic voltammetric solutions were deoxygenated by bubbling nitrogen (high purity, Delta Products) for at least 15 min and solutions for controlled potential electrolysis for at least 30 min before reaction; and a nitrogen atmosphere was maintained over the solutions during the course of the measurement. The nitrogen was dried and deoxygenated as described previously.[12]

Extraction of controlled potential electrolysis solutions was done with reagent grade hexane. The solution from the cathode compartment was pipetted into a separatory funnel containing 100 ml each of hexane and water. The hexane extracts were combined and backwashed with three 100-ml portions of water to remove DMF. The hexane layer was then run through several layers of filter paper to remove water and the solvent removed on a rotary evaporator.

Syntheses. 9-MF. The method of preparation was essentially that of Scherf and Brown[31] and Murphy and Hauser[32] using 1,2-dimethoxyethane solvent, phenyllithium (Alpha Products, 1.4 M in 70:30 benzene–ether) as the proton-abstracting agent, and methyl iodide. Benzene extraction and $CaCl_2$ drying produced a yellow oil, which was chromatographed on neutral alumina. The 9-MF (first fraction off) was decolorized with charcoal. Prior to electrolysis the 9-MF was dissolved in benzene and filtered through a short column of alumina. The filtrate was evaporated to dryness under nitrogen giving a product of mp 44–45 °C (lit.[33] 45 °C).

9-BF. Essentially the same method as given by Scherf and Brown[31] and Murphy and Hauser[32] was used here, employing 1,2-dimethoxyethane, phenyllithium, and benzyl chloride, followed by ether extraction and $CaCl_2$ drying. The crude product was recrystallized from methanol giving a species melting at 135 °C (lit.[33] 134–135 °C).

9-PF. The procedure of Kovache[34] and Mathieu[35] was followed for this species, yielding a product with mp 145 °C (lit.[33] 145 °C).

DBF. The method of Scherf and Brown[31] was utilized, yielding a product melting at 147–148 °C (lit.[31] 146 °C).

DiMF. A procedure essentially the same as that for DBF was used.[31] The product exhibited a mp of 95–96 °C (lit.[33] 95–96 °C). Alumina filtration of a benzene solution of DiMF was performed prior to electrochemical use, as noted above for 9-MF.

DPF. Attempts to use the procedure of Gilman[36] and Gorsich were unsuccessful, and a modified procedure had to be developed. 2-Phenylbenzoic acid (25 g) was dissolved in 300 ml of methanol and 2 ml of concentrated H_2SO_4 was added. This mixture was then refluxed for 18 h. The methanol was stripped off with a rotary evaporator and the residue washed with water until rinsings were neutral. The product was dissolved in ether, dried with $CaCl_2$, placed in a 300-ml three-neck flask, and purged several times with nitrogen. Phenyllithium (0.25 mol) was added slowly over a period of 60–75 min. The mixture was cooled and stirred for 12 h under nitrogen. Then 10% (v/v) HCl in methanol was added until the solution was acid to litmus. The solution was then extracted with water several times until the extracts were neutral to litmus. The ether layer was shaken with $CaCl_2$ and evaporated on a rotary evaporator, and 200 ml of acetic acid was added to the residue. This solution was refluxed for 15 min, at which time DPF crystallized out. This was recrystallized from methanol to give a product with mp 223 °C (lit.[37] 222 °C).

Anal. Calcd for $C_{25}H_{18}$: C, 94.32; H, 5.68, mol wt, 318. Found: C, 94.22; H, 5.68, mol wt, 318.

BMF. 9-Benzylfluorene (5 g, 0.02 mol) was added to 50 ml of dioxane in a three-neck, 300-ml flask which was purged with nitrogen several times. Potassium (0.78 g, 0.02 mol) was added with nitrogen flowing. The flask was again purged. The solution was refluxed for 2 h and cooled, and 5 ml of methyl iodide (slight excess) was added with a syringe. The solution was stirred for 2 h under nitrogen, 40 ml of water containing 4 ml of HCl was added, and the solution was repeatedly extracted with benzene. The benzene extracts were backwashed with water to remove dioxane, dried with $CaCl_2$, and evaporated to dryness. The crude BMF was recrystallized three times from hexane to give a product with mp 99 °C.

Anal. Calcd for $C_{21}H_{18}$: C, 93.33; H, 6.67, mol wt, 270. Found: C, 93.31; H, 6.70, mol wt, 270.

PBF and PMF. 9-PF (50 g, 0.02 mol) was dissolved in 50 ml of 1,2-dimethoxyethane in a 300 ml, three-neck flask. After thorough purging with nitrogen 0.02 mol of phenyllithium was added with a syringe. The mixture was refluxed for 2 h, cooled to room temperature, and 3.0 g of benzyl chloride slowly added from a syringe. The solution was stirred for 2 h under nitrogen and 40 ml of water containing 4 ml of concentrated HCl was added. The reaction mixture was extracted several times with benzene and the extracts were combined and backwashed with water to remove the solvent. The benzene extracts were then dried with $CaCl_2$, filtered, and evaporated to dryness. The crude PBF was recrystallized from ethanol to give a product with mp 141 °C (lit.[33] 140 °C).

Anal. Calcd for $C_{20}H_{16}$: C, 93.97; H, 6.03. Found: C, 93.85; H, 6.05.

PMF was prepared similarly except that methyl iodide was, of course, used instead of benzyl chloride. The pure PMF had mp 84 °C (lit.[33] 85 °C).

Prior to electrolysis these species were filtered through alumina, as explained above.

9-Phenyl-9-deuteriofluorene. As above, the anion of 9-PF was prepared by dissolving 3.0 g of 9-PF in 40 ml of dioxane in a three-neck flask, purging with nitrogen, adding 0.015 mol of phenyllithium, and refluxing for 2 h under nitrogen. The red anion was clearly seen. After cooling to room temperature, 5 ml of 99+% D_2O (an excess) was added by syringe. This solution was stirred for 2 h under nitrogen, and then 40 ml of water containing 4 ml of HCl was added. Benzene extraction, water backwashing, $CaCl_2$ drying, and evaporation to dryness then followed. Crude, deuterated 9-PF was dissolved in benzene, the solution filtered through a small column of neutral alumina, and the filtrate evaporated under a stream of nitrogen followed by vacuum drying for 2 h. The NMR of 9-PF exhibits a peak for the 9 proton at δ 5.05,[35] while the deuterated material prepared as above had no detectable absorption in the range δ 4.75–5.25, indicating complete deuteration of the 9 position.

9-Benzyl-9-deuteriofluorene. This material was prepared in essentially the same manner as the deuterated 9-PF. To 2.50 g (0.01 mol) of 9-BF in 40 ml of dioxane was added 0.012 mol of phenyllithium. After refluxing, 5 ml of D_2O was added, then the H_2O–HCl mixture, followed by benzene extraction. The benzene extracts were water backwashed, dried with $CaCl_2$, and evaporated to dryness. Methanol was used to recrystallize the product. Alumina filtration was also used prior to electrochemical experiments. The NMR of 9-BF[35] exhibits a doublet centered at δ 3.10 due to the benzyl protons, and a triplet due to the 9-position proton centered at δ 4.20. The deuterated product prepared as described above exhibited only a singlet with integrated area corresponding to two protons at δ 3.10, but no signal at δ 4.20, indicating complete deuterium substitution at the 9 position.

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Registry No.—9-BF, 1572-46-9; 9-PF, 789-24-2; 9-MF, 2523-37-7; DBF, 4709-64-2; PBF, 35377-96-9; BMF, 61076-90-2; DPF, 20302-14-1; DiMF, 4569-45-3; PMF, 56849-83-3; 2-phenylbenzoic acid, 947-84-2; phenyllithium, 591-51-5; methyl iodide, 74-88-4; benzyl chloride, 100-44-7; 9-phenyl-9-deuteriofluorene, 61076-91-3; D_2O, 7789-20-0; 9-benzyl-9-deuteriofluorene, 15480-52-1.

References and Notes

(1) Taken in part from the Ph.D. Thesis of A. L. Lagu, The University of Cincinnati, May 1974.
(2) G. J. Hoijtink, J. Van Shooten, E. de Boer, and W. J. Aalbersbert, *Recl. Trav. Chim. Pays-Bas*, **73**, 355 (1954).
(3) G. J. Hoijtink, *Recl. Trav. Chim. Pays-Bas*, **73**, 895 (1954).
(4) P. S. Given and M. E. Peover, *J. Chem. Soc.* 385 (1960); *Collect. Czech. Chem. Commun.*, **25**, 3195 (1960).
(5) G. J. Hoijtink and J. Van Shooten, *Recl. Trav. Chim. Pays-Bas*, **71**, 1089 (1952).
(6) J. Janata and H. B. Mark, Jr., *J. Phys. Chem.*, **72**, 3616 (1968).
(7) (a) N. H. Velthorst and G. J. Hoijtink, *J. Am. Chem. Soc.*, **87**, 4529 (1965); (b) *ibid.*, *89*, 209 (1967).
(8) C. D. Ritchie and R. E. Uschold, *J. Am. Chem. Soc.*, **89**, 1721 (1967).
(9) A. Streitwieser, Jr., "Molecular Orbital Theory," Wiley, New York, N.Y., 1962, pp 414–415.
(10) J. Janata, J. Gendell, R. G. Lawton, and H. B. Mark, Jr., *J. Am. Chem. Soc.*, **90**, 5226 (1968).
(11) J. R. Jezorek and H. B. Mark, Jr., *Anal. Lett.*, **3**, 515 (1970).
(12) J. R. Jezorek, A. Lagu, T. Siegel, and H. B. Mark, Jr., *J. Org. Chem.*, **38**, 788 (1973).
(13) K. Bowden and A. F. Cockerill, *J. Chem. Soc. B*, 173 (1970).
(14) J. Herovsky and J. Kuta, "Principles of Polarography", Academic Press, New York, N.Y., 1966, pp 73–115.
(15) J. Tomes, *Collect. Czech. Chem. Commun.*, **9**, 12 (1937).
(16) J. Janata and H. B. Mark, Jr., *Anal. Chem.*, **39**, 1876 (1967).
(17) A. J. Jones, *Rev. Pure Appl. Chem.*, **18**, 253 (1968).
(18) G. Hafelinger and A. Streitwieser, Jr., *Chem. Ber.*, **101**, 672 (1968).
(19) R. Asami, M. Levy, and M. Szwarc, *J. Chem. Soc.*, 361 (1962).
(20) R. Waack and M. Doran, *J. Am. Chem. Soc.*, **85**, 1651 (1963).
(21) C. K. Mann, J. L. Webb, and H. M. Walborsky, *Tetrahedron Lett.*, 2249, (1966).
(22) J. A. Kerr, *Chem. Rev.*, **66**, 465 (1966).
(23) S. W. Benson, *J. Chem. Educ.*, **42**, 502 (1965).
(24) G. W. H. Scherf and R. K. Brown, *Can. J. Chem.*, **39**, 1388 (1961).
(25) E. G. Janzen, W. B. Harrison, and J. B. Pickett, *J. Organomet. Chem.*, **16**, 48 (1969).
(26) R. N. Adams, "Electrochemistry at Solid Electrodes", Marcel Dekker, New York, N.Y., 1969.
(27) C. K. Mann and K. K. Barnes, "Electrochemical Reactions in Nonaqueous Systems", Marcel Dekker, New York, N.Y., 1970, pp 201–243.
(28) L. R. LaPaglia, *J. Mol. Spectrosc.*, **6**, 427 (1961).
(29) D. K. Means, Ph.D. Thesis, University of Michigan, 1970.
(30) N. S. Moe, *Acta Chem. Scand.*, **21**, 1389 (1967).
(31) G. W. H. Scherf and R. K. Brown, *Can. J. Chem.*, **38**, 697 (1960).
(32) W. S. Murphy and C. R. Hauser, *J. Org. Chem.*, **31**, 85 (1966).
(33) G. W. H. Scherf and R. K. Brown, *Can. J. Chem.*, **39**, 1388 (1961).
(34) A. Kovache, *Ann. Chim. (Paris)*, **10**, 205 (1918).
(35) A. Mathieu, *Bull. Soc. Chim. Fr.*, 1526 (1971).
(36) H. Gilman and R. Gorsich, *J. Org. Chem.*, **23**, 550 (1958).
(37) R. G. Clarkson and M. Gomberg, *J. Am. Chem. Soc.*, **52**, 2881 (1930).

Observations on Bromine Rearrangement during Demethylation of Bromomethoxybenzoic Acids

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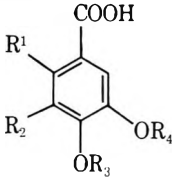
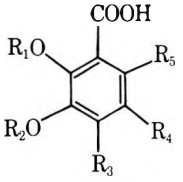
Several aspects of the requirements for concomitant bromine rearrangement during HBr–HOAc demethylation of bromodimethoxybenzoic acids were explored. Formation of 3-bromo-4,5-dihydroxybenzoic acid from 2-bromo-4,5-dihydroxybenzoic acid and isovanillic acid from 2-iodo-4,5-dimethoxybenzoic acid indicated a relationship between halogen loss from its original position and a OH group para to it. This assumption was corroborated when 4-bromo-2,6-dimethoxybenzoic acid resulted in 5-bromoresorcinol. Conversion of 4-bromo-2,3-dimethoxybenzoic acid to 4-bromo-2,3-dihydroxybenzoic acid confirmed the necessity of also locating the halogen to be migrated ortho to the carboxylic acid group. Explanations for these and previous results are proposed.

Perhaps the best studied and most interesting compounds for examining the requisite factors for bromine migration on aromatic compounds (or more aptly, debromination–rebromination) are the bromomethoxybenzoic acids. This series of compounds is well suited to such an investigation since a wide variety of mono- and dimethoxy systems can be devised and synthesized to test several aspects of the mechanism. The various products obtained can be readily analyzed and prepared alternately if needed.

The initial rearrangement observed by Tomita and coworkers[1] when demethylation of 2-bromo-4,5-dimethoxybenzoic acid (**1**) by HBr–HOAc led to 3-bromo-4,5-dihydroxybenzoic acid (**2**) prompted their exploration of several more discernible requirements. For example, they[2-4] found that 2-bromo-3,4-dimethoxybenzoic acid also yields 3-bromo-4,5-dihydroxybenzoic acid (**2**) and 2-bromo-5-methoxybenzoic acid gives 4-bromo-3-hydroxybenzoic acid while 2-bromo-4-methoxybenzoic acid only produces 3-bromophenol. Further experiments indicated that replacement of the carboxylic acid group with an acetyl, aldehyde, or methyl moiety or substitution of chlorine for bromine on the ring caused only ether cleavage but no halogen migration to occur. They also observed that use of 48% HBr as the demethylating reagent formed some rearranged product as well as 3,4-dihydroxybenzoic acid while HCl–HOAc, aqueous HCl, HI, or $AlCl_3$ brought about only demethylation.



1, R_1 = Br; R_2 = H; R_3 = R_4 = Me
2, R_1 = R_3 = R_4 = H; R_2 = Br
6, R_1 = Br; R_2 = R_3 = R_4 = H
7, R_1 = I; R_2 = H; R_3 = R_4 = Me
12, R_1 = R_2 = R_4 = H; R_3 = Me



3, R_1 = R_2 = Me; R_3 = R_4 = R_5 = H
4, R_1 = R_2 = Me; R_3 = R_4 = H; R_5 = Br
5, R_1 = R_2 = R_3 = R_5 = H; R_4 = Br
8, R_1 = R_2 = Me; R_3 = Br; R_4 = R_5 = H
9, R_2 = Me; R_3 = NO_2; R_1 = R_4 = R_5 = H
10, R_1 = R_2 = Me; R_3 = NO_2; R_4 = R_5 = H
11, R_1 = R_2 = Me; R_3 = R_5 = H; R_4 = Br
13, R_1 = R_2 = R_4 = R_5 = H; R_3 = Br
14, R_1 = R_2 = R_3 = R_4 = H; R_5 = Br

Subsequent work by Pettit and Piatak[5] expanded this rearrangement to the o-veratric acid (**3**) series by converting 6-bromo-2,3-dimethoxybenzoic acid (**4**) to 5-bromo-2,3-dihydroxybenzoic acid (**5**) and added the nitro group as a potential alternative to the acid moiety by reporting the formation of 3,4-dihydroxynitrobenzene along with 2-bromo-4,5-dihydroxynitrobenzene during reaction of 2-bromo-4,5-dimethoxynitrobenzene with HBr–HOAc.

Results and Discussion

The position and relationships of ring substituents on the starting compounds and their products from the previous work[1-5] implies that the reaction sequence involves (a) demethylation of the methoxyl groups; (b) loss of bromine from the ring as the critical key step; and (c) rebromination of the resultant phenolic acid at a more favorable location. Loss of the bromine atom in the second step appears to occur when it occupies a position which is not favored by simple bromination of the corresponding phenolic acid and is situated either ortho or para to a potential hydroxy group and ortho to the carboxylic acid moiety. The latter criteria have, however, not been rigidly tested since only one example[4] in which the original methoxyl was meta to the bromine was used, and only examples where the halogen atom is ortho to the acid group have been employed. Therefore, we undertook the HBr–HOAc reaction of some model compounds to query the validity of the reaction sequence and provide further information about the character and relationships of the functional groups.

In order to test the first step of the sequence bromohydroxy acid **6** was chosen as a model, since migration of the bromine should occur with this compound even if methoxyl cleavage proceeds initially. Further examination of this part of the mechanism included 6-iodo acid **7**. Hopefully, the more reactive iodine atom[6] would allow for less energetic and, consequently, controllable reaction conditions enhancing the possibility of isolating significant intermediates. Use of iodine would also expand the range of halogens capable of undergoing the rearrangement. Two additional acids, 4-bromo-2,6-dimethoxybenzoic acid and 4-bromo-o-veratric acid (**8**), were chosen to verify the necessity of orienting the bromine ortho or para to one methoxy group and ortho to the carboxylic acid moiety.

Of the four desired model compounds only **8** was essentially unknown via a synthetic route. The others could be prepared by available literature methods except for iodo acid **7**, which was best made by direct iodination of veratraldehyde using the iodine–silver trifluoroacetate method[7] followed by oxidation of the aldehyde moiety. The 4-bromo acid **8** prepara-

tion started with the nitration of *o*-vanillin acetate using a combination of procedures by Dey and Kutti[8] and Ichikawa et al.[9] The resultant nitro aldehyde was then oxidized and hydrolyzed to nitro acid **9**, which upon prolonged treatment with diazomethane gave the methyl ester of nitro acid **10**. Comparison of an NMR spectrum of the 4-nitro ester with those of methyl 2,3-dimethoxy-5-nitrobenzoate[10] and methyl 2,3-dimethoxy-6-nitrobenzoate[11] revealed the original structural assignments to be correct.

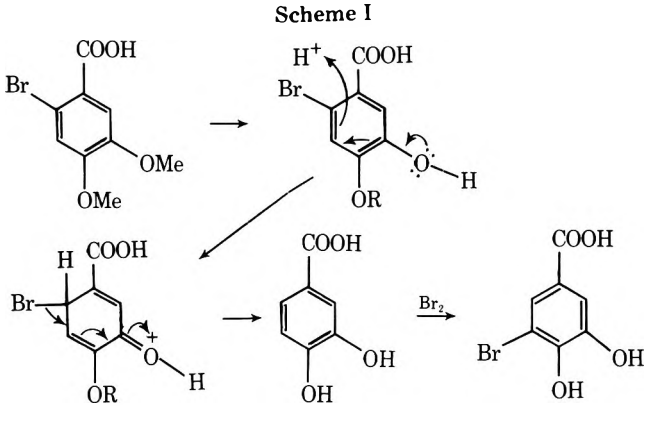
Conversion of the nitro moiety to a bromine and hydrolysis of the resultant bromo ester to the desired 4-bromo acid **8** was carried out without rigid characterization of the two intermediates because they did not crystallize. The desired acid **8** had mp 137–138 °C, quite different from mp 87–89 °C for 6-bromo acid[5] **4** and mp 120 °C for 5-bromo acid[12] **11**. An NMR spectrum of acid **8** had aromatic proton doublets at δ 7.44 and 7.79 with J = 8.5 Hz consistent with the normal coupling constant range of ortho protons. The 6-bromo acid **4** had doublets at δ 6.85 and 7.29 with J = 9.0 Hz indicating the shielding influence of the methoxyl moiety on the adjacent C-4 proton. As might be expected, the aromatic protons for 5-bromo acid **11** appeared at δ 7.25 and 7.85 (J = 2.0 Hz).

Demethylation and/or migration reactions were accomplished in heavy-walled Pyrex tubes. Products were identified by their physical and spectroscopic characteristics and by comparison with specimens synthesized by alternate routes when possible. For example, 5-bromo acid **2** secured from reaction **6** was related to material made by brominating protocatechuic acid.[1] Reaction of 6-iodo acid **7** resulted in isovanillic acid (**12**) identified by mp 250–255 °C (lit.[13] mp 255–257 °C) and an appropriate NMR spectrum. Similarly delineated was 5-bromoresorcinol, the product from reaction of 4-bromo-2,6-dimethoxybenzoic acid, except that it was found to be best characterized as 5-bromo-1,3-dimethoxybenzene.[14]

The structure of 4-bromophenolic acid **13** formed in the HBr–HOAc reaction of 4-bromo acid **8** was also elucidated spectroscopically. Although its melting point (227.5–229 °C) was comparable to that of the potential rearrangement product 5-bromo acid **5** (mp[5] 222–223 °C), an NMR spectrum of **13** had aromatic proton doublets at δ 7.03 and 7.24 (J = 9.0 Hz) which were more appropriate for two ortho protons. An NMR spectrum of **5** had these doublets at δ 7.14 and 7.35 with J = 2.0 Hz while the third isomer, 6-bromo acid[5] **14**, had values of δ 6.73 and 6.86 (J = 7.0 Hz) for its aromatic protons. The identity of **13** was confirmed by comparison with a sample prepared from **8** by $AlCl_3$ demethylation, a method which does not lead to rearrangement.[2,5]

Evaluation of the above and former[1-5] results discloses some unique aspects about the overall reaction and leads us to postulate the mechanism depicted to Scheme I. Initially, cleavage of the methoxy group para (or even ortho) to the halogen will occur. Demethylation of this one in preference to the C-4 methoxyl is favored because the latter will be rendered less basic by the electron-withdrawing effects of the carboxyl.[15] This change will permit the more inductive hydroxyl group to assist protonation of the carbon bearing the halogen. Bromine migration is possible with a para hydroxyl moiety as evidenced by the conversion of 2-bromo acid **6** to 3-bromo acid 2. alternatively, both methoxy groups could be cleaved before the protonation step but the isolation of isovanillic acid (**12**) from the reaction of iodo acid **7** supports the former interpretation. Rebromination and, hence, halogen migration will result when the formation of protocatechuic acid, which promotes bromination at C-5, is complete.

Scheme I



The decarboxylation of 4-bromo-2,6-dimethoxybenzoic acid during its demethylation coupled with the previous[3] conversion of 2-bromo-4-methoxybenzoic acid to 3-bromophenol tends to also confirm the supposition that the halogen should be ortho or para to at least one oxygen functionality. In both of these examples, one or more methoxy groups were situated meta to the bromine while the carboxylic acid was either ortho or para.

Perhaps the most curious outcome is the isolation of 4-bromophenolic acid **13**, a product of only demethylation, from bromo acid **8**. It appears that bromine loss from the aromatic rings is greatly influenced by its position with respect to the acid group. It can best be explained by a deactivating effect of the carboxyl group upon protonation of the C-4 position bearing the bromine.[15] This effect apparently negates any activating influence by the ortho oxygen moiety. When the carboxylic acid is located ortho to the bulky bromine (Scheme I), however, it is twisted out of plane and loses a large part of its influence permitting the hydroxyl group para to the bromine to assist protonation and, thus, bring about bromine loss.

Experimental Section

The ^1H NMR spectra were recorded with a Varian A-60A instrument. Unless otherwise noted, $CDCl_3$ was used as the solvent with Me_4Si as the internal standard. IR spectra were taken on KBr disks with a Perkin-Elmer 237B instrument. Melting points are uncorrected and were observed with a Fisher-Johns apparatus.

HBr–HOAc Reaction of 2-Bromo-4,5-dihydroxybenzoic Acid (6). The 2-bromo acid[2] (0.5 g) was heated with a 46% HBr–HOAc solution (10 ml) in a sealed tube for 3 h at 130 °C. The solution was evaporated under a stream of nitrogen, and the product was recrystallized from water to yield 3-bromo acid **2** [mp 226–228 °C (lit.[1] mp 222 °C); NMR (Me_2SO) δ 7.44 (d, 1, J = 2.0 Hz), 7.59 (d, 1, J = 2.0 Hz)], identical in all respects with a sample prepared by brominating 3,4-dihydroxybenzoic acid.[1]

2-Iodo-4,5-dimethoxybenzaldehyde. A solution of iodine (29.2 g) in CCl_4 (160 ml) was added to veratraldehyde (19.0 g) and CF_3CO_2Ag (25.0 g) with shaking. The reaction mixture was stirred for 4 h, the yellow AgI collected by filtration, and the filtrate washed with 5% $NaHSO_3$. Removal of the solvent and crystallization of the residue from methanol (500 ml) gave 27.0 g (81.9%) of the 2-iodoaldehyde: mp 145–146 °C; NMR δ 3.88 (s, 3), 3.92 (s, 3), 7.27 (s, 1), 7.34 (s, 1), 10.12 (s, 1).

Anal. Calcd for $C_9H_9IO_3$: C, 37.01; H, 3.11. Found: C, 36.95; H, 3.13.

Rilliet[16] reported mp 128 °C for this compound obtained via diazotization of 2-amino-4,5-dimethoxybenzaldehyde and reaction with KI.

2-Iodo-4,5-dimethoxybenzoic Acid (7). The iodo aldehyde (13.1 g) was oxidized by addition to $KMnO_4$ (37.0 g) in water (200 ml). The mixture was heated at 40 °C with stirring for 1.5 h, then filtered. Acidification of the filtrate and recrystallization of the product from ethanol–water gave 3.29 g (28%): mp 159–160 °C; NMR δ 3.71 (s, 3), 3.75 (s, 3), 7.38 (s, 1), 7.42 (s, 1).

Anal. Calcd for $C_9H_9IO_4$: C, 35.08; H, 2.95. Found: C, 34.52; H, 2.97.

HBr–HOAc Reaction with 2-Iodo-4,5-dimethoxybenzoic Acid (7). A 0.5-g sample of iodo acid **7** was heated at 50 °C with 10 ml of 46% HBr/HOAc overnight. Some decomposition occurred as evidenced by the darkness of the reaction. Removal of the solvent under a stream of nitrogen and recrystallization of the residue from water yielded 0.16

g of isovanillic acid (**12**), mp 216–220 °C. Recrystallization from water (Norite A) resulted in mp 250–255 °C (lit.[13] mp 255–257 °C); NMR δ 3.89 (s, 3), 6.94 (d, 1, J_{AB} = 9.0 Hz), 7.35 (d, 1, J = 1.7 Hz), 7.41 (1, J_{AB} = 9.0, J_{AM} = 1.7 Hz).

Demethylation of 4-Bromo-2,6-dimethoxybenzoic Acid. A sample of 4-bromo-2,6-dimethoxybenzoic acid[17] (0.5 g) was sealed in a glass tube with 40% HBr in glacial HOAc (5 ml). The tube was heated to 130 °C during 100 min, kept at 130–142 °C for 65 min, and then cooled. The solution was evaporated in vacuo, and the residue was taken up in ether and washed with dilute $NaHCO_3$ and water. The product was treated with diazomethane overnight. Recrystallization of the methylated material from MeOH–petroleum ether gave 0.3 g (75%) of 5-bromo-1,3-dimethoxybenzene: mp 60.5–62.5 °C; ν_{max} 1580, 1215, 1165, 1050 cm^{-1}; NMR δ 3.74 (s, 6), 6.35 (t, 1, J = 2.0 Hz), 6.62 (d, 2, J = 2.0 Hz). A melting point of 66 °C was reported by Dean and Whalley.[14]

4-Nitro-2-hydroxy-3-methoxybenzaldehyde. A procedure combining the methods of Dey and Kutti[8] and Ichikawa et al.[9] gave the best results. Finely powdered *o*-vanillin acetate (30 g) was added to a stirred mixture of fuming HNO_3 (100 ml) and concentrated H_2SO_4 (20 ml) at −15 °C over 1 h. After the reaction mixture had been stirred for 40 min at −5 to −15 °C, it was poured into ice water (ca. 700 g). The resultant oil was recovered with benzene and washed with dilute $NaHCO_3$ and water. Recrystallization of the residue from methanol gave 12 g of material, mp 134–137 °C, which proved to be two compounds by TLC.

All of the nitrated material was therefore hydrolyzed in 2% NaOH (700 ml) by refluxing for 20 min. Storage of the solution overnight at ambient temperature gave an orange precipitate which was collected. Acidification of the filtrate yielded the 4-nitro isomer which was recrystallized from methanol–water (Norite A) to give 22 g (72.2%) of product with mp 92–93.5 °C; ν_{max} 3100, 1670, 1525 cm^{-1}. A melting point of 92–93 °C was reported by both Dey and Kutti[8] and Ichikawa et al.[9]

The orange precipitate from the hydrolysis was suspended in hot water and acidified. The resultant brown material was recrystallized from methanol (Norite A) to yield the 6-nitro isomer as yellow needles: mp 104–107 °C; ν_{max} 3050, 1670, 1500 cm^{-1}. Ichikawa[9] reported mp 104 °C, while Dey and Kutti[8] observed only 72–73 °C.

4-Nitro-2-hydroxy-3-methoxybenzoic Acid (9). Silver nitrate (50 g) was added to the above 4-nitro aldehyde (10 g) suspended in a solution of NaOH (22 g) in water (1 l.) at 70 °C. The mixture was refluxed for 5 h, then filtered hot. Acidification of the filtrate formed a brown precipitate which was recrystallized from methanol–water (Norite A) to yield 6 g (55.5%) of pale yellow flakes, mp 205–206.5 °C. Repeated recrystallization from the same solvent gave an analytical sample of **9** with mp 206.5–208 °C; ν_{max} 3000, 1640, 1510 cm^{-1}; NMR δ 3.74 (s, 3), 7.32 (d, 1, J = 8.7 Hz), 7.72 (d, 1, J = 8.7 Hz).

Anal. Calcd for $C_8H_7NO_6$: C, 45.08; H, 3.31; N, 6.57. Found: C, 44.96, 45.06; H, 2.97, 3.43; N, 6.59, 6.76.

The nitro acid **9** was methylated with diazomethane to methyl 4-nitro-2-hydroxy-3-methoxybenzoate which had mp 112–114 °C (from methanol); ν_{max} 3130, 1680, 1540 cm^{-1}; NMR δ 4.01 (s, 3), 4.05 (s, 3), 7.16 (d, 1, J = 8.0 Hz), 7.67 (d, 1, J = 8.0 Hz).

Anal. Calcd for $C_9H_9NO_6$: C, 47.58; H, 3.99; N, 6.17. Found: C, 47.77; H, 3.98; N, 6.43.

Methyl 4-Nitro-2,3-dimethoxybenzoate. Freshly prepared diazomethane (ca. 6 g) in ether was added to nitro acid **9** (6.0 g) dissolved in ether, and the solution was stored for 3 days at room temperature. Removal of the solvent and crystallization of the residue from methanol resulted in 2.5 g (36.8%) of ester which gave an analytical sample having mp 40–42 °C; ν_{max} 1750, 1555 cm^{-1}; NMR δ 3.94 (s, 3), 3.98 (s, 3), 4.03 (s, 3), 7.55 (s, 2).

Anal. Calcd for $C_{10}H_{11}NO_6$: C, 49.80; H, 4.60; N, 5.81. Found: C, 50.25, 50.16; H, 4.66, 4.33; N, 5.53, 5.57.

Hydrolysis of the ester with 2 N KOH on a steam bath for 2 h and acidification of the red solution gave 4-nitro acid **10:** mp 157–159 °C; ν_{max} 3190, 1735, 1595, 1630, 1470 cm^{-1}. Majima and Okazaki[18] indicated mp 94–95 °C for the 4-nitro acid they obtained by oxidizing 2,3-dimethoxy-4-nitrotoluene.

4-Bromo-2,3-dimethoxyoxbenzoic Acid (8). The 4-nitro ester (1.0 g) was reduced with 10% Pd/C (75 mg) in ethanol (20 ml) under 3 atm hydrogen. The catalyst was removed with Celite, and the filtrate evaporated to give an oil with infrared bands at 3440, 1670, 1580 cm^{-1} and NMR signals at δ 3.83 (s, 6), 3.90 (s, 3), 4.60 (s, 2), 6.48 (d, 1, J = 8.5 Hz), 7.49 (d, 1, J = 8.5 Hz).

The amino ester was taken up in water (20 ml) containing 48% HBr (4.0 ml) and cooled to 5 °C. A solution of $NaNO_2$ (0.37 g) in water (1.5 ml) was introduced, and the mixture was stored at 5 °C for 1 h. A slurry of CuBr prepared from $CuSO_4$ (0.7 g), NaBr (1.8 g), concentrated H_2SO_4 (0.7 g), Cu powder (0.44 g), and water (10 ml) was added, and the diazotization mixture was stirred at ambient temperature overnight. The product was recovered with ether. It failed to crystallize, but had infrared bands at 1700 and 1550 cm^{-1} and NMR signals at δ 3.91 (s, 3), 3.95 (s, 6), 7.34 (s, 2).

The bromo ester was hydrolyzed with 5% NaOH (20 ml) by heating at reflux for 2.5 h. The reaction mixture was filtered, and the filtrate acidified. The bromo acid **8** was recovered with ether and crystallized from methanol to yield 1.06 g (98.2%), which gave an analytical sample after repeated recrystallizations from the same solvent. It had mp 137–188 °C; ν_{max} 2970, 1690, 1585 cm^{-1}; NMR δ 3.93 (s, 3), 4.13 (s, 3), 7.44 (d, 1, J = 8.5 Hz), 7.79 (d, 1, J = 8.5 Hz).

Anal. Calcd for $C_9H_9BrO_4$: C, 41.39; H, 3.47. Found: C, 41.59, 41.76; H, 3.19, 3.51.

4-Bromo-2,3-dihydroxybenzoic Acid (13). A. HBr–HOAc Reaction. A 0.2-g sample of bromo acid **8** was sealed in a tube with 6.0 ml of a 40% solution of HBr gas in glacial HOAc. The tube was heated to 130 °C in 100 min, maintained at 130–140 °C for 65 min, then cooled. The red solution was evaporated in vacuo, water added to the residue, and the mixture evaporated again. Since an NMR spectrum indicated the presence of acetate moieties, the material was treated with 5% NaOH (10 ml) for 1 h on a steam bath. Acidification of the solution, recovery of the acid with ether, and recrystallization of the product from methanol–water gave 0.1 g (55.5%), mp 227.5–229 °C. Repeated recrystallizations from the same solvent produced **13** melting at 226–228 °C; ν_{max} 3545, 2950, 1680 cm^{-1}; NMR (Me_2SO) δ 7.03 (d, 1, J = 9.0 Hz), 7.24 (d, 1, J = 9.0 Hz).

Anal. Calcd for $C_7H_5BrO_4$: C, 36.08; H, 2.16. Found: C, 35.75, 35.84; H, 2.21, 2.13.

DaRe and Cimatoribus[19] reported the isolation of 4-bromo-2,3-dihydroxybenzoic acid, mp 225–227 °C, from a natural source.

B. $AlCl_3$ Reaction. Anhydrous $AlCl_3$ (2.5 g) was added to bromo acid **8** in benzene (16 ml), and the mixture was refluxed for 4 h. Additional $AlCl_3$ (1.5 g) was introduced and refluxing was continued for 2 h. The cooled reaction mixture was decomposed with concentrated HCl (10 ml) and water (7 ml), and the product isolated with ether. Recrystallization of acid **13** from methanol–water yielded 0.8 g (44.4%), mp 224–228 °C, identical with the sample from A by mixture melting point and comparison of infrared and NMR spectra.

Registry No.—**2,** 61203-46-1; **6,** 61203-47-2; **7,** 61203-48-3; **8,** 61203-49-4; **9,** 61203-50-7; **10,** 61203-51-8; **12,** 645-08-9; **13,** 61203-52-9; 2-iodo-4,5-dimethoxybenzaldehyde, 61203-53-0; iodine, 7553-56-2; veratraldehyde, 120-14-9; 4-bromo-2,6-dimethoxybenzoic acid, 61203-54-1; 5-bromo-1,3-dimethoxybenzene, 20469-65-2; 4-nitro-2-hydroxy-3-methoxybenzaldehyde, 20041-61-6; *o*-vanillin acetate, 7150-01-8; HNO_3, 7697-37-2; 6-nitro-2-hydroxy-3-methoxybenzaldehyde, 2426-86-0; diazomethane, 334-88-3; methyl 4-nitro-2-hydroxy-3-methoxybenzoate, 61203-55-2; methyl 4-nitro-2,3-dimethoxybenzoate, 61203-56-3; methyl 4-amino-2,3-dimethoxybenzoate, 61203-57-4; methyl 4-bromo-2,3-dimethoxybenzoate, 61203-58-5; $AlCl_3$, 7446-70-0.

References and Notes

(1) M. Tomita and T. Kugs, *Yakugaku Zasshi*, **75**, 1354 (1955).
(2) M. Tomita, Y. Kondo, and S. Tanaka, *Yakugaku Zasshi*, **76**, 1119 (1956).
(3) M. Tomita, S. Kura, and S. Tanaka, *Yakugaku Zasshi*, **76**, 1122 (1956).
(4) M. Tomita and K. Fujitani, *Yakugaku Zasshi*, **76**, 1125 (1956).
(5) G. R. Pettit and D. M. Piatak, *J. Org. Chem.*, **25**, 721 (1960).
(6) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", McGraw-Hill, New York, N.Y., 1968, p 439.
(7) R. N. Hazeldine and A. G. Sharpe, *J. Chem. Soc.*, 993 (1952).
(8) B. B. Dey and V. A. Kutti, *Proc. Natl. Inst. Sci. India*, **6**, 641 (1940).
(9) M. Ichikawa, Y. Takaki, and H. Ichigas, *Yakugaku Zasshi*, **81**, 768 (1961).
(10) C. S. Gibson, J. L. Simonsen, and M. G. Rau, *J. Chem. Soc.*, **111**, 69 (1917).
(11) M. Tomita and K. Hirai, *Yakugaku Zasshi*, **78**, 798 (1958).
(12) W. Davies, *J. Chem. Soc.*, **123**, 1575 (1923).
(13) A. Klemenc, *Chem. Ber.*, **49**, 1371 (1916).
(14) N. B. Dean and W. B. Whalley, *J. Chem. Soc.*, 4638 (1954).
(15) We wish to thank a referee for this suggestion.
(16) A. Rilliet, *Helv. Chim. Acta*, **5**, 547 (1922).
(17) F. P. Doyle, J. H. C. Nayler, H. R. J. Waddington, J. C. Hanson, and G. R. Thomas, *J. Chem. Soc.*, 497 (1963).
(18) R. Majima and Y. Okazaki, *Chem. Ber.*, **49**, 1482 (1916); *Sci. Rep. Tohoku Imp. Univ.*, **5**, 215 (1916).
(19) DaRe and L. Cimatoribus, *Chem. Ber.*, **95**, 2912 (1962).

Ring Opening Reactions with Diphenylcyclopropylcarbinol with Bromine

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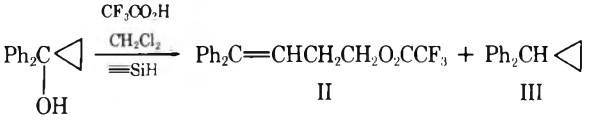
The reactions of diphenylcyclopropylcarbinol with 1 and 2 equiv of bromine in acetic acid have been carried out. In the first case the products are 1-acetoxy-2,4-dibromo-1,1-diphenyl-1-butanol and 2,4-dibromo-1,1-diphenyl-1-butene. In the latter case no dibromo acetate is formed, and it has been demonstrated that this product in the presence of excess bromine is converted to the latter two products. The dibromo acetate is not formed upon treatment of 4-bromo-1,1-diphenyl-1-butene with bromine in acetic acid. The mechanistic implications of these observations are considered.

With regard to their possible reactions with bromine the cyclopropylcarbinols may be considered to be difunctional compounds capable of undergoing the ring opening reactions of cyclopropanes or the elimination of water by the bromine acting in its capacity as a Lewis acid. This capability has been demonstrated in several studies of the bromination of 3,5-cyclocholestan-6β-ol as well as its methyl ether and acetate derivatives; the product in each case being an essentially quantitative yield of 3β,5α,6β-tribromocholestane.[1] When treated with a deficiency of bromine in ether at 0 °C cholesteryl bromide was isolated, and it was proposed that this material served as an intermediate in the formation of the tribromide. The formation of cholesteryl bromide was proposed as a consequence of first an S_Ni replacement of the 6β-hydroxyl group by bromine followed by an *i*-steroid rearrangement. The possible simultaneous loss of hydroxyl and ring opening nucleophilic attack of bromine at the 3 position was not considered, though it will be shown subsequently that this possibly exists.

In searching for a model system in which to examine the bifunctional character of the cyclopropylcarbinols, diphenylcyclopropylcarbinol (DPCC, I) was chosen because the products could be expected to be readily identified and analyzed by proton and carbon NMR spectroscopy and the expected benzhydryl-like carbocation formed by loss of hydroxyl would be relatively stable and unlikely to undergo extensive rearrangement.

The treatment of DPCC with trifluoroacetic acid in the presence of triethyl- or triphenylsilane has been reported to yield both the olefin ester II and diphenylcyclopropylmethane (III).[2] The latter arises from the trapping of the diphenylcyclopropylcarbinyl cation by the hydride, while II may arise from a nucleophilic attack of the acid on the cyclopropyl ring of the cation or by a concerted process of such a ring opening with the loss of water. The latter explanation was preferred as no 1,1-diphenyl-1-butene was found among the products—a fact attributed to a lack of electrophilic character in the cyclopropyl methylenes of the cation.

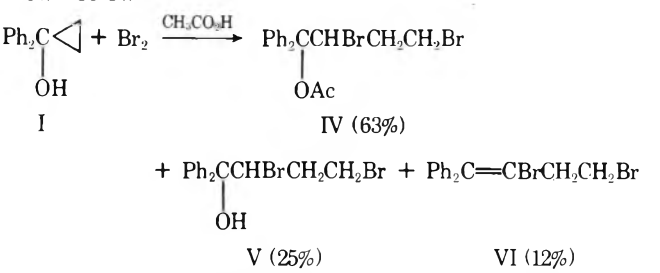


DPCC, I II III

During the course of the study described here, Skell, Day, and Shea[3] reviewed, corrected, and extended the understanding of the reactions of bromine with cyclopropane and several alkylcyclopropanes. In order to avoid the free-radical chain process, the reaction must be conducted in the dark. The ionic reaction is often sluggish, leading to a complex mixture of isomeric mono-, di-, and tribromoalkanes which require a sequence of bromination, dehydrobromination, and rearrangement steps which are initiated by electrophilic attack of bromine on the cyclopropyl ring system.

Results

The reaction of diphenylcyclopropylcarbinol in the dark with 1 equiv of bromine in acetic acid is over in about 3 h at room temperature. Conventional workup of the reaction mixture by drowning in water, extraction, and a wash with bicarbonate to remove excess acetic acid gave the products shown below.



I IV (63%) V (25%) VI (12%)

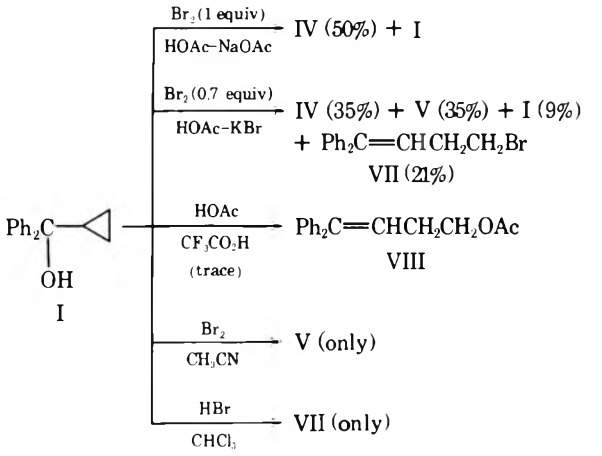
The structures of each were determined by proton and carbon NMR spectroscopy, elemental and/or high-resolution mass spectrometry, and synthesis or comparison with known compounds from the literature. When the reaction was conducted directly in the NMR probe using perdeuterioacetic acid or worked up by removing the solvent at reduced pressure no dibromo olefin VI was noted, and the products were IV and V only in essentially equal amounts. Thus, VI appears not to be a direct reaction product (see also below).

When I is reacted in the same fashion with 2 equiv of bromine the color is not discharged after several days. However, the reaction was found to be over essentially after 3 h or less as above. The products were the dibromo alcohol V (43%) and the dibromo olefin VI (57%) only. Indeed, if one followed the course of the reaction in the NMR probe in perdeuterioacetic acid it became apparent that as the dibromo acetate IV was created it was destroyed by the excess bromine forming the mixture of V and VI. In an independent experiment pure IV in acetic acid was treated with bromine to also give V and VI. In fact, in a similar experiment the dibromo alcohol V was rapidly dehydrated by bromine in acetic acid to form VI. Such dehydrations of tertiary alcohols with bromine have been observed before.[4]

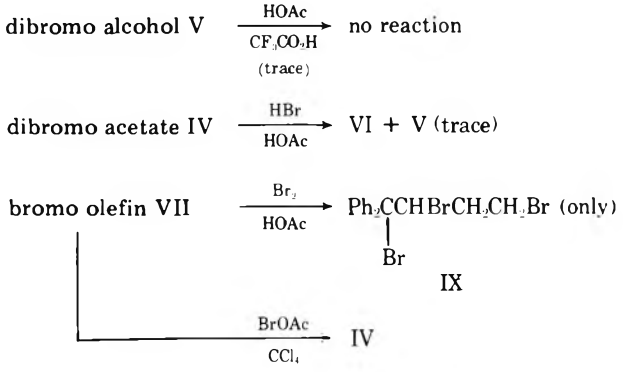
A variety of reactions of DPCC and related compounds have been carried out in an attempt to explicate the mechanism of the reaction. These are summarized in Schemes I and II and will be mentioned as pertinent to the subsequent discussion. Of particular interest, however, is the observation that when the reaction medium is buffered with sodium acetate the reaction with bromine is greatly slowed and only the dibromo acetate IV is formed. In contrast, when the medium contains added potassium bromide the bromine color is discharged quite rapidly. While this might be due only to a normal salt effect, the appearance of the bromo olefin VII as a new product suggests the possible presence of hydrogen bromide or an altered mode of reaction.

Finally, the bromo olefin VII (Scheme II) when treated with

Scheme I



Scheme II



bromine in acetic acid yields a quantitative conversion to the tribromide IX. No evidence for the formation of the dibromo acetate IV could be found. In contrast, when V is treated with acetyl hypobromite high yields of IV result plus smaller amounts of IX presumably formed by the incomplete conversion of the bromine to hypobromite.

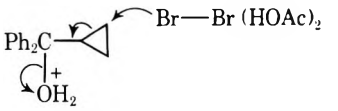
Discussion

The formation of the dibromo alcohol V when DPCC (I) is brominated in acetic acid or in an aprotic solvent such as acetonitrile is reasonably the result of a conventional electrophilic attack of bromine on the cyclopropane ring just as pictured by Skell, Day, and Shea.[3] Subsequent dehydration of V by bromine or some other acid accounts for the formation of the dibromo olefin VI.

Of greater interest in this study is the dibromo acetate IV. This product is not formed by the prior esterification of DPCC and then electrophilic ring bromination, for DPCC fails to esterify under any usual experimental conditions. Indeed, treatment of DPCC in acetic acid with acid yields the ring-opened acetate VIII, and no derivatives of VIII are found in the bromination. Furthermore, attempts to acetylate the dibromo alcohol V also under a variety of conditions failed in each case.

The rate of bromination of DPCC is greatest in acetic acid containing potassium bromide where some small amounts of hydrogen bromide may be present. In buffered acetic acid the reaction is slowest, while the reaction in acetic acid is intermediate in rate. Thus, it appears likely that the reaction is acid catalyzed. Since the esterification results discussed above rule out the likely formation of the diphenylcyclopropylcarbinyl cation during the bromination, a more unusual pathway for the formation of IV is called for.

Nucleophilic attack of bromine on DPCC with a concomitant loss of water can be pictured as



The acetic acid is included because it is known that complexes of the acid with bromine exist.[5] The result of a process such as that pictured would be the formation of the bromo olefin VII and a positive bromine stabilized by the acetic acid or more likely present as acetyl hypobromite. The formation of VII in appreciable amounts when excess bromide ion is present results from trapping of the positive bromine entity by bromide. Finally, it was demonstrated that the acetyl hypobromite will add to VII in acetic acid to yield IV. The evidence of Carey and Tremper[2] that the ring opening of DPCC to form II may involve a nucleophilic attack on the cyclopropane ring may be taken as supporting evidence for the mechanism proposed here. Thus, bromine may attack cyclopropane rings in either an electrophilic or nucleophilic sense.

The evidence concerning the bromination of 3,5-cyclocholestan-6β-ol can now be reassessed. In an aprotic solvent the formation of cholesteryl bromide occurs by nucleophilic attack of the bromine on the cyclopropane ring at C-3 with loss of the hydroxyl. When there is a deficiency of bromine the reaction terminates, but with adequate bromine the observed tribromide is formed. Unfortunately, the bromination of the cycloalcohol in acetic acid has not been reported.

Experimental Section

General. Diphenylcyclopropylcarbinol was obtained from Aldrich and used directly. Proton and carbon-13 NMR spectra were obtained on JEOL MH-100 and FX-60 FT instruments, respectively. All chemical shifts are referenced to tetramethylsilane. Combustion analyses were obtained from Galbraith Laboratories, Knoxville, Tenn., and high-resolution mass spectral analyses were performed by Mr. G. Gabel on the Consolidated Electronics Corp. Model 21-110B mass spectrometer in the Biochemistry Department, Texas A and M University.

Cyclopropyldiphenylcarbinol. Reactions with Acetic Acid. A. A solution of 1.12 g (5.0 mmol) of diphenylcyclopropylcarbinol was prepared in 40 ml of glacial acetic acid and 0.80 g (5.0 mmol) of bromine was added. The mixture was allowed to stand overnight at room temperature in the dark. The reaction mixture was then poured into 100 ml of water and extracted with 3 × 50 ml of chloroform, the combined chloroform extracts were washed with 6% sodium bicarbonate, and the chloroform was removed on a rotary evaporator. The whole crude reaction product was analyzed by proton NMR as consisting of 63% 1-acetoxy-2,4-dibromo-1,1-diphenylbutane, 25% 2,4-dibromo-1,1-diphenyl-1-butanol, and 12% 2,4-dibromo-1,1-diphenyl-1-butene.

The crude product was dissolved in boiling hexane and, upon cooling, deposited 1-acetoxy-2,4-dibromo-1,1-diphenylbutane: mp 112–113 °C; NMR ($CDCl_3$) δ 1.65 (m, 1 H), 2.04 (s, 3 H), 2.50 (m. 1 H), 3.60 (m, 2 H), 6.24 (dd, 1 H, J = 12 and 3 Hz); ^{13}C NMR ($CDCl_3$) δ 22.1 (q), 31.2 (t). 37.7 (t), 56.6 (d), 86.3 (s), 127.0 (d), 127.5 (d), 128.1 (d), 129.1 (d), 139.6 (s), 169.0 (s).[6]

Anal. Calcd for $C_{18}H_{18}O_2Br_2$: C, 50.6; H, 4.5; Br, 37.4. Found: C, 50.87; H, 4.39; Br, 37.4.

The other products are described below.

B. A solution of 1.12 g (5 mmol) of diphenylcyclopropylcarbinol in 40 ml of glacial acetic acid was treated with 1.60 g (10 mmol) of bromine. The reaction mixture was treated in all respects as before. After standing overnight a reddish color still persisted; however, no starting material remained at this time. The workup was as before. The NMR analysis of the whole product gave 43% 2,4-dibromo-1,1-diphenyl-1-butanol and 57% 2,4-dibromo-1,1-diphenyl-1-butene.

C. The reaction of 1.12 g (5 mmol) of diphenylcyclopropylcarbinol with 0.80 g (5 mmol) of bromine was carried out in a solvent prepared by reacting 3 g of anhydrous sodium carbonate with 40 ml of glacial acetic acid, then adding 4 ml of acetic anhydride. The reaction in the dark became colorless only after 5 days. Workup of the reaction as above showed over ca. 50% of the dibromo acetate above plus unreacted starting material.

Other Reactions of DPCC. A. Reaction with Bromine in Acetonitrile. A solution of 1.12 g (5 mmol) of diphenylcyclopropylcar-

binol in 40 ml of acetonitrile was reacted overnight at room temperature in the dark with 0.80 g (5 mmol) of bromine. The standard workup was used. Evaporation of the solvent gave a quantitative yield of a yellow oil which could not be distilled without decomposition. However, the NMR of the oil was that of a pure compound assigned the structure 2,4-dibromo-1,1-diphenyl-1-butanol (V): NMR (CCl_4) δ 2.00 (m, 1 H), 2.30 (m, 1 H), 2.82 (s, 1 H, OH), 3.58 (m, 2 H), 5.47 (dd, 1 H, J = 6 and 1 Hz), 7.2–7.7 (m, 10 H); IR (neat) 3560 cm^{-1}(OH).

Anal. Calcd for $C_{16}H_{16}OBr_2$: mol wt, 383.9543. Found: mol wt, 383.9548.

B. With Hydrobromic Acid. A solution of 2.0 g (0.9 mmol) of diphenylcyclopropylcarbinol in 20 ml of benzene was stirred with 25 ml of 48% hydrobromic acid for 1 h at room temperature. The reaction mixture was washed with water and dilute sodium bicarbonate. The solvent was evaporated, yielding 2.3 g (88%) of light yellow oil, 4-bromo-1,1-diphenyl-1-butene (VII). Purification by high-vacuum short-path distillation gave a product pure by NMR: NMR (CCl_4) δ 2.68 (q, 2 H), 3.40 (t, 2 H), 6.12 (t, 1 H), 7.25 (m, 10 H).

Anal. Calcd for $C_{16}H_{15}Br$: mol wt, 286.0357. Found: mol wt, 286.0364.

C. Reaction with Acetic Acid. A solution of 1.12 g (5 mmol) of diphenylcyclopropylcarbinol in 40 ml of glacial acetic acid was treated with one drop of trifluoroacetic acid at 80 °C for 3 h. The standard workup was used. The product was a slightly brown oil which gave the NMR spectrum expected for pure 4-acetoxy-1,1-diphenyl-1-butene:[2] NMR ($CDCl_3$) δ 2.02 (s, 3 H), 2.44 (t, 1 H, J = 6 Hz), 2.50 (t, 1 H, J = 6 Hz), 4.16 (t, 2 H, J = 6 Hz), 6.18 (t, 1 H, J = 6 Hz), 7.38 (m, 10 H).

Other Reactions. A. 1,2,4-Tribromo-1,1-diphenylbutane. A 5% solution of bromine in carbon tetrachloride was added slowly and dropwise to a solution of 500 mg of 4-bromo-1,1-diphenyl-1-butene (VII) in ca. 10 ml of carbon tetrachloride until the color persisted. The solution was washed with dilute sodium sulfite and the solvent evaporated. Attempted short-path distillation led to decomposition of the product. However, the whole crude product had the NMR of a single pure compound and gave the correct high-resolution MS for $C_{16}H_{15}Br_3$. The structure was assigned as 1,2,4-tribromo-1,1-diphenylbutane (IX) based on the NMR (CCl_4): δ 2.1 (m, 1 H), 2.95 (m, 1 H), 3.70 (m, 2 H), 5.52 (dd, 1 H, J = 7 and 2 Hz), 7.65 (m, 10 H).

Anal. Calcd for $C_{16}H_{15}Br_3$: mol wt, 447.9364. Found: mol wt, 447.9374.

B. Reaction of VII with Bromine in Acetic Acid. The following experiment was carried out in the MH-100 NMR in a standard 5-mm tube. A mixture of ca. 80 mg of VII in 0.6 ml of perdeuterioacetic acid was treated with slightly more than 1 equiv of bromine. The NMR spectrum changed quickly to that of the tribromide IX. No trace of the dibromo acetate IV was evidenced.

C. Reaction of VII with Acetyl Hypobromite. A solution of acetyl hypobromite in carbon tetrachloride was generated as described by Rolston and Yates[7] from 1.5 g of silver acetate. A solution of 1.0 g of VII in 10 ml of carbon tetrachloride was added at −20 °C. After warming to room temperature, the reaction mixture was filtered, washed, and concentrated to give 1.4 g of crude product which analyzed by NMR as 72% of dibromo acetate IV, and 28% of the tribromide IX.

D. Treatment of the Dibromo Acetate IV with Hydrogen Bromide in Acetic Acid. A solution of approximately 200 mg of the dibromo acetate IV in 1 ml of acetic acid was treated by bubbling in hydrogen bromide at room temperature for 2 min. After standing overnight the reaction mixture was worked up in the usual way. An NMR analysis of the product indicated that it was the dibromo olefin VI contaminated with a trace of the dibromo alcohol V.

E. Reactions Which Failed to Yield Product. The following reactions were attempted but only starting material was recovered: (1) Repeated attempts were made to acetylate the DPCC I and the dibromo alcohol V. Among these may be listed acetic anhydride and acetyl chloride both with and without pyridine. (2) The dibromo alcohol V did not react on standing with acetic acid. Catalysis by either small amounts of trifluoroacetic acid or 70% perchloric acid did not alter the starting material.

Acknowledgment. Grateful appreciation is extended to the Robert A. Welch Foundation for their support of this work.

Registry No.—I, 5785-66-0; IV, 61076-21-9; V, 61076-22-0; VI, 51752-40-0; VII, 6078-95-1; IX, 61076-23-1; bromine, 7726-95-6; 4-acetoxy-1,1-diphenyl-1-butene, 24104-21-0; acetyl hypobromite, 4254-22-2.

References and Notes

(1) C. W. Shoppee, R. W. Rees, G. H. R. Summers, and G. D. Phillips, *J. Chem. Soc.*, 2786 (1959), and references cited therein.
(2) F. A. Carey and H. S. Tremper, *J. Am. Chem. Soc.*, **91**, 2961 (1969).
(3) P. S. Skell, J. C. Day, and K. J. Shea, *J. Am. Chem. Soc.*, **98**, 1195 (1976).
(4) (a) V. I. Pansevich-Kolyada and N. A. Prilzhaev, *J. Gen. Chem. USSR (Engl. Transl.)*, **21**, 571 (1951); (b) D. W. Grant and R. Shilton, *J. Chem. Soc., Perkin Trans. 1*, 135 (1974).
(5) R. E. Buckles and J. F. Mills, *J. Am. Chem. Soc.*, **75**, 552 (1953).
(6) The structure has been confirmed by W. H. Watson of these laboratories by x-ray crystallography, and the data will be published elsewhwere.
(7) J. H. Rolston and K. Yates, *J. Am. Chem. Soc.*, **91**, 1469 (1969).

Structural Effects in Solvolytic Reactions. 19. The Relative Electron Releasing Capability of Methyl, Phenyl, and Cyclopropyl Groups as Measured by the Tool of Increasing Electron Demand

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The rates of solvolysis of aryldimethylcarbinyl (*tert*-cumyl) and 1-aryl-1-phenyl-1-ethyl *p*-nitrobenzoates with representative substituents in the aryl ring were determined in 80% aqueous acetone in order to test, by the application of the tool of increasing electron demand, the relative capability of methyl, phenyl, and cyclopropyl groups to stabilize a carbonium ion center. The *tert*-cumyl system yields a ρ^+ of −4.72 and the 1-aryl-1-phenyl-1-ethyl system yields one of −3.23. These data, together with the earlier reported value of ρ^+ for 1-aryl-1-cyclopropyl-1-ethyl system, −2.78, reveal that the relative electron releasing abilities of these groups increase in the order methyl < phenyl < cyclopropyl, supporting the conclusions reached earlier based on both rate and equilibria studies, but in direct contradiction to conclusions based on ^{13}C NMR shifts.

The extent and the consequences of the stabilization of carbonium ion centers by attached groups have received considerable attention in recent years. For many years, the main tool in such studies has been the solvolytic behavior of appropriate derivatives. With the advent of ^{13}C NMR and the ability to prepare and observe carbonium ions under stable ion conditions, workers in the field have utilized ^{13}C shifts to estimate electron densities at the carbonium carbon and to

Table I. Rates of Solvolysis of *tert*-Cumyl and 1-Aryl-1-phenyl-1-ethyl *p*-Nitrobenzoates and Related Derivatives in 80% Aqueous Acetone

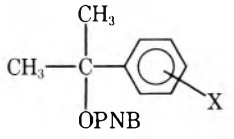
Registry no.	System	Substituent in aryl	$k_1 \times 10^5$, s^{-1} T_1, °C	T_2, °C	25 °C	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
23852-76-8	1	*p*-CH_3O			372		
23852-75-7		*p*-CH_3	577 (75)	37.5 (50)	1.54[a]	23.8	−5.1
7429-06-3		*p*-H	391 (100)	33.6 (75)	0.072[a]	24.8	−8.2
40543-93-9		*p*-CF_3	238 (150)	25.7 (125)	8.36×10^{-5} [a]	29.2	−6.7
60921-48-4		3,5-$(CF_3)_2$	219 (175)	22.2 (150)	7.50×10^{-7} [a]	33.9	−0.3
60921-49-5	2	*p*-CH_3O			322[b]		
60921-50-8		*p*-H	320 (75)	20.0 (50)	0.785[b,c]	24.2	−5.3
60921-51-9		*p*-CF_3	107 (100)	7.36 (75)	8.95×10^{-3} [a]	27.1	−4.5
60921-52-0		3,5-$(CF_3)_2$	126 (125)	10.2 (100)	4.31×10^{-4} [a]	29.1	−3.8
41327-36-0	3[d]	*p*-CH_3O			33 000		
41327-37-1		*p*-H	8.91 (0)		241	20.8	−5.5
41327-38-2		*p*-CF_3	83.8 (50)		3.88	22.9	−6.4
41327-39-3		3,5-$(CF_3)_2$	111 (75)	7.42 (50)	0.315°	23.6	−9.1

[a] Calculated from rates at higher temperatures. [b] Calculated by multiplying the rate of the benzoate by the factor 20.8 (ref 10). [c] Lit.[4b] $k_1^{25} = 6.81 \times 10^{-8}$ s^{-1}. [d] Reference 9.

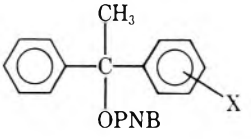
deduce therefrom the relative electron releasing properties of various groups to the carbonium carbon. For example, from a study of the ^{13}C shifts of the carbonium carbon in the *tert*-butyl cation, the phenyldimethyl, and the cyclopropyldimethyl carbonium ions, Olah and White proposed that electron release from these groups to an electron deficient center increases in the order methyl < phenyl > cyclopropyl.[3] But there are much rate[4] and equilibrium data[5,6] that indicate that the electron release follows the order methyl < phenyl < cyclopropyl.

The tool of increasing electron demand[7,8] offers considerable promise for arriving at an objective conclusion in cases where such ambiguity is present. It is possible to estimate the magnitude of the electron density at the developing electron deficient center by observing the effect of substituents in the aromatic ring (ρ^+). The quantitative aspects of the Hammett treatment facilitate realizing a quantitative estimate of the electron deficiency at the developing carbonium ion center. Numerous systems have now been subjected to this test, yielding consistent unambiguous results.[8]

We therefore decided to apply this tool to examine the electron releasing properties of methyl, phenyl, and cyclopropyl. This was achieved by synthesizing and determining the rates of solvolysis of representative derivatives of two systems (**1, 2**) for comparison with the data already available for the third (**3**).[9]



1



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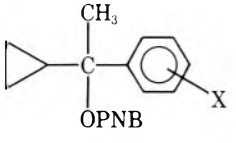


3

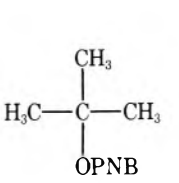
Results

Synthesis. The synthesis of 1-aryl-1-cyclopropyl-1-ethyl *p*-nitrobenzoates (**3**) was described earlier.[9] The *tert*-cumyl alcohols (1-OH) were synthesized by the addition of the appropriate Grignard reagents to acetone. Similarly, the addition of the Grignard reagents to acetophenone furnished **2**-OH. The alcohols were converted to *p*-nitrobenzoates by successive treatment with *n*-butyllithium and *p*-nitrobenzoyl chloride. The properties of the *p*-nitrobenzoates are summarized in Table III.

Kinetic Studies. The rates of solvolysis of the *p*-nitrobenzoates were determined in 80% aqueous acetone following the standard titrimetric procedure. 1-*p*-Anisyl-1-phenyl-1-ethyl *p*-nitrobenzoate (**2**, X = *p*-OCH_3) was too unstable to be isolated; hence, the benzoate was prepared and solvolyzed and the rate of the *p*-nitrobenzoate was calculated by multiplying the rate of the benzoate by the factor 20.8.[10] The rate data, together with activation parameters, are tabulated in Table I.

Discussion

It was previously concluded from a study of the solvolysis of *tert*-butyl, *tert*-cumyl, and cyclopropyldimethylcarbinyl *p*-nitrobenzoates (**4, 5, 6**) that the electron releasing ability



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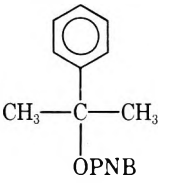

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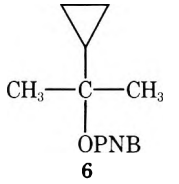
	4	**5**
Rel rate (25°C)	1.00	969
$\delta^{13}C^+$	328.8	254.8



6

	6
Rel rate (25°C)	503 000
$\delta^{13}C^+$	280.8

of methyl, phenyl, and cyclopropyl increases in the order methyl < phenyl < cyclopropyl.[4] Relief of B strain is not a significant factor in the major changes in the rates of solvolysis of these derivatives.[4] Hence the observed rate enhancement is attributed to the greater effectiveness of phenyl and cyclopropyl groups in delocalizing the positive charge. Clearly, according to these results, cyclopropyl is far more efficient than phenyl in delocalizing such charge. Olah and co-workers previously examined the ^{13}C chemical shifts for the carbonium ion carbon in **4, 5,** and **6** and concluded from the observed values that the phenyl (δ $^{13}C^+$ 254.8 ppm) must be more electron releasing than the cyclopropyl group (δ $^{13}C^+$ 280.8

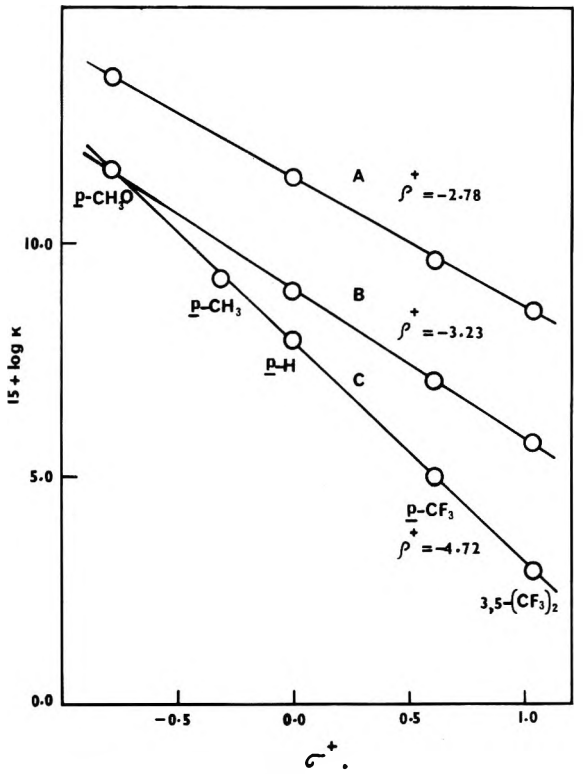


Figure 1. Log k–σ^+ plot for the solvolysis of (A) 1-aryl-1-cyclopropyl-1-ethyl, (B) 1-aryl-1-phenyl-1-ethyl, and (C) *tert*-cumyl *p*-nitrobenzoates in 80% aqueous acetone at 25 °C.

Table II. Relative Solvolytic Reactivities of *tert*-Cumyl, 2-Aryl-3-methyl-2-butyl, 1-Aryl-1-phenyl-1-ethyl, and 1-Aryl-1-cyclopropyl-1-ethyl *p*-Nitrobenzoates in 80% Aqueous Acetone

Substituent in aryl	Relative rate			
	1	9[a]	2	3
p-CH_3O	1.00	0.20	0.87	89
p-H	1.00	0.13	10.9	3 350
p-CF_3	1.00	0.16	107.0	46 400
3,5-$(CF_3)_2$	1.00	0.19	575.0	420 000

[a] Registry no. are, respectively, 41327-33-7, 41366-66-9, 41327-34-8, 41327-35-9.

Table III. Properties of *p*-Nitrobenzoates

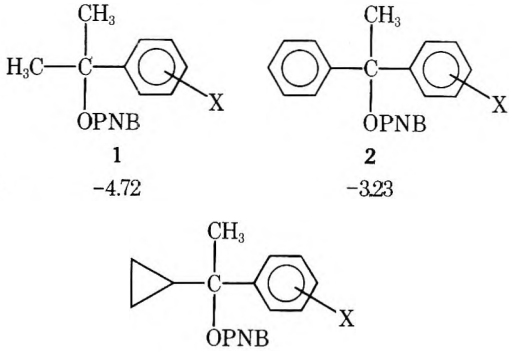
System	Substituent in aryl	Mp, °C	Anal.
1	*p*-CH_3O	90 dec[a]	C, H, N
	p-CH_3	106–107.4[b]	C, H, N
	p-H	133–134[c]	
	p-CF_3	110.5–111[d]	C, H, N, F
	3,5-$(CF_3)_2$	89	C, H, N, F
2	*p*-H	135 dec	C, H, N
	p-CF_3	121.5–122	C, H, N, F
	3,5-$(CF_3)_2$	138–139	C, H, N, F

[a] Lit.[15] mp 83–84 °C. [b] Lit.[15] mp 108–109 °C. [c] Lit. mp 136–137 °C: L. F. King, *J. Am. Chem. Soc.*, **61**, 2383 (1939). [d] Lit.[15] mp 110–111 °C.

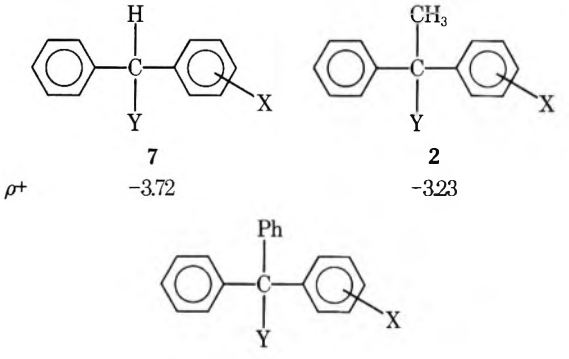
ppm).[4,11] Hence, the observed solvolytic results fail to correlate with the ^{13}C shifts, although it has been proposed that such shifts do indeed provide a measure of the electron density in such ions.[4,12] Consequently, there exists a major discrepancy between the results realized in solvolytic studies and the conclusions based on ^{13}C shifts as to the relative ability of the phenyl and cyclopropyl groups in stabilizing the carbonium ion center.

An alternative approach for testing this discrepancy is to apply the tool of increasing electron demand. After all, this tool has provided consistent unambiguous results in numerous systems. The determination of ρ^+ in **1**, **2**, and **3** makes it possible to evaluate the effectiveness of these groups in stabilizing the carbonium ion, utilizing ρ^+ as a measure of the electron demand in the transition state.

The value of ρ^+ for the solvolysis of *tert*-cumyl *p*-nitrobenzoates in 80% aqueous acetone is −4.72 (correlation coefficient 0.999).[13-15] The 1-aryl-1-phenyl-1-ethyl *p*-nitrobenzoates (**2**) yield ρ^+ of −3.23 (correlation coefficient 0.999) and the 1-aryl-1-cyclopropyl-1-ethyl *p*-nitrobenzoates (**3**) yield one of −2.78[9] (Figure 1). Hence, ρ^+ for the cyclopropyl system is more positive than for the phenyl system, thereby reaffirming the greater ability of the cyclopropyl group over the phenyl group in delocalizing the charge.

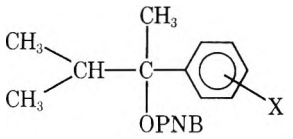


It is of interest to examine by means of this tool the relative electron releasing effect of hydrogen as a substituent at the carbonium ion center. The value of ρ^+ for the benzhydryl system (**7**) is −3.72, considerably more negative than ρ^+ for



the diarylmethyl system (−3.23), which in turn is more negative than ρ^+ (−2.52) for the triarylmethyl system (**8**).[16,17] Thus, the electron releasing properties, as measured by this tool, increase hydrogen < methyl < phenyl. The three aromatic groups of **8** delocalize the charge more effectively than the two aromatic groups of **7** or the two aromatic and one methyl group of **2**. It should be noted that the ρ^+ for 1-cyclopropyl-1-aryl-1-ethyl system (**3**) approaches the value observed for the triarylmethyl system (**8**). Consequently, a cyclopropyl group plus a methyl group is nearly as effective as two phenyl groups in delocalizing charge to the electron deficient center.

A comparative study of the rates of solvolysis of the 1-aryl-1-phenyl-1-ethyl system (**2**) and of the 1-aryl-1-cyclopropyl-1-ethyl system (**3**) with the closely related *tert*-cumyl and 2-aryl-3-methyl-2-butyl systems (**9**) ($\rho^+ = -4.76$[9]) is



9 $\rho^+ = -4.76$

presented in Table II. Thus the electron releasing power of an isopropyl group is similar to that of a methyl group. With increasing electron demand at the cationic center, the rate enhancement observed for **3** is much greater than that observed for **2**. This is in agreement with the greater stabilizing effect of the cyclopropyl group compared with the phenyl group.

These results have important implications. Many different approaches are now available for establishing the relative order of stabilization of a cationic center by methyl, phenyl, and cyclopropyl groups. The earlier solvolytic and equilibrium studies revealed that the trend of delocalization of charge increases in the order methyl < phenyl < cyclopropyl.[4] From a study of the ^{13}C shifts of alkyl carbonium ions Olah concluded that a phenyl group is more effective in stabilizing a cationic center than a cyclopropyl group.[3] However, the application of the tool of increasing electron demand supports the conclusions reached earlier based on solvolysis and equilibria studies. Therefore, caution is in order at this time in utilizing ^{13}C shifts to draw conclusions as to the charge densities in carbonium ions.

Experimental Section

All melting points are uncorrected. IR spectra were taken on a Perkin-Elmer Model 137 spectrometer and NMR spectra were recorded on a Varian T-60 spectrometer.

Preparation of Tertiary Alcohols. The *tert*-cumyl alcohols were prepared by the addition of the appropriate Grignard reagents to acetone in ether. 1-Aryl-1-phenyl-1-ethylcarbinols were also similarly prepared starting from acetophenone. The following procedure for the Grignard reaction is representative. A solution of the ketone (30 mmol) in ether (25 ml) was slowly added to a solution of the Grignard reagent (32.5 mmol, prepared by reacting the aryl halide with magnesium in ether) at 0 °C. After the addition, the reaction mixture was stirred at room temperature for 1 h and then refluxed for 2 h. The reaction mixture was then decomposed with ice-cooled ammonium chloride and extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate and solvent evaporated. The tertiary alcohols were used for *p*-nitrobenzoate preparation without further purification.

Preparation of *p*-Nitrobenzoates. The *p*-nitrobenzoates were obtained by treating the tertiary alcohols with *n*-butyllithium and *p*-nitrobenzoyl chloride.[18] The properties and analysis of the *p*-nitrobenzoates prepared in this study are summarized in Table III.

Kinetic Procedure. The procedure employed for determining the rate constants was described earlier.[18]

References and Notes

(1) Postdoctoral research associate on a grant supplied by Exxon Research and Engineering Co.
(2) Graduate research assistant on a grant (GP 31385) supported by the National Science Foundation.
(3) G. A. Olah and A. M. White, *J. Am. Chem. Soc.*, **91**, 5801 (1969); G. A. Olah and P. W. Westerman, *ibid.*, **95**, 7530 (1973).
(4) (a) H. C. Brown and E. N. Peters, *J. Am. Chem. Soc.*, **95**, 2400 (1973); (b) *ibid.*, **99**, 1712 (1977).
(5) N. C. Deno and A. Schriesheim, *J. Am. Chem. Soc.*, **77**, 3051 (1955); N. C. Deno, H. G. Richey, Jr., J. S. Liu, D. N. Lincoln, and J. O. Turner, *ibid.*, **87**, 4533 (1965).
(6) For an excellent review and discussion, see H. G. Richey, Jr., "Carbonium Ions", Vol. III, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N.Y., 1972, Chapter 25.
(7) P. G. Gassman and A. F. Fentiman, Jr., *J. Am. Chem. Soc.*, **92**, 2549 (1970).
(8) H. C. Brown et al., *J. Am. Chem. Soc.*, **97**, 7442, 7449, 7454 (1975), and references cited therein.
(9) H. C. Brown, E. N. Peters, and M. Ravindranathan, *J. Am. Chem. Soc.*, in press.
(10) H. C. Brown and K. Takeuchi, *J. Am. Chem. Soc.*, **90**, 2691 (1968).
(11) More recently, Olah has taken the position from a study of ^{13}C shifts in certain secondary alkenyl cations that the electron release from methyl, phenyl, and cyclopropyl groups to an electron deficient center increases in the order methyl $\ll$ phenyl $\lesssim$ cyclopropyl. G. A. Olah and R. J. Spear, *J. Am. Chem. Soc.*, **97**, 1539 (1975).
(12) It has been pointed out that ^{13}C shifts depend upon several important factors in addition to charge density. B. V. Cheney and D. M. Grant, *J. Am. Chem. Soc.*, **89**, 5319 (1967).
(13) The value of ρ^+ for the solvolysis of *tert*-cumyl chlorides in 90% acetone at 25 °C is −4.54[14] and for the solvolysis of *tert*-cumyl *p*-nitrobenzoates in 70% acetone at 100 °C is −3.74.[15]
(14) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).
(15) H. Tanida and H. Matsumura, *J. Am. Chem. Soc.*, **95**, 1586 (1973).
(16) E. N. Peters and H. C. Brown, *J. Am. Chem. Soc.*, **95**, 2397 (1973).
(17) N. C. Deno and W. L. Evans, *J. Am. Chem. Soc.*, **79**, 5804 (1957).
(18) H. C. Brown and E. N. Peters, *J. Am. Chem. Soc.*, **97**, 1927 (1975).

Revised Structure of the Dimer of 3,3,6,6-Tetramethylcyclohexyne

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Received September 28, 1976

The dimerization of 3,3,6,6-tetramethylcyclohexyne has been reinvestigated and the structure of the dimer reassigned as a moncyclic conjugated enyne (3).

The dimer of 3,3,6,6-tetramethylcyclohexyne (**1**) was described by us in 1972[1] and was assigned structure **2** on the

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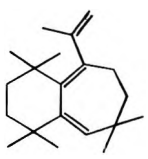

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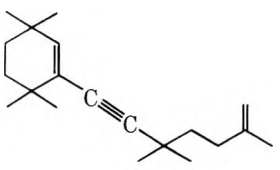
basis of spectroscopic evidence and partial degradation. The formation of **2** was interpreted through dimerization of **1** to a cyclobutadiene and subsequent rearrangement.

Another structure considered[1] for the dimer was **3**, which



3

was consistent with most of the data, but the dimer lacked acetylenic infrared absorption at 2250–2270 cm^{-1}, expected for vinylacetylenes,[2] and **3** would not have been expected to give the observed acetic acid in oxidation with permanganate–periodate.

An intensive but unsuccessful effort to find independent

evidence for the supposed cyclobutadiene intermediate has forced reconsideration of the structural assignment of the dimer. For the reasons which follow, we now conclude that the dimer is **3**.

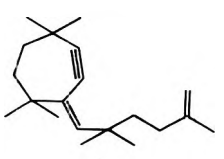
The original objections to **3** are swept away by two observations. First is that while there is indeed no easily detectable C≡C stretching band in the infrared, there is an intense band at 2211 cm^{-1} in the Raman spectrum, which was not available to us in the earlier work, and a thick film infrared spectrum does show a weak band at 2220 cm^{-1}. Second is that the permanganate–periodate oxidation method of von Rudolf[3,4] has been found unreliable in our hands for the detection of acetic acid product, since blank reactions with the solvent, *tert*-butyl alcohol or pyridine, give GLC peaks with the retention time of acetic acid.

More positive evidence for **3** has also been gathered. The ^{13}C NMR spectrum shows four olefinic carbons at 109.5, 128.5, 142.1, and 146.5 ppm from Me_4Si, with splitting in the off-resonance decoupled spectrum showing one proton on the carbon at 142.1 ppm and two protons on the carbon at 109.5 ppm. The spectrum shows two signals in the acetylenic region[5-7] at 80.3 and 95.5 ppm, neither being split by off-resonance decoupling.

Irradiation of the dimer in ether solution with ultraviolet light converted it to an isomer, as shown by mass spectrometry and analysis. The structure of the isomer will not be assigned here, but its spectroscopic properties bear significantly upon the structure of its progenitor.[8] Loss of the conjugated unsaturation is shown by the disappearance of the UV band at 227 nm, there being only weak end absorption in the photoproduct. The ^{13}C NMR spectrum of the photoisomer shows loss of the two olefinic carbons at 128.5 and 142.1 ppm. The acetylenic carbons appear still as bands at 81.7 and 87.2 ppm. The Raman spectrum confirms the existence of the acetylenic group at 2222 cm^{-1} and shows disappearance of a C=C stretching band at 1620 cm^{-1}, present before irradiation. The infrared spectrum shows acetylenic absorption at 2241 cm^{-1}, and with a band at 1660 cm^{-1} suggests that the terminal methylene group (which appeared at 1650 cm^{-1} in the cyclohexyne dimer[1]) was unaffected by irradiation. The ^1H NMR spectrum shows a terminal methylene group still present at δ 4.69 (at δ 4.65 before irradiation[1]) but the single olefinic peak at δ 5.54 in the dimer is missing in its photoisomer.

The ^{13}C NMR spectra of the dimer and the photoisomer strongly suggest that the isopropenyl group[1] is remote from the site of structural change, since the chemical shifts assigned to the three carbons of that group are essentially unchanged (22.7, 109.5, and 146.5 ppm in the dimer; 22.7, 109.3, and 146.9 ppm in the photoisomer). This leaves a conjugated enyne as the only plausible chromophore for the UV absorption in the dimer at 227 nm. Conjugated enynes generally possess UV absorptions in the 225–230-nm region.[9]

To summarize the structural requirements for the cyclohexyne dimer as reported here and previously,[1] it contains a conjugated enyne with the double bond trisubstituted, an isopropenyl group not conjugated with the other unsaturation present, three pairs of methyl groups with three different chemical shifts (^{1}NMR), none of the three showing spin–spin splitting, one group $-CH_2CH_2-$ which appears as a complex pair of multiplets at δ 1.8–2.4 and 1.2–1.7, and one group $-CH_2CH_2-$ which appears as a singlet at δ 1.46. Also, these groups must be so arranged as to give $\alpha,\alpha,\alpha',\alpha'$-tetramethyladipic acid upon oxidation with permanganate–periodate. Only structure **3** seems plausibly to meet all of these requirements. Structure **4** is a formal possibility, but would not be expected to have the observed stability.



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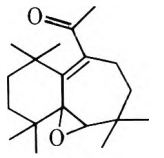
An interesting ozonolysis product of the dimer was previously assigned structure **5**, in agreement with its spectroscopic properties, and reasonably formed from structure **2**.



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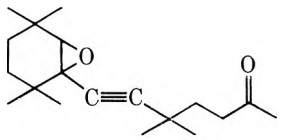

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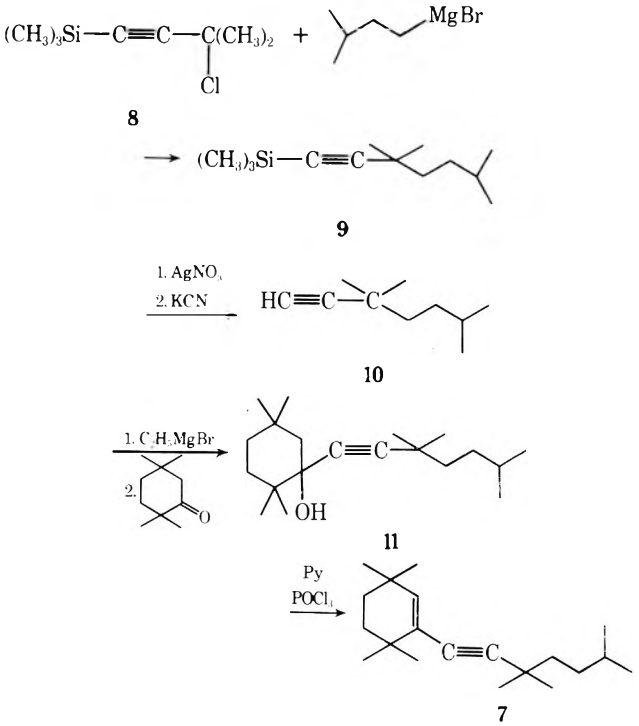
The ozonolysis product may now be assigned structure **6**, which seems equally satisfactory in relation to the spectroscopic data. The infrared spectrum of this product does contain a weak band at about 2235 cm^{-1} attributable to the triple bond but previously discounted. While it may be surprising that the triple bond survived ozonolysis, it has been observed by others that in compounds with both double and triple bonds, ozone attacks the double bonds preferentially.[10]

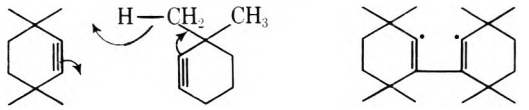
Synthetic approaches to **3** were investigated to further confirm the structure. All attempts were unsuccessful, but a related compound, **7**, was prepared by the route outlined in Scheme I.

Scheme I



Compound **7** had Raman bands at 2200 and 1611 cm^{-1}, corresponding to those at 2211 and 1620 cm^{-1} in **3**. The most convincing case for the structures of both **3** and **7**, however, is found in the comparison of their ^1H NMR spectra. The protons remote from the isopropenyl (or isopropyl) group in the two molecules display nearly identical signals, with singlets at δ 5.63 (1 H), 1.41 (4 H), 1.20 (6 H), 1.08 (6 H), and 0.97 (6 H) in **7** corresponding respectively to those at δ 5.54, 1.46, 1.23, 1.05, and 0.97 in **3**. The isopropyl group in **7** appears as a doublet (6 H, J = 6 Hz) at δ 0.87, while the peaks at δ 1.75 and 4.64 in **3**, attributed to the isopropenyl group, are missing in **7**.

The reassignment of the tetramethylcyclohexyne dimer as **3** rather than **2** reopens the question of mechanism of dimerization. While a cyclobutadiene intermediate is still a formal



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possibility, there is no evidence to support it. Rather, a concerted [$_{\pi}2 + _{\sigma}4$] mechanism (**12**) or a two-step process through biradical **13** seems a simpler explanation. The reaction appears to be unprecedented for acetylenes, strained or otherwise. It may be viewed as further indication of the reluctance to form cyclobutadienes when other pathways, with or without precedent, are available.

Experimental Section[11]

1-(3',3',6',6'-Tetramethyl-1'-cyclohexenyl)-3,3,6-trimethylhept-1-yn-6-ene (3). An improved procedure for generation of 3,3,6,6-tetramethylcyclohexyne dimer uses active magnesium[12] in place of sodium.[1] The advantage of magnesium is that none of the previously described dihydro dimer[1] is formed. The magnesium was prepared by reaction of 12.7 g (0.134 mol) of anhydrous magnesium chloride with 9.8 g (0.251 g-atom) of potassium in 100 ml of refluxing tetrahydrofuran under argon. Magnesium was subsequently transferred from the cooled reaction mixture with a syringe.

To a mixture of approximately 10 mg-atoms of magnesium in 40 ml of tetrahydrofuran, a solution estimated by GLC analysis to contain 0.479 g (1.62 mmol) of 1,2-dibromo-3,3,6,6-tetramethylcyclohexene and 0.043 g (0.17 mmol) of 1-bromo-2-chloro-3,3,6,6-tetramethylcyclohexene in 10 ml of tetrahydrofuran was added; and the resulting mixture was stirred for 11 h at room temperature. The reaction mixture was then filtered to remove the unreacted magnesium, and the filtrate was poured into 100 ml of water and extracted twice with diethyl ether. The combined ether extracts were dried over $MgSO_4$ for 12 h. The $MgSO_4$ was removed by filtration. Concentration on a rotary evaporator followed by concentration in vacuo for 2 h at 1.0 mm gave 0.167 g of a yellow oil whose NMR spectrum and infrared spectrum were indistinguishable from those reported for **3**[1] and which was shown by GLC analysis on a column of 10% Ucon 550X on Chromosorb A at 200 °C, flow rate of 100 ml/min, to contain only hydrocarbon **3** (yield 0.61 mmol, 68%). Rinsing the unreacted magnesium several times with diethyl ether gave higher yields (up to 90%) of **3**.

The Raman spectrum possessed intense bands at 2920, 2211, and 1620 cm^{-1}, with numerous weak bands including one at 1650 cm^{-1}. The ^{13}C NMR spectrum in $CDCl_3$ solution included three methyl signals (quartets with off-resonance decoupling) at 22.7, 28.55, and 29.46 ppm downfield from tetramethylsilane. There were four aliphatic CH_2 signals (triplets with off-resonance decoupling) at 33.60, 33.92, 34.72, and 41.91 ppm; one olefinic $=CH_2$ at 109.45 ppm; one olefinic carbon split to a doublet with off-resonance decoupling at 142.05 ppm; and seven signals for carbons not bonded to hydrogens at 29.12, 31.63, and 32.60 ppm (quaternary), 80.25 and 95.52 ppm (acetylenic), and 128.46 and 146.51 ppm (olefinic).

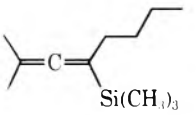
1-Trimethylsilyl-3-methyl-3-chloro-1-butyne (8). A mixture of 3.5 g (22.4 mmol) of 1-trimethylsilyl-3-methylbut-1-yn-3-ol and 14 g of concentrated hydrochloric acid was stirred for 30 min, diluted with 25 ml of water, and extracted with pentane. The pentane extract was dried over $MgSO_4$, and then concentrated to yield 3.1 g of a light yellow oil. Chromatography of this oil on 50 g of silica gel (pentane eluent) yielded 2.4 g of **8** (13.8 mmol, 62%), 98% pure by GLC. The NMR spectrum of this oil contained only two singlets at δ 0.18 (9 H) and 1.82 (6 H). The IR spectrum possessed absorptions at 2180 cm^{-1} (medium, sharp) and 860 cm^{-1} (strong, broad) among others. Distillation of the product from a similar preparation gave a colorless liquid, bp 54.5–55 °C (17 mm) [lit.[13] bp 49 °C (14 mm)] with $n^{24}D$ 1.4424 (lit.[13] $n^{20}D$ 1.4415).

1-Trimethylsilyl-3,3,6-trimethyl-1-heptyne (9). A solution of 3-methylbutylmagnesium bromide was prepared from 6.4 g (267 mg-atoms) of magnesium turnings and 40 g (265 mmol) of 3-methyl-1-bromobutane in 100 ml of diethyl ether. A solution of 3.4 g (19.5 mmol) of 1-trimethylsilyl-3-methyl-3-chloro-1-butyne (**8**) in 5 ml of diethyl ether was added over a period of 45 min to 76 ml of the solution of 3-methylbutylmagnesium bromide. The resulting mixture was stirred overnight under argon at room temperature and then heated under reflux for 4 h. The reaction mixture was then cooled with an ice bath, poured into 200 ml of 1 M HCl, and extracted three times with diethyl ether. The combined ether extracts were dried over $MgSO_4$ and concentrated on a rotary evaporator to yield 4 g of a yellow oil which was found by GLC analysis to contain at least seven components, in addition to a small amount of solvent. A small amount (0.28 g) of a white solid, mp 117–123 °C, was also isolated but not examined in detail.

Two of the components of the reaction mixture which comprised ca. 41% (estimated by GLC peak area analysis) of the crude product were isolated by GLC. The component in excess was found to have an IR spectrum with absorption at 2180 (medium, sharp) and 850 cm^{-1} (strong, broad) among others and an NMR spectrum with absorptions at δ 0.14 (s, 9 H), 0.89 (doublet, J = 5 Hz, 6 H), 1.16 (s, 6 H), and 2.15–1.20 (complex signal, 5 H), and was assigned the structure **9**.

Anal. Calcd for $C_{13}H_{26}Si$: C, 74.20; H, 12.45. Found: C, 74.30; H, 12.42.

The other component had an IR spectrum with absorptions at 1950 (medium, sharp) and 840 cm^{-1} (strong, broad) among others and an NMR spectrum with absorptions at δ 0.04 (s, 9 H), 0.88 (d, J = 5.5 Hz, 6 H), 1.61 (s, 6 H), 2.10–1.70 (m, 2 H), and 1.50–1.00 (m, 3 H), and was assigned structure **14**. The ratio of **9**:**14** was 1.27:1.00 as judged by the areas of the two GLC peaks.



14

3,3,6-Trimethyl-1-heptyne (10). A solution of 1.0 g (5.9 mmol) of silver nitrate in 3 ml of water and 3 ml of 95% ethanol was added dropwise to a solution of 0.17 g (0.81 mmol) of **9** in 6 ml of absolute ethanol. A white, cloudy mixture resulted which was stirred at room temperature for 40 min. A solution of 2 g (30.8 mmol) of potassium cyanide in 4 ml of water was then added slowly. The resulting solution was extracted with 50 ml of pentane, and the extract was dried over $MgSO_4$. The bulk of the pentane was distilled off (distillate bp up to 40 °C) and the residue (0.51 g) was examined for absorptions in its IR spectrum to confirm the presence of a terminal acetylene in the product mixture. A sharp absorption at 3300 cm^{-1} confirmed the presence of a terminal triple bond,[14] and no absorption which would indicate the presence of ethanol (i.e., a hydroxyl absorption at ca. 3400 cm^{-1}) could be detected in the same spectrum, so this material was used for the next reaction without purification. GLC analysis of this oil showed the presence of only one component in addition to pentane.

1-(3',3',6',6'-Tetramethyl-1'-cyclohexenyl)-3,3,6-trimethyl-1-heptyne (7). A solution of ethylmagnesium bromide in diethyl ether was prepared from 21 g (0.202 mol) of ethyl bromide and 4.8 g (0.20 g-atom) of magnesium in 100 ml of diethyl ether. Titration of a hydrolyzed aliquot of this solution immediately prior to its use showed it to be 1.90 M. The crude product of the previous reaction was purified by chromatography on 20 g of silica gel; elution with 80 ml of pentane and concentration yielded 0.5 g of a presumed mixture of pentane and **10**. A solution of this material in 2 ml of diethyl ether was added under nitrogen dropwise to 2 ml (3.8 mmol) of the ethylmagnesium bromide solution. The resulting mixture was stirred for 5 h and then cooled with an ice bath. To the cooled reaction mixture, a solution of 0.55 g (3.57 mmol) of 2,2,5,5-tetramethylcyclohexanone[1] in 2 ml of diethyl ether was added over a period of 5 min. The ice bath was allowed to warm to room temperature, and the reaction mixture was stirred overnight (ca. 13 h). The reaction mixture was then treated with 20 ml of saturated ammonium chloride solution and extracted twice with diethyl ether. The combined ether extracts were dried over $MgSO_4$ and concentrated to yield 0.70 g of a light yellow oil. The IR spectrum of this oil possessed bands at 3450 and 1705 cm^{-1} indicating the presence of some alcohol and unreacted ketone in the crude product. No band was detected at 3300 cm^{-1}, indicating the absence of any unreacted **10**.

The above oil was mixed with 1 ml of pyridine and cooled with an ice bath. To this mixture was added a solution of 1 ml of phosphorus oxychloride in 2.5 ml of pyridine. The resulting mixture was stirred and cooled for 30 min and then heated to 90 °C for 60 min. The reaction mixture was then cooled, poured onto ice, and extracted twice with pentane. The combined pentane extracts were dried over $MgSO_4$ and concentrated to yield 0.65 g of a light yellow oil. The crude product was then chromatographed on 40 g of alumina (Woelm, activity I); elution with 250 ml of pentane yielded 39.1 mg of a colorless oil. Elution with 250 ml of 1:1 pentane/diethyl ether yielded 0.1 g (18%) of unreacted ketone as identified by its IR spectrum. Elution with 400 ml of diethyl ether yielded a small additional amount of unreacted ketone.

GLC analysis of the oil eluted with pentane indicated the presence of a component with a retention time close to that of **3**. This component was isolated by GLC (yield 9 mg). Its IR spectrum possessed absorptions of medium intensity at 2920, 1460, 1380, 1365, and 872 cm^{-1}, in addition to other weak absorptions. A 220-MHz NMR spectrum showed signals at δ 5.63 (s, 1 H), 1.41 (s, 4 H, superimposed on a multiplet from δ 1.68 to 1.27, 5 H), 1.20 (s, 6 H), 1.08 (s, 6 H), 0.97 (s, 6 H), and 0.87 (doublet, J = 6 Hz, 6 H). The Raman spectrum possessed intense bands at 2200 and 1611 cm^{-1} in addition to other weak bands.

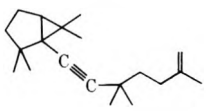
Anal. Calcd for $C_{20}H_{34}$: C, 87.51; H, 12.49. Found: C, 87.93; H, 12.47.

The mass spectrum of the oil eluted with pentane possessed peaks at *m/e* 274 (12.98), 259 (10.20), 205 (22.36), and 203 (20.51) (calculated mass of parent ion of **7**, 274). In addition, a peak at *m/e* 166 (4.11%) was present indicating the presence of 3,3,6,6-tetramethyl-1-ethylcyclohexene ($C_{12}H_{22}$, mol wt 166) in this oil. In the 10-eV mass spectrum, the intensities of the *m/e* 274 and 166 peaks increased to 44.35 and 27.01, respectively.

Registry No.—**1**, 37494-11-4; **3**, 59129-90-7; **6**, 61075-98-7; **7**, 61075-99-8; **8**, 18387-63-8; **9**, 61076-00-4; **10**, 61076-01-5; **11**, 61076-02-6; **14**, 61104-52-7; 1-trimethylsilyl-3-methylbut-1-yn-3-ol, 5272-33-2; 3-methyl-1-bromobutane, 107-82-4; 2,2,5,5-tetramethylcyclohexanone, 15189-14-7; 3,3,6,6-tetramethyl-1-ethylcyclohexene, 61076-03-7.

References and Notes

(1) D. E. Applequist, P. A. Gebauer, D. E. Gwynn, and L. H. O'Connor, *J. Am. Chem. Soc.*, **94**, 4272 (1972).
(2) A. A. Petrov, Yu. I. Porfiryeva, and G. I. Semenov, *J. Gen. Chem. USSR (Engl. Transl.)*, **27**, 1250 (1957).
(3) E. von Rudolf, *Can. J. Chem.*, **34**, 1413 (1956).
(4) E. von Rudolf, *Can. J. Chem.*, **33**, 1714 (1955).
(5) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, Chapter 3.
(6) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, Chapter 3.
(7) (a) D. E. Dorman, M. Jautelet, and J. D. Roberts, *J. Org. Chem.*, **38**, 1026 (1973); (b) J. M. Kornprobst and J. P. Doucet, *J. Chim. Phys. Phys.-Chim. Biol.*, **71**, 1129 (1974).
(8) One possible structure consistent with all of the observations is the following:



This and other possibilities are discussed in the Ph.D. Dissertation of C. N. Bush, University of Illinois, 1975.
(9) (a) R. S. Macomber, *Tetrahedron Lett.*, 4639 (1970); (b) G. Zweifel and N. L. Polston, *J. Am. Chem. Soc.*, **92**, 4068 (1970); (c) J. C. Hamlet, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 2652 (1951); (d) E. N. Marvell and J. Tashiro, *J. Org. Chem.*, **30**, 3991 (1965).
(10) P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).
(11) Melting points and boiling points are uncorrected. ^1H NMR spectra were recorded on Varian T-60, A-60A, HR-100, or HR-220 instruments. ^{13}C NMR spectra were recorded on Varian XL-100 or JEOL FX-60 instruments. Raman spectra were taken on a Spex Ramalab Model RS2 spectrometer. Mass spectra were recorded by C. Cook and associates on a MAT CH-5 instrument. J. Nemeth and associates performed the microanalyses.
(12) (a) R. D. Rieke and P. M. Hudnall, *J. Am. Chem. Soc.*, **94**, 7178 (1972); (b) R. D. Rieke and S. E. Bales, *ibid.*, **96**, 1775 (1974).
(13) M. F. Shostakovskii, N. V. Konarov, V. P. Kuznetsova, and I. I. Igonina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 510 (1962); *Chem. Abstr.*, **57**, 15138c (1962).
(14) N. B. Colthup, L. H. Daly, and I. E. Wiberly, "Introduction to Infrared and Raman Spectroscopy", Academic Press, New York, N.Y., 1964, p 202.

Notes

Optical Rotations and Absolute Configurations of 3-*tert*-Butylcyclohexene and of *trans*-3-*tert*-Butyl-6-methylcyclohexene

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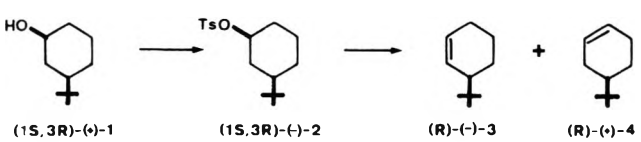
In connection with our interest in the asymmetric bromination of alkenes,[1] the chiroptical properties of some alkyl substituted cyclohexene derivatives were needed. In this paper we report the hitherto unknown relationship between optical rotations and absolute configurations of 3-*tert*-butylcyclohexene and of *trans*-3-*tert*-butyl-6-methylcyclohexene. The optical rotation of 4-*tert*-butylcyclohexene[1d] has also been revised.

(*R*)-(−)-3-*tert*-Butylcyclohexene (**3**) of high optical purity was obtained through an improvement of the route already followed[1d] for the preparation of the optically active 4-*tert*-butyl isomer (**4**), consisting in the dehydrotosylation of the tosylate (**2**) of (+)-*cis*-3-*tert*-butylcyclohexanol (**1**) (Scheme I). The (1*S*,3*R*) configuration had been firmly established[2]

Scheme I

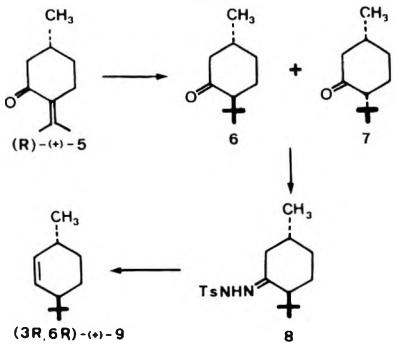


for (+)-**1** by the ORD curve of (+)-3-*tert*-butylcyclohexanone arising from its oxidation. A value of $[\alpha]^{30}D$ +7.9° has been reported[2] for **1** obtained by resolution of the acid phthalate through the brucine salt and a very high optical purity was suggested by the obtainment of (+)-3-*tert*-butylcyclohexanone with the same optical rotation ($[\alpha]^{24.5}D$ +25°) starting both from (+)-**1** and the diastereoisomeric (+)-*trans*-3-*tert*-butylcyclohexanol, which had been independently resolved through its 3β-acetoxy-Δ^5-etienate.[2] In our hands the resolution of the acid phthalate of (±)-**1** with brucine led to both enantiomeric alcohols, the dextrorotatory one having higher optical purity ($[\alpha]^{25}D$ +8.9 and −8.1°). Treatment of both enantiomers with tosyl chloride afforded, after crystallization, the corresponding tosylates with very close absolute values of optical rotation ($[\alpha]^{25}D$ −23.1 and +22.7°, respectively). Heating of (−)-**2** in quinoline gave a mixture of 3- and 4-*tert*-butylcyclohexene (**3** and **4**) in a 38:62 ratio. After chromatographic separation on a $AgNO_3/SiO_2$ column, the two olefins had the following rotations: (*R*)-**3**, $[\alpha]^{25}D$ −6.2°; (*R*)-**4**, $[\alpha]^{25}D$ +82.8°. The latter value is somewhat higher than the rough estimate of the maximum optical rotation previously made for **4**[1d] starting from a sample of (+)-**1** of lower optical purity and based on the maximum rotation ($[\alpha]^{30}D$ +7.9°) reported at that time for **1**.

(3*R*,6*R*)-(+)-*trans*-3-*tert*-Butyl-6-methylcyclohexene (**9**), $[\alpha]^{25}D$ +117.[6] was obtained from optically pure natural (+)-pulegone (**5**) according to Scheme II.

The addition of methylmagnesium iodide to (+)-**5** in the presence of cuprous chloride, which acts as catalyst for 1,4 addition,[3] gave, as reported,[4] a 7:3 mixture of ketones **6** and **7**. The major diastereoisomer **6** was separated as the tos-

Scheme II



ylhydrazone 8, which was transformed into pure **9**, which should also be optically pure, by treatment with an excess of butyllithium. Since the last reaction does not involve[5] the chiral centers C(2) and C(5), the (3*R*,6*R*) absolute configuration resulted for (+)-**9** from the known *R* configuration of (+)-pulegone[6] and from the established[4] trans relationship of the two alkyl substituents in the major product **6** of the 1,4 Grignard addition to **5**. This was unambiguously confirmed by the NMR spectra of several products of anti addition to **9**, which will be described elsewhere.[7]

It can be emphasized that the molecular rotation of (3*R*,6*R*)-**9**, [M]D +179.1°, is very similar to that of the corresponding *trans*-2-menthene (**10**, [M]D +185°).[8,9] According

10 11

to Brewster's treatment of the optical activity of endocyclic olefins,[9] if a dextrorotatory contribution of 130° by the methyl group to the [M]D of (+)-**9** is assumed (a value leading to a reasonable agreement between calculated and experimental values of [M]D for several terpene olefins[9]), (*R*)-**3** would be expected to be dextrorotatory. This is in contrast with the experimental value of [M]D −8.6°.

Furthermore, the Mills[10] and Brewster[9] empirical rules predict a positive rotation for compounds having configuration **11** when the substituent X is more polarizable than hydrogen, unless C=C > X > CH_3 in polarizability. However, Eliel has suggested[11] that the *tert*-butyl group is less polarizable than methyl, which is less polarizable than vinyl, and the octet refraction values reported by Brewster[12] support this assumption. Therefore it can be concluded that, while the optical rotation of *trans*-3-*tert*-butyl-6-methylcyclohexene (**9**) is conformable to the expectation, that of the simple 3-*tert*-butyl derivative **3** is not.[13] We are currently investigating the cause of this apparent anomaly by far ultraviolet, ORD, and CD studies on the present and other simple substituted cyclohexenes.

Experimental Section

Melting points were determined on a Kofler block and are uncorrected. NMR spectra were registered with a JEOL C-60HL spectrometer from $CDCl_3$ solutions using Me_4Si as internal standard. GLC analyses of the mixture of **6** and **7** and of olefins **3**, **4**, and **9** were performed on a Perkin-Elmer Model F 11 instrument fitted with a 2-m glass column, 3 mm i.d., packed with 10% Carbowax 20M on silanized 80–100 mesh Chromosorb W. IR spectra for comparisons were registered on liquid films with a Perkin-Elmer Model 257 double-beam grating spectrophotometer. Optical rotations were measured in $CHCl_3$ solutions with a Perkin-Elmer Model 141 photoelectric polarimeter. The reference compounds (±)-**3** and (±)-**4** were prepared according to the reported methods.[14,15] $MgSO_4$ was always used as the drying agent. Petroleum ether refers to the fraction bp 30–50 °C.

(+)- and (−)-*cis*-3-*tert*-Butylcyclohexanol (1). The resolution of (±)-**1** was carried out as reported.[2] The brucine salt of *cis*-3-*tert*-butylcyclohexyl hydrogen phthalate was prepared by mixing 80 g of acid phthalate and 105 g of brucine in acetone. Most of the solvent was evaporated, benzene was added, and the solution was left overnight in a refrigerator. The precipitate (64 g) had $[\alpha]^{25}D$ −18.8° (c 1.5). Concentration of the mother liquors gave a second crop (23 g), $[\alpha]^{25}D$ −18.6°. Three crystallizations from benzene of a sample of the two combined fractions gave a brucine salt with $[\alpha]^{25}_{589}$ −18.7°, $[\alpha]^{25}_{546}$ −22.7°, $[\alpha]^{25}_{436}$ −55.0°, $[\alpha]^{25}_{365}$ −137.3°.

A warm solution of 50 g of this salt in MeOH was treated with 2 N aqueous HCl (30 ml), diluted with water, and extracted with ether. The extract was washed with 2 N HCl and water, dried, and concentrated. Dilution with petroleum ether yielded 20 g of crystalline *cis*-3-*tert*-butylcyclohexyl hydrogen phthalate. After recrystallization from ethyl ether–petroleum ether, this product had mp 123–123.5 °C, $[\alpha]^{25}_{589}$ +14.7°, $[\alpha]^{25}_{546}$ +16.9°, $[\alpha]^{25}_{436}$ +32.3°, $[\alpha]^{25}_{365}$ +58.7° (c 2.8) (lit.[2] mp 104.5–107 °C, $[\alpha]^{30}D$ +14°).

Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 70.80; H, 7.90.

A suspension of the acid phthalate from several preparations (80 g), $[\alpha]^{25}D$ +14.7°, in 50% aqueous KOH was steam distilled. Ether extraction and distillation under reduced pressure gave 40 g of pure **1**, mp 39–40 °C, $[\alpha]^{25}_{589}$ +8.9°, $[\alpha]^{25}_{546}$ +10.1°, $[\alpha]^{25}_{436}$ +17.0°, $[\alpha]^{25}_{365}$ +26.0° (c 4.4) (lit.[2] liquid at room temperature, $[\alpha]^{30}D$ +7.9°).

The mother liquors from which the brucine salt was separated were evaporated and the residue was treated with 2 N aqueous HCl. Extraction with ether, evaporation, and crystallization from ethyl ether–petroleum ether yielded the (−)-acid phthalate, $[\alpha]^{25}D$ −13.0°. Saponification of this product as described above afforded (−)-**1**, $[\alpha]^{25}D$ −8.1°.

Tosylates of (+)- and (−)-*cis*-3-*tert*-Butylcyclohexanol (2). Tosyl chloride (9.5 g) was added to a stirred solution of (+)-**1** (5.8 g, $[\alpha]^{25}D$ +8.9°) in dry pyridine (60 ml) at 0 °C. After standing overnight at 5 °C, the mixture was treated with cold 2 N aqueous HCl and extracted with ether. Evaporation of the washed (2 N aqueous HCl and water) and dried extract followed by crystallization of the residue from petroleum ether yielded 8.5 g of **2**, mp 85–87 °C [lit.[16] (±)-**2**, mp 58–59.5 °C], $[\alpha]^{25}_{589}$ −23.1°, $[\alpha]^{25}_{546}$ −26.3°, $[\alpha]^{25}_{436}$ −45.1°, $[\alpha]^{25}_{365}$ −71.0° (c 4.0), unchanged after two crystallizations.

Anal. Calcd for $C_{17}H_{26}SO_3$: C, 65.77; H, 8.44. Found: C, 65.80; H, 8.60.

A second crop of **2** had $[\alpha]^{25}D$ −22.8°.

Similar treatment of (−)-**1**, $[\alpha]^{25}D$ −8.1°, gave, after crystallization from petroleum ether, the dextrorotatory tosylate, mp 85–86 °C, $[\alpha]^{25}D$ +22.7° (c 4.0). A sample with $[\alpha]^{25}D$ +6° was obtained as the third crop from the mother liquors.

(−)-3-*tert*-Butylcyclohexene (3) and (+)-4-*tert*-Butylcyclohexene (4). A solution of (−)-**2** (5.0 g, $[\alpha]^{25}D$ −23.1°) in dry quinoline (80 ml) was heated at 180 °C for 4 h, then treated with cold 2 N aqueous HCl and extracted with ether. Evaporation of the washed (2 N, HCl and water) and dried extract gave 2.6 g of a mixture of **3** and **4** in a 38:62 ratio (GLC), which was chromatographed on a 45 × 1.8 cm column filled with 10% $AgNO_3$ on silica gel (Woelm, dry-column grade) eluting with petroleum ether. Fractions (25 ml) were collected, whose composition was checked by GLC. Fractions 9–13 contained pure **3** which, after being freed from solvent by preparative GLC, had an IR spectrum identical with that of racemic **3**[14] (main absorption bands at 1387, 1362, 1223, 1136, 890, 865, 765, 723, 642 cm^{-1}); NMR δ 0.90 [s, $(CH_3)_3C$–, 9 H], 5.67 (m, $W_{1/2} \sim 4$ Hz, –CH=, 2 H); $[\alpha]^{25}_{589}$ −6.2°, $[\alpha]^{25}_{546}$ −7.4°, $[\alpha]^{25}_{436}$ −16.1°, $[\alpha]^{25}_{365}$ −32.3° (c 3.6). Fractions 14–16 consisted of mixtures of **3** and **4**; fractions 17–27 gave pure **4**, with an IR spectrum identical with that of racemic **4**,[15] $[\alpha]^{25}_{589}$ +82.8°, $[\alpha]^{25}_{546}$ +94.2°, $[\alpha]^{25}_{436}$ +160.3°, $[\alpha]^{25}_{365}$ +247.1°.

(−)-*trans*-2-*tert*-Butyl-5-methylcyclohexanone Tosylhydrazone (8). Natural (+)-pulegone (**5**) [$[\alpha]^{20}D$ +22.5° (neat), 100% optical purity,[17] 35 g] was reacted with methylmagnesium iodide (from 6.2 g of magnesium and 36 g of methyl iodide) in the presence of freshly prepared cuprous chloride[18] (0.75 g), as described,[4] except that ethyl ether was used as the solvent instead of tetrahydrofuran. The 7:3 mixture (GLC) of **6** and **7** obtained (28 g) was dissolved in absolute ethanol (200 ml), tosylhydrazine (31 g) was added, and the mixture was refluxed for 8 h. Evaporation of the solvent left a semisolid residue which was dissolved in methanol. After standing overnight at −10 °C, the tosylhydrazone **8** crystallized (20 g), mp 138–140 °C. Concentration of the mother liquors and standing at −10 °C yielded a second fraction (8 g), identical with the first one. After repeated recrystallizations from methanol until a constant optical rotation and melting point were reached, **8** had mp 145–146 °C, $[\alpha]^{25}_{589}$ −33.7°, $[\alpha]^{25}_{546}$ −39.0°, $[\alpha]^{25}_{436}$ −72.3°, $[\alpha]^{25}_{365}$ −126.5° (c 3.1); NMR δ 0.86 [overlapping s and d, $(CH)_3C$– and CH_3–, 12 H], ~1.1–2.1 (7 cyclohexane H), 2.41 (s, $CH_3C_6H_4$–, 3 H), 2.70 [2 m, $J \sim 10$ Hz, >CHC$(CH_3)_3$, 1 H],

7.32 and 7.92 (2 d, $-C_6H_4-$, 4 H), 8.38 (m, >NH, 1 H).

Anal. Calcd for $C_{18}H_{28}N_2SO_2$: C, 64.26; H, 8.39; N, 8.33; S. 9.53. Found: C, 63.98; H, 8.20; N. 8.18; S, 10.05.

(+)-*trans*-3-*tert*-Butyl-6-methylcyclohexene. A 2.2 M solution of butyllithium in hexane (75 ml) was added dropwise to a stirred suspension of the tosylhydrazone 8 (13.2 g) in anhydrous ethyl ether (140 ml) at 0 °C under a nitrogen atmosphere. The solid 8 first dissolved, then a white precipitate was formed, which turned to yellow and finally to orange. The reaction mixture was stirred at 0 °C for 2 h, left for 12 h at room temperature under nitrogen, and then hydrolyzed. The organic layer was separated, washed with 10% aqueous Na_2CO_3 and water, dried, and evaporated. The residue was dissolved in petroleum ether and filtered through a 40 × 2.5 cm column of silica gel. Evaporation and distillation of the eluate yielded pure (GLC) **9**: bp 72–73 °C (18 mm); $[\alpha]^{25}_{589}$ +117.6°, $[\alpha]^{25}_{546}$ +134.3°, $[\alpha]^{25}_{436}$ +235.5°, $[\alpha]^{25}_{365}$ +378.2° (*c* 6, $CHCl_3$); NMR δ 0.86 [overlapping s and d, $(CH_3)_3C-$ and CH_3-, 12 H], 5.52 (m, $W_{1/2} \sim 4$ Hz, $-CH=$, 2 H).

Anal. Calcd for $C_{11}H_{20}$: C, 86.60; H, 13.24. Found: C, 86.84; H, 13.25.

Acknowledgment. Financial support by the Consiglio Nazionale delle Ricerche (Roma) is gratefully appreciated.

Registry No.—(+)-**1**, 61116-78-7; (+)-1 phthalate, 61062-48-4; (−)-**1**, 61116-79-8; (+)-**2**, 61138-74-7; (−)-**2**, 31062-01-8; 3, 61062-49-5; 4, 61062-50-8; 5, 89-82-7; 6, 56782-80-0; 7, 56816-94-5; 8, 61062-51-9; 9, 61116-80-1.

References and Notes

(1) (a) G. Berti and A. Marsili, *Tetrahedron*, **22**, 2977 (1966); (b) G. Bellucci, C. Giordano, A. Marsili, and G. Berti, *ibid.*, **25**, 4515 (1969); (c) G. Bellucci, F. Marioni, and A. Marsili, *ibid.*, **25**, 4167 (1969); (d) G. Bellucci, G. Berti, F. Marioni, and A. Marsili, *ibid.*, **26**, 4627 (1970).
(2) C. Djerassi, E. J. Warawa, R. E. Wolff, and E. Eisenbraun, *J. Org. Chem.*, **25**, 917 (1960).
(3) G. H. Posner, *Org. React.*, **19**, 1 (1972).
(4) C. Djerassi, P. A. Hart, and E. J. Warawa, *J. Am. Chem. Soc.*, **86**, 78 (1964).
(5) R. H. Shapiro and M. J. Heath, *J. Am. Chem. Soc.*, **89**, 5734 (1967).
(6) E. J. Eisenbraun and S. M. McElvain, *J. Am. Chem. Soc.*, **77**, 3383 (1955), and references cited therein.
(7) The addition of XY reagents to **9** gave anti diaxial and diequatorial adducts, in all of which the protons α to X and Y clearly appeared to be coupled with axial protons α to the methyl and *tert*-butyl groups, showing that both the alkyl substituents were equatorial. This also ruled out the possibility of epimerization of ketone **6** at C(2) prior to tosylhydrazone formation (work in progress from this laboratory).
(8) N. L. McNiven and J. Read, *J. Chem. Soc.*, 153, 159 (1952).
(9) J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5493 (1959).
(10) J. A. Mills, *J. Chem. Soc.*, 4976 (1952).
(11) E. L. Eliel, *Tetrahedron Lett.*, **No. 8**, 16 (1960). See also R. J. D. Evans and S. R. Landor, *J. Chem. Soc.*, 2553 (1965).
(12) J. H. Brewster, *Top. Stereochem.*, **2**, 1 (1967).
(13) A number of instances where the configuration found differed from that predicted on the basis of Brewster's approach have been also reported for some norbornane derivatives: J. A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff, and D. Willner, *J. Am. Chem. Soc.*, **83**, 3986 (1961).
(14) J.-C. Richer and C. Freppel, *Can. J. Chem.*, **46**, 3709 (1968).
(15) J. Sicher, F. Šipoš, and M. Tichy, *Collect. Czech. Chem. Commun.*, **26**, 84 (1961).
(16) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).
(17) E. Beckmann and M. Pleissner, *Justus Liebigs Ann. Chem.*, **262**, 1 (1891), report $[\alpha]_D$ +22.53°, and J. Doeuvre and H. Perret, *Bull. Soc. Chim. Fr.*, **2**, 298 (1935), report $[\alpha]_D$ +22.58°.
(18) R. N. Keller and H. D. Wycoff, *Inorg. Synth.*, **2**, 1 (1946).

Mechanistic Aspects of the Wolff–Kishner Reaction. 6. Comparison of the Hydrazones of Benzophenone, Fluorenone, Dibenzotropone, and Dibenzosuberone

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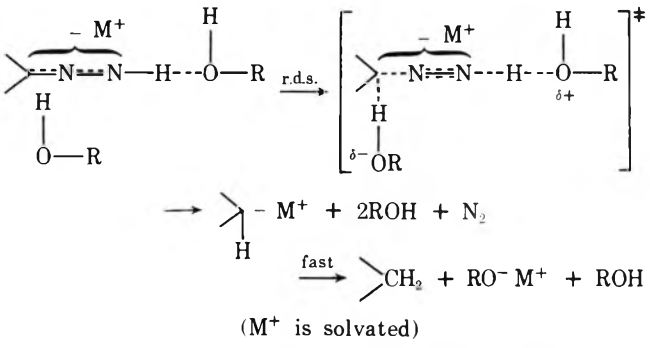
A careful determination[1] of the kinetic and activation parameters of the Wolff–Kishner reaction of benzophenone hydrazone in two hydroxylic solvents (butyl carbitol and 1-decanol) as a function of the cation (K, Na, Li, and Mg) in the alkoxide catalyst, the concentration of the latter, and as a function of the presence of dicyclohexyl-18-crown-6 has led to the conclusion that the rate-determining step involves the hydrazone anion and a minimum of two solvent molecules: one hydroxylic solvent molecule that functions as a proton source, and another solvent molecule that acts as a base in the scission of the N–H bond. The rate-limiting step for the Wolff–Kishner reaction of benzophenone hydrazone in a hydroxylic solvent can thus be represented as follows:



The experimental results also suggest that the reactivity of the hydrazone anion increases with the dissociation of the ionic pair.

In this paper we wish to report the comparison of the behavior of benzophenone hydrazone (I) in the Wolff–Kishner reaction with that of three structurally related compounds (II, III, IV) in which the stabilization of the partial negative charge at the reactive carbon atom should vary as a function of the differences in coplanarity, aromaticity, and antiaromaticity.[2]

Results and Discussion

The kinetics of the Wolff–Kishner reaction of I–IV were determined in butyl carbitol using the sodium butyl carbito-

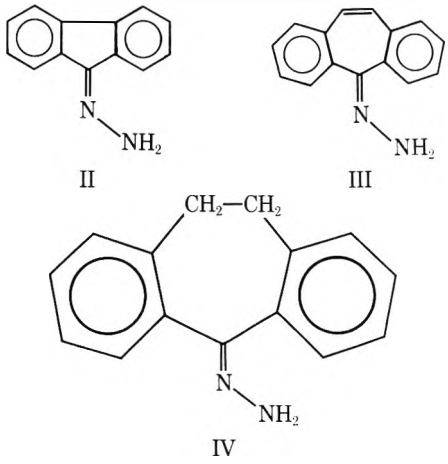


Table I. Rate Constants and Activation Parameters for the Wolff-Kishner Reaction of I-IV

Compd	$k^{150.5°} \times 10^3$, M^{-1} s^{-1}	$\Delta H^{\ddagger}$, kcal/mol[c]	$\Delta S^{\ddagger}$, eu[c]
I	2.71[a]	28.8 ± 0.5	−3.1 ± 1.1
II	254[a,b]	25.6 ± 0.4	−1.5 ± 0.9
III	1.62[a]	29.1 ± 1.5	−3.3 ± 3.2
IV	0.280[a]	30.2 ± 0.7	−4.4 ± 1.6

[a] Standard deviations of these values are less than 5%. [b] Extrapolated from 91.7–131.0 °C. [c] Errors quoted in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are equal to 1.96 × (standard errors) which gives a 96% "confidence level" (N. C. Barford, "Experimental Measurements: Precision, Error and Truth", Addison-Wesley, Reading, Mass., 1967).

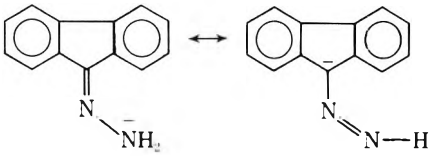
Table II. Kinetic Results for the Wolff–Kishner Reaction of Fluorenone Hydrazone (II), Dibenzotropone Hydrazone (III), and Dibenzosuberone Hydrazone (IV)

Expt no.	Hydrazone	$[HyH]_0$, M	$[RO^-Na^+]$, M Init	$[RO^-Na^+]$, M Final	Temp, °C	$t_f/t_{1/2}$	$k_1 \times 10^5$, s^{-1}	$k_2 \times 10^2$, $M^{-1}\ s^{-1}$
121	II	0.060	0.0274	0.0254	131.0	8.7	148	6.22
117	II	0.040	0.0945	0.0920	111.3	8.3	99.9	1.17
119	II	0.049	0.0587	0.0575	111.3	7.1	63.2	1.19
120	II	0.041	0.0248	0.0224	111.3	1.2	24.7	1.14
123	II	0.047	0.1031	0.1005	91.2	6.6	16.9	0.178
122	II	0.058	0.0592	0.0584	91.2	1.9	9.37	0.171
142	III	0.043	0.0108	0.0106	195.2	8.4	40.3	4.50
141	III	0.032	0.0770	0.0755	195.2	12.3	339	5.32
145	III	0.033	0.123	0.122	171.8	7.8	90.8	0.860
146	III	0.033	0.114	0.114	150.5	5.8	17.2	0.171
147	III	0.035	0.136	0.136	150.4	7.1	18.4	0.153
110	IV	0.043	0.0865	0.0815	195.6	8.1	66.1	0.94
109	IV	0.039	0.1310	0.1265	195.6	10.9	106	0.981
111	IV	0.033	0.154	0.152	171.6	5.6	19.4	0.147
137	IV	0.035	0.126	0.124	171.5	5.1	16.5	0.153
113	IV	0.028	0.697	0.697	171.6	13	124	0.206
138	IV	0.027	0.158	0.158	150.6	1.6	3.94	0.0281
139	IV	0.028	0.492	0.486	150.6	6.4	12.0	0.0279

late catalyst as described elsewhere.[1] Compounds I, III, and IV were studied in the temperature range 150.4–195.6 °C, while II, because of its higher reactivity, was studied in the temperature range 91.2–131.0 °C. A comparison of the rate constants (at 150.5 °C) and of the activation parameters is given in Table I.

While the relative rates of the Wolff–Kishner reaction of I–IV show significant differences, it is apparent from the comparison of the activation parameters that, except for the case of II, the rates are governed primarily by the differences in the enthalpies of activation. The entropies of activation of I, III, and IV fall into a narrow range of -3.75 ± 0.65 eu and it can be assumed that the transition states of the rate-determining steps of all three compounds have similar structures. The relatively small increase in the enthalpies of activation as we proceed from I to III and IV appears to reflect the increasingly more costly proton transfer from a hydroxylic solvent molecule to the sp^2 carbon atom of the hydrazone moiety. It is apparent, however, that the antiaromaticity of the potential dibenzotropyl carbanion has a small effect on the reactivity of III.

The behavior of fluorenone hydrazone (II), on the other hand, stands out in accord with the expected highly stabilized carbanion character of the hydrazone anion:



The results listed in Table I clearly demonstrate that the proposed high electron density at the carbon terminal of the hydrazone anion of II causes a significant decrease in the enthalpy of activation, most likely because of the relatively easier transfer of a proton from oxygen to carbon. The more positive entropy of activation in the case of II suggests that, again because of the relatively greater stability of the fluorenyl carbanion, the transition state lies closer to the product of the rate-limiting step, i.e., the nitrogen molecule is more highly separated in the case of II than in the analogous systems I, III, and IV.

Experimental Section

Materials. The preparation of benzophenone hydrazone and the purification of butyl carbitol have been described elsewhere.[1]

Fluorenone hydrazone was purchased from Aldrich Chemical Co. and crystallized from ethanol before use.

Dibenzotropone hydrazone and **dibenzosuberone hydrazone** could not be prepared in the usual manner[3] since this procedure yielded the corresponding alcohols in 40–60% yield. The hydrazones were obtained by allowing the ketones to react for 2 h with an excess of 95% hydrazine in refluxing ethylene glycol under nitrogen. The reaction mixture was cooled and diluted with water, and the hydrazones were extracted with benzene and recrystallized from petroleum ether. Dibenzotropone hydrazone (III), mp 78 °C.

Anal. Calcd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72. Found: C, 82.42; H. 5.31; N, 12.44.

Dibenzosuberone hydrazone (IV), mp 82 °C.

Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.90; H, 6.19; N, 12.50.

Kinetic Experiments. The apparatus, procedure, treatment, and accuracy of the data and the results for benzophenone hydrazone were reported elsewhere.[1] The kinetic results obtained with the hydrazones of fluorenone (II), dibenzotropone (III), and dibenzosuberone (IV) are summarized in Table II.

Acknowledgment. We wish to thank the National Science Foundation for partial support under GP-11480, The MHW Laboratories, Garden City, Mich., for the microanalyses, and the University of Detroit for a Teaching Fellowship (for C.E.A.).

Registry No.—I, 5350-57-2; II, 13629-22-6; III, 61047-37-8; IV, 61047-38-9; dibenzotropone, 2222-33-5; dibenzosuberone, 1210-35-1; hydrazine, 302-01-2.

References and Notes

(1) For the preceding paper in this series see H. H. Szmant and C. E. Alciaturi, *J. Am. Chem. Soc.*, in press. From the Ph.D. Dissertation of C.E.A., 1972.
(2) J. A. Hirsch, "Concepts in Theoretical Organic Chemistry", Allyn and Bacon, Boston, Mass., 1974, pp 56–58.
(3) H. H. Szmant and C. McGinnis, *J. Am. Chem. Soc.*, **72**, 2890 (1950).

Structure Assignments and Reactivities of Bromochlorocarbene–Olefin Adducts

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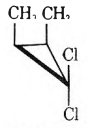
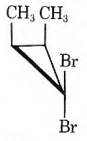
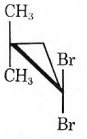
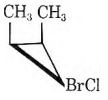
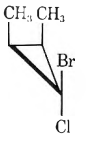
Bromochlorocarbene appears to have been the first dihalocarbene with dissimilar halogens to have been added to olefins from which geometrically isomeric adducts are possible

Table I. ^1H and ^{13}C NMR Chemical Shifts[a]

Registry no.		Ring protons	Methyl protons	C-1	C-2, C-3	Methyl C
1120-67-8		1.72	1.24	67.13	26.99	8.11
3591-57-9		1.65	1.09	40.14	27.96	10.48
32264-50-9		1.65	1.12			
61216-64-6	 (mixed isomers)	1.46 1.65	1.09	57.61 51.50	27.42 27.71	10.53 8.01
61216-65-7		1.47	1.10	57.71	27.47	10.48

[a] Parts per million downfield from Me_4Si.

without altering the spatial relations of groups on the originally olefinic carbons.[2] The early reports[2,3] indicated that both isomers had been formed from indene,[2] cyclopentene, and cyclohexene,[3] and the behavior of the isomers differed so greatly toward silver ions as to become subsequently exemplary of certain electrocyclic reactions.[4] A more recent report[5] has criticized the absence of experimental details in the early work. The latter workers were unable to achieve the separations claimed in one of the early reports.[3]

In other carbene–olefin additions that lead to isomer pairs structure assignments have been based on the postulate $J_{HH(HF)cis} > J_{HH(HF)trans}$ for vicinal spin coupling constants in cyclopropanes.[6] As this rule cannot be applied to the bromochlorocarbene–olefin adducts, direct evidence for structural assignments for such isomer pairs has not appeared previously, and those assignments that have been made[4] are dependent upon analogies to relative reactivities of compounds where the structure assignments were based on the above postulate.

The matter of separability of the isomer pairs was studied using the bromochlorocarbene adducts of *cis*-2-butene, cyclohexene, cyclopentene, and styrene. In each of the four cases partial separation (60% valley between isomer peaks) was achieved by isothermal GLC using a 76 m × 0.12 mm open tubular column and retention times of 1–3 h. The gas chromatograms showed both isomers to be present in each case in ratios of 1.0 ± 0.2 where the uncertainty range is of instrumental origin.

^1H NMR spectra of the purified isomer pairs also indicated the lack of formational stereoselectivity,[7] and reaction kinetics described below are fitted best by an isomer ratio of unity. Virtual absence of stereoselectivity is of interest in view of the uncertainty of relative importance of steric and polarizability factors in carbene additions by Doering and Hoffmann's procedure.[8] Use of this method for the addition of fluorochlorocarbene[6a] and fluorobromocarbene[9] to cyclohexene gave products having isomer ratios of 1.5 and 1.7, respectively, with sterically unfavorable geometry predominating.

Partial reaction of the isomer pairs in ethanolic silver perchlorate solution showed one isomer in each pair to be considerably more reactive than the other. Gravimetric analysis of the precipitated silver halide and mass spectra of the organic products showed that chlorine is removed preferentially from one isomer of 6-bromo-6-chlorobicyclo[3.1.0]hexane as reported by Skell and Sandler[3] and also from the less reactive isomer of 1-bromo-1-chloro-*cis*-2,3-dimethylcyclopropane. On the other hand, neither isomer of 1-bromo-1-chloro-2-phenylcyclopropane lost chlorine; only bromine was lost to silver ions by both isomers.

The 7-bromo-7-chlorobicyclo[4.1.0]heptanes behave still differently toward silver ions in that below 65 °C both halogens are lost from about half the molecules, and the remainder lose only bromine. This observation is in conflict with an early communication[3] but is made less surprising by the recent reports that cyclohexene-1-carboxaldehyde is a minor product from similar reactions of 7,7-dibromonorcarane[10] with analogous carbonyl-containing products forming from related compounds.

The large difference in silver ion promoted solvolysis rates of the two isomers of 1-bromo-1-chloro-*cis*-2,3-dimethylcyclopropane permitted isolation of the less reactive isomer in high purity as evidenced by the absence of a strong, polarized band found near 323 cm^{-1} in the Raman spectrum of the isomer mixture.[11] Chemical shifts in the ^1H and ^{13}C NMR spectra of this single isomer, an equimolar mixture of both isomers, and the corresponding dibromo- and dichlorodimethylcyclopropanes are presented in Table I.

Comparison of the ^1H NMR spectra reveals no difference in the methyl proton signals from the two bromochloro isomers and the dibromo compound, but the multiplets attributable to the ring protons of the bromochloro isomers, though overlapped at 60 MHz, were resolved at 100 MHz.[12] The appearance of the ring proton signals at higher fields for the less reactive isomer and for the dibromo compound favors this isomer having bromine cis to the methyl groups.[13]

Stronger evidence for this assignment comes from the ^{13}C

Table II. Reaction of 1,1-Dibromo-*cis*-2,3-dimethylcyclopropane in Ethanolic Silver Perchlorate[a]

Time, s	[H⁺], mM	% reaction	$10^4 k$, $M^{-1} s^{-1}$
2700	1.7	4.6	2.36
9960	5.6	15.2	2.29
30 180	13.8	37.5	2.30
88 800	26.6	72.3	2.47
267 780	34.8	94.6	2.22
			2.33 ± 0.07

[a] Initial concentrations: 36.8 mM halide and 75.4 mM silver perchlorate in 80% (vol) ethanol–water at 25.0 °C.

Table III. Rate of Acid Formation from Mixed Isomers of 1-Bromo-1-chloro-2-phenylcyclopropane[a]

Time, min[b]	22	65	179	590	1429	3763
Obsd [H⁺], mM	10.6	19.0	26.7	33.3	40.9	47.2
Calcd [H⁺], mM[c]	10.3	19.1	26.7	33.0	40.3	47.2

[a] 0.0486 M dihalocyclopropane and 0.44 M silver perchlorate initially in 95% (vol) ethanol–water at 92.8 °C. [b] Timing was begun at mixing at room temperature. After 12.5 min, to allow for mixing and thermal equilibration, 6.6 mM acid had formed which has been attributed solely to reaction of the more reactive isomer. [c] Based on a 1:1 initial isomer ratio and pseudo-first-order rate constants of 1.94×10^{-2} and 7.5×10^{-4} min^{-1}.

NMR chemical shifts shown in Table I for the same set of compounds. Only the assumption that the methyl carbons are more strongly influenced by the closer halogen is required. The assignment of the signals to the carbons giving rise to them is based on the multiplicities and J_{CH} values in coupled spectra. The ^{13}C NMR chemical shifts agree roughly with values estimated by addition of monohalo substituent effects.[14] The small difference in chemical shifts of the corresponding ring carbons of the bromochloro isomers may reflect a difference in ring strains.[15]

That the less reactive isomer of 1-bromo-1-chloro-*cis*-2,3-dimethylcyclopropane has bromine cis to the methyls is in agreement with the reported trends of acetolysis rates of monohalocyclopropanes and cyclopropyl tosylates.[16] This structure assignment receives further support from a partial electron diffraction analysis of the less reactive isomer.[17]

Rate constants for the silver ion assisted reactions in aqueous ethanol depend linearly on the concentrations of both halocyclopropane and silver salt as demonstrated in Table II for 1,1-dibromo-*cis*-2,3-dimethylcyclopropane. This observation is in contrast to the recent communication of Bach and Willis[18] in which a quadratic dependence on silver ion concentration was employed and may reflect the result of differences in initial concentrations. Generally, the rates were measured using pseudo-first-order conditions with a large excess of silver ions as illustrated in Table III for the mixed isomers of 1-bromo-1-chloro-2-phenylcyclopropane.

These reactions were usually followed by the formation of titratable acid, but the same rate constant was obtained in several cases by following the rate of decrease in silver ion concentration or decrease of reactant concentration in petroleum ether extracts of the reaction solution. Thermal rearrangement prior to reaction with silver ions was excluded in the case of the methanolysis of 1,1-dibromo-*cis*-2,3-dimethylcyclopropane by the several hundredfold faster reaction of the rearrangement product, (*E*)-3,4-dibromo-2-pentene,[19] and in other cases by the equality of the rate of reactant disappearance in extracts of the reacting solutions and the rate of acid formation in the same solutions.

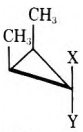
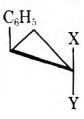
The products of these reactions in general were the alcohols and ethers expected by analogy to the product studies of Sandler[20] on reactions of dibromo- and dichlorocyclopropanes.

The structures of the 1-bromo-1-chloro-2-phenylcyclopropane isomers shown in Table IV are assigned by analogy to the dimethyl compounds so as to have the more reactive isomer be that with bromine trans to the phenyl. This assignment is preferred also by analogy to the acetolysis rates of *cis*- and *trans*-1-chloro-2-phenylcyclopropane.[16a] Presence of the second halogen would not be expected to impair the latter comparison (vide infra).

The second-order rate constants in Table IV provide three comparisons of the effect of chlorine vs. bromine as the remaining halogen. Bromine is removed faster from the more reactive isomer of 1-bromo-1-chloro-2-phenylcyclopropane (where chlorine is the remaining halogen) than from 1,1-dibromo-2-phenylcyclopropane (where bromine is the remaining halogen); the ratio k_{ClBr}/k_{BrBr} is 3.17. Similarly in the dimethyl series, k_{ClBr}/k_{BrBr} is seen to be 1.72 at 25 °C. When chlorine is removed from the dichlorodimethyl compound and from the less reactive bromochloro isomer, the ratio k_{ClCl}/k_{BrCl} is 1.25. A faster reaction when chlorine, rather than bromine, is the remaining halogen is seen also in other dihalocyclopropanes[21] and may indicate that only a small amount of positive charge is transferred to C-1 in the transition state as has been suggested for acetolysis,[16] hydrolysis,[22] and on theoretical grounds.[23] Whether the charge at C-1 is small because little weakening of the carbon–halogen bond has occurred in the activated complex or because ring opening and charge transfer to C-2 and C-3 is synchronous with carbon–halogen bond cleavage cannot be ascertained from these data. The latter possibility has been proposed by DePuy et al., however, for acetolyses.[24]

That ring opening is probably concerted with carbon–halogen bond breaking in the silver ion assisted solvolyses is a satisfactory explanation for the rather small difference in rate constants at 92.8 °C for chlorocyclopropane (2.18×10^{-7} $M^{-1} s^{-1}$) and 1,1-dichlorocyclopropane (1.3×10^{-7} $M^{-1} s^{-1}$)

Table IV. Silver Ion Assisted Solvolysis Rate Constants[a]

	X–Y			
	Br–Br	Cl–Br	Br–Cl	Cl–Cl
	100 ± 5 (25.0)	172 ± 5 (25.0)	93 ± 7 (92.8)	116 ± 8 (92.8)
	23 (92.8)[b] (3234-51-3)[c]	73 (92.8) (61158-74-5)	2.8 (92.8) (61158-75-6)	0.160 ± 0.006 (92.8) (2415-80-7)

[a] Rate constants × 10^5 ($M^{-1} s^{-1}$) in 95% ethanol initially containing 0.42 ± 0.03 M silver perchlorate. Temperatures in parentheses. [b] Extrapolated from lower temperatures. [c] Registry no.

in 0.42 M ethanolic (95%) silver perchlorate. In view of the well-known low reactivity of *gem*-dihalides toward silver ions[25] this difference would otherwise by surprisingly small.

An approximate value of 970 for k_{Br}/k_{Cl} at 92.8 °C for removal of bromide and chloride from the dimethylcyclopropyl compounds was obtained using an activation enthalpy of 20.6 kcal/mol for the more reactive bromochloro isomer. For bromo- and chlorocyclopropane the ratio was 400 ± 25, and for acetolyses of the monohalo compounds at 100 °C the ratio has been reported to be 32.[16c] According to Hammond's postulate,[26] the larger ratio for the silver ion promoted ethanolyses would seem to indicate greater progress along the reaction coordinate than has been postulated for the effect of alkyl substituents in the acetolysis reactions.

Experimental Section

Infrared spectra were determined on neat liquids using Beckman IR-5A and Perkin-Elmer 521 spectrophotometers. ^{1}H NMR spectra were recorded with JEOL Minimar and Varian A-60 and HA-100 spectrometers using 15–20% carbon tetrachloride solutions. ^{13}C NMR spectra were obtained on 20% hexadeuterioacetone solutions using a JEOL FX-60 spectrometer. Analytical GLC was performed with a Hewlett-Packard 5700-A gas chromatograph using a 76 m × 0.2 mm open tubular column coated with OV-17. An Autoprep 700 with a glass 2.7 m × 8 mm column packed with SE-30 on Chromosorb was used for preparative separations. Hewlett-Packard 5930 and Perkin-Elmer 270 GS–mass spectrometers were used. Microanalyses were performed by Galbraith Laboratory, Knoxville, Tenn.

Halocyclopropanes. Dihalocyclopropanes were prepared by carbene addition to the appropriate olefins except for 1,1-dichlorocyclopropane, which was prepared with chlorocyclopropane by vapor phase photochlorination of cyclopropane.[27] The dihalocarbenes were generated from the appropriate haloform and potassium *tert*-butoxide alcoholate.[8] The physical properties of the adducts agreed with published values[3,5,8,20,28] for each compound. Cyclopropyl bromide was obtained from Aldrich Chemical Co. and was found to contain less than 2% impurities.

1-Bromo-1-chloro-*cis*-2,3-dimethylcyclopropanes. Chlorodibromomethane (0.34 mol) was added over 1 h to a stirred mixture of 0.50 mol of potassium *tert*-butoxide alcoholate, 1 mol of *cis*-2-butene, and 250 ml of petroleum ether (bp 38–57 °C) held at −10 °C. Stirring was continued for 3 h while the temperature rose to room level. The mixture was washed with water (3 × 50 ml) and dried before being distilled first through a 0.5-m Vigreux column and then through a Teflon annular still under reduced pressure. The yield was 50 g (0.27 mol, 80%): bp 72–73 °C (38 mm); n^{25}D 1.4856; d^{25} 1.453; IR (film) 3020, 2936, 1127, 945, 717 cm^{-1} (s).

Anal. Calcd for C_5H_8ClBr: C, 32.73; H, 4.40. Found: C, - 32.58; H, 4.39.

Reaction of *endo*-1-Bromo-*exo*-1-chloro-*cis*-2,3-dimethylcyclopropane in Methanolic Silver Perchlorate. The less reactive isomer (1.22 mmol) in 4 ml of methanol containing 3.61 mmol of silver perchlorate was heated in a sealed vial at 64 °C for 27 h. The precipitate was collected in a Gooch crucible, washed, and dried at 120 °C to a constant weight of 183.4 mg (1.28 mmol silver chloride equivalent). The remaining silver salt in the combined filtrate and washings was precipitated with excess 0.3754 M aqueous sodium chloride. The resulting mixture was extracted (2 × 2 ml) with petroleum ether. Aliquots of the aqueous layer (17 ml) were neutralized with 0.0107 M methanolic sodium methoxide and required 6.85 ± 0.01 ml per ml of aqueous solution indicating the formation of 1.25 mmol of acid during the reaction. The neutralized aliquots were titrated by Mohr's method to determine by difference that 1.22 mmol of silver ions had been consumed in the reaction. GC–MS of the petroleum ether extracts showed one major component with molecular ion masses of 178 and 180 in a ratio of about one, consistent with an assignment of this major product as 3-bromo-4-methoxy-2-pentene. The chromatograms also showed a minor component that had molecular ion masses of 134 and 136 in a ratio of 3:1 as expected for 3-chloro-4-methoxy-2-pentene. The ratio of bromopentene to chloropentene in the petroleum ether extracts was 9:1.

Kinetic Studies. Temperatures were constant within 0.1 °C. Runs at 25 °C were quenched by pipetting aliquots into excess aqueous sodium chloride. The quenched mixtures were then titrated first with methanolic sodium methoxide to the thymol blue end point and then with silver perchlorate by Volhard's or Mohr's method. For runs at elevated temperatures aliquots of the reaction solutions were first cooled to 0 °C and sealed in glass ampules before being immersed in the constant temperature bath. Thermal expansion was approximately corrected for with the formula $k = (1 + 10^{-3}t)k_{app}$ where t is the bath Celsius temperature and k_{app} is the uncorrected, observed rate constant.

Registry No.—Bromochlorocarbene, 13590-47-1; *cis*-2-butene, 590-18-1; cyclohexene, 110-83-8; cyclopentene, 142-29-0; dibromocarbene, 4371-77-1.

References and Notes

(1) To whom correspondence should be addressed.
(2) W. E. Parham and R. R. Twelves, *J. Org. Chem.*, **22**, 730 (1957).
(3) P. S. Skell and S. R. Sandler, *J. Am. Chem. Soc.*, **80**, 2042 (1958).
(4) R. T. Morrison and R. N. Boyd, "Organic Chemistry", 3d ed, Allyn and Bacon, Boston, Mass., 1973, p 947; R. E. Lehr and A. P. Marchand, "Orbital Symmetry", Academic Press, New York, N.Y., 1972, pp 80, 173.
(5) D. Seyferth, S. P. Hopper, and T. F. Jula, *J. Organomet. Chem.*, **17**, 193 (1969).
(6) (a) T. Ando, H. Yamanaka, S. Terabe, A. Horike, and W. Funasaka, *Tetrahedron Lett.*, 1123 (1967); (b) P. D. Ellis and G. E. Maciel, *Mol. Phys.*, **20**, 433 (1971).
(7) Stereoselectivity as used here is defined by G. L. Closs, *Top. Stereochem.*, **3**, 203 (1968). See also W. Kirmse, "Carbene Chemistry", 2d ed, Academic Press, New York, N.Y., 1971, p 288 ff; N. Bodor, M. J. S. Dewar, and J. S. Wasson, *J. Am. Chem. Soc.*, **94**, 9095 (1972); R. Hoffmann, C. C. Levin, and R. A. Moss, *ibid.*, **95**, 629 (1973).
(8) W. V. E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **76**, 6162 (1954).
(9) D. Seyferth and S. P. Hopper, *J. Organomet. Chem.*, **51**, 77 (1973).
(10) C. B. Reese and M. R. D. Stebles, *Tetrahedron Lett.*, 4427 (1972); P. Warner, J. Fayos, and J. Clardy, *ibid.*, 4473 (1973); D. B. Ledlie, J. Knetzer, and A. Gitterman, *J. Org. Chem.*, **39**, 708 (1974).
(11) We are indebted to Professors Steven F. Watkins and N. T. Yu for the Raman spectra.
(12) We are indebted to Dr. R. Ettinger and Varian Associates for 100-MHz ^{1}H NMR spectra.
(13) K. B. Wiberg, D. E. Barth, and P. H. Schertler, *J. Org. Chem.*, **38**, 378 (1973).
(14) K. M. Crecely, R. W. Crecely, and J. H. Goldstein, *J. Phys. Chem.*, **74**, 2680 (1970); G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, Chapter 3.
(15) W. Saenger and C. H. Schalbe, *J. Org. Chem.*, **36**, 3401 (1971).
(16) (a) J. W. Hausser and N. J. Pinkowski, J. Am. Chem. Soc., **89**, 6981 (1967); (b) P. v. R. Schleyer, W. F. Sliwinski, G. W. VanDine, U. Schollkopf, J. Paust, and K. Fellenberger, *ibid.*, **94**, 125 (1972); (c) W. F. Sliwinski, T. M. Su, and P. v. R. Schleyer, *ibid.*, **94**, 133 (1972).
(17) We are indebted to Dr. Denis A. Kohl for the electron diffraction study.
(18) R. D. Bach and C. L. Willis, *J. Am. Chem. Soc.*, **97**, 3845 (1975). See especially note 12.
(19) D. C. Duffey, J. P. Minyard, and R. H. Lane, *J. Org. Chem.*, **31**, 3865 (1966); W. L. Waters, W. S. Linn, and M. C. Caserio, *J. Am. Chem. Soc.*, **90**, 6741 (1968).
(20) S. R. Sandler, *J. Org. Chem.*, **32**, 3876 (1967).
(21) D. C. Duffey, unpublished results.
(22) J. H. Ong and R. E. Robertson, *Can. J. Chem.*, **52**, 2660 (1974).
(23) D. T. Clark and G. Smale, *Tetrahedron*, **25**, 13 (1969).
(24) C. H. DePuy, L. G. Schnack, J. W. Hausser, and W. Wiedemann, *J. Am. Chem. Soc.*, **87**, 4006 (1965); **88**, 3343 (1966); S. J. Cristol, R. M. Sequeira, and C. H. DePuy, *ibid.*, **87**, 4007 (1965).
(25) A. Tchakirian, *C. R. Acad. Sci.*, **196**, 1026 (1933); P. Petrenko-Kritchenko, *J. Prakt. Chem.*, **120**, 225 (1929).
(26) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).
(27) W. E. Parham and E. E. Schweizer, *Org. React.*, **13**, 55–90 (1963), and references cited therein.
(28) P. G. Stevens, *J. Am. Chem. Soc.*, **68**, 620 (1946).

Syntheses of the Syn and Anti Isomers of [2.2](1,4)Naphthalenophane-1,13-diene

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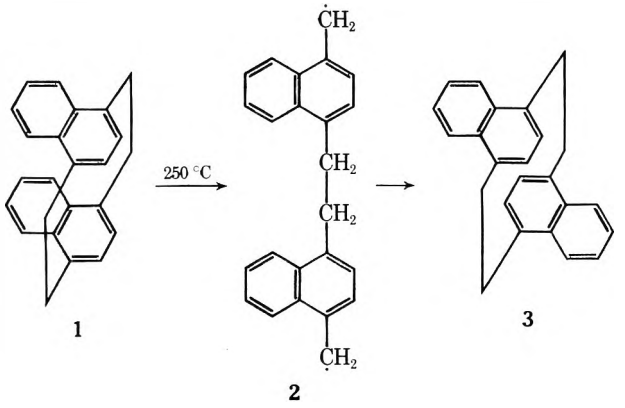
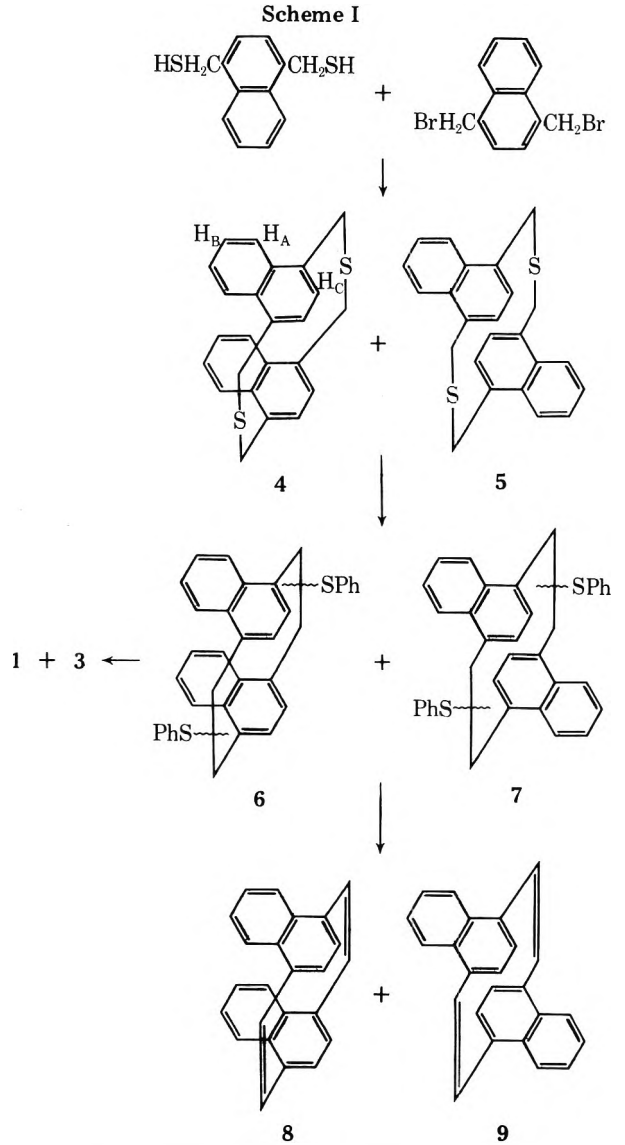
A synthesis of *anti*-[2.2](1,4)naphthalenophane (**3**) was first reported by Cram in 1963,[1] and later, via an improved method, by Brown and Sondheimer.[2] In 1969, Wasserman and Keehn reported a synthesis of *syn*-[2.2](1,4)naphthalenophane (**1**) and its thermal conversion on melting to *anti*-[2.2](1,4)naphthalenophane (**3**).[3] It was suggested that the



thermal conversion of the syn to anti isomer probably proceeded via an intermediate diradical **2**.

Since it would be desirable to have thermally stable syn and anti isomers of the naphthalenophanes for a comparative study of their physical and chemical properties, we undertook the syntheses of the syn and anti isomers of [2.2](1,4)-naphthalenophane-1,13-diene (**8** and **9**), which no longer have the possibility of thermal ring opening to a diradical such as **2**. The synthetic approach followed the general procedure we have described recently for preparing cyclophanedienes,[4] and is outlined in Scheme I.

Scheme I



A coupling reaction between 1,4-bis(bromomethyl)naphthalene and 1,4-bis(mercaptomethyl)naphthalene,[5] carried out as described earlier for similar couplings,[6] gave a mixture of the syn and anti isomers of 2,15-dithia[3.3](1,4)naphthalenophane (**4** and **5**). These were separated and purified by chromatography over silica gel, giving the syn isomer **4** in 11% yield and the anti isomer **5** in 53% yield.

Treatment of either pure **4** or pure **5** with benzyne, generated in situ by the reaction of anthranilic acid with isoamyl nitrite in 1,2-dichloroethane, led to essentially the same mixture, as analyzed by NMR, of the syn and anti stereoisomers represented by **6** and **7**. In proof of these structural assignments, the yellow oil, containing the mixture of **6** and **7** derived from the pure syn isomer **4**, was heated with Raney nickel in ethanol. As expected, this gave a mixture of the known syn and anti isomers of [2.2](1,4)naphthalenophane (**1** and **3**) in a ratio of 1:2.7. When the benzyne–Stevens rearrangement product from the pure anti isomer **5** was likewise treated with Raney nickel, the syn and anti isomers, **1** and **3**, were again formed and in essentially the same ratio. This suggests that the benzyne–Stevens rearrangements of **4** and **5** involve the same intermediate.

When the mixture of **6** and **7** was oxidized with *m*-chloroperbenzoic acid in chloroform, a mixture of the corresponding bis sulfoxides was formed in quantitative yield as a yellow oil. Pyrolysis of this yellow oil at 300 °C in a gradient sublimator gave a crystalline solid which was chromatographed over silica gel. From the first eluate fraction pure anti isomer **9** was isolated as white crystals, mp 252 °C dec, in 4% yield. From the second eluate fraction the pure syn isomer **8** was obtained as white crystals, mp 200 °C dec, in 0.6% yield.

The two isomers are readily distinguishable from their ^{1}H NMR spectra. In the anti isomer **9** the H_c protons feel the ring current of the opposite naphthalene ring and appear at high field (τ 4.26), whereas in the syn isomer **8**, this effect is much smaller and the H_c protons appear at τ 3.28.

The deshielding effect of the benzene ring current on bridging vinyl hydrogens has already been noted for the examples of [2.2]paracyclophane-1,9-diene, where the signal for the vinyl protons is at τ 2.80,[4] and of [2.2.2](1,3,5)cyclophane-1,9,17-triene, where the vinyl protons are at τ 2.63.[7] As would be expected, the deshielding effect of the naphthalene ring current is even greater so that the signal for the vinyl protons of the anti isomer **9** appears at τ 2.55 and that of the syn isomer **8** at τ 2.36, a truly remarkable chemical shift for an unconjugated vinyl proton.

Experimental Section[8]

Syn and Anti Isomers of 2,15-Dithia[3.3](1,4)naphthalenophane, 4 and 5. A solution of 628 mg of 1,4-bis(bromomethyl)naphthalene and 440 mg of 1,4-bis(mercaptomethyl)naphthalene[5] in 200 ml of benzene was added dropwise under a nitrogen atmosphere to a boiling solution of 355 mg of potassium hydroxide in 1.0 l. of ethanol. When the addition was complete (48 h), the reaction mixture was concentrated and the residue was extracted with chloroform. Concentration of the extract followed by chromatography over silica gel, using chloroform for elution, gave 560 mg (75%) of a colorless solid whose NMR spectrum indicated it to be a mixture of **4** and **5**. The anti isomer, **5**, proved to be sparingly soluble in benzene and the syn isomer could be removed by benzene extraction. Chromatography of the crude syn isomer **4**, so obtained, over silica gel using a 1:1 benzene–hexane mixture for elution gave 83 mg (11%) of the pure syn isomer **4** as colorless prisms: mp 230–235 °C dec; NMR ($CDCl_3$) doublet of doublets at τ 2.14 (4 H, J = 6.5, J' = 3.5 Hz, H_A), a doublet of doublets at 2.94 (4 H, J = 6.5, J' = 3.5 Hz, H_B), a singlet at 3.07 (4 H, H_C), and an AB quartet at 5.67 (8 H, J = 15 Hz, CH_2S–); mass spectrum *m/e* 372.098 (calcd for $C_{24}H_{20}S_2$, 372.100).

Anal. Calcd for $C_{24}H_{20}S_2$: C, 77.40; H, 5.41. Found: C, 77.25; H, 5.45.

The samples of anti isomer **5** from the extraction and chromatography were combined and sublimed at 200 °C at 0.03 mm to give 395 mg (53%) of pure anti isomer **5** as white crystals: mp 280 °C dec; NMR ($CDCl_3$) a doublet of doublets at τ 1.90 (4 H, J = 6.0, J' = 3.0 Hz, H_A), doublet of doublets at 2.40 (4 H, J = 6.0, J' = 3.0 Hz, H_B), a singlet

at 3.73 (4 H, H_C), an AB quartet at 5.46 (4 H, J = 15 Hz, $-CH_2S-$) and at 6.05 (4 H, J = 15 Hz, $-CH_2S-$); mass spectrum m/e 372.100 (calcd for $C_{24}H_{20}S_2$, 372.101).

Anal. Calcd for $C_{24}H_{20}S_2$: C, 77.40; H, 5.41. Found: C, 77.31; H, 5.27.

Benzyne–Stevens Rearrangement of 4 and 5. To a boiling solution of 74 mg of **5** and 210 mg of isoamyl nitrite in 30 ml of 1,2-dichloroethane under a nitrogen atmosphere there was added dropwise a solution of 68 mg of anthranilic acid in 10 ml of 1,2-dichloroethane. The addition required 1.5 h and the resulting reaction mixture was boiled under reflux for an additional 15 min. After concentration of the reaction mixture under reduced pressure, the residue was taken up in carbon tetrachloride and transferred to a silica gel column. Elution with benzene gave 60 mg (58%) of a pale yellow oil: mass spectrum m/e 524 (calcd for $C_{36}H_{28}S_2$, 524); NMR spectrum ($CDCl_3$) showing complex multiplets at τ 1.0, 2.0–3.6, 4.0–4.6, and 5.0–7.0, suggesting the presence of a mixture of **6** and **7**.

Similarly, when 19 mg of pure **4** was treated in an analogous way, there was isolated 17 mg (64%) of a pale yellow oil showing a parent molecular ion at m/e 524 and an essentially identical NMR spectrum as above.

Raney Nickel Desulfurization of the Benzyne–Stevens Rearrangement Products. A solution of 60 mg of the yellow oil (mixture of **6** and **7**) from the benzyne–Stevens rearrangement of pure **5** and 1 g of Raney nickel catalyst in 30 ml of absolute ethanol containing enough benzene for solubility of the organic constituents was boiled under reflux for 20 h. After removal of the catalyst and solvent, the residue was chromatographed over silica gel using a 1:2 mixture of carbon tetrachloride–hexane for elution. The first fraction of eluate gave 15 mg (41%) of the pure anti isomer **3**: mp 298–301 °C;[2] NMR ($CDCl_3$) a doublet of doublets at τ 2.26 (4 H, J = 6.0, J' = 3.0 Hz, H_A), a doublet of doublets at 2.59 (4 H, J = 6.0, J' = 3.0 Hz, H_B), a singlet at 4.23 (4 H, H_C), and an A_2B_2 multiplet at 6.1–7.2 (8 H, $-CH_2-$).

From the second fraction of eluate there was isolated 6 mg (16%) of white crystals of the pure syn isomer **1**: mp 242–245 °C;[3] NMR ($CDCl_3$) a doublet of doublets at τ 2.51 (4 H, J = 6.0, J' = 3.0 Hz, H_A), a doublet of doublets at 3.15 (4 H, J = 6.0, J' = 3.0 Hz, H_B), a singlet at 3.28 (4 H, H_C), and an A_2B_2 multiplet at 6.0–6.8 (8 H, $-CH_2-$).

Similarly, when 17 mg of the benzyne–Stevens rearrangement product from the pure syn isomer **4** was subjected to Raney nickel desulfurization, the products were the anti isomer **3** in 40% yield and the syn isomer **1** in 15% yield.

Syn and Anti Isomers of [2.2](1,4)Naphthalenophane-1,13-diene, 8 and 9. A solution of 59.5 mg of the benzyne–Stevens rearrangement product from **5** and 40 mg of *m*-chloroperbenzoic acid (85%) in 10 ml of chloroform was allowed to stand at room temperature overnight under a nitrogen atmosphere. The chloroform solution was washed successively with aqueous sodium bicarbonate and water, dried, and concentrated to give the corresponding bis sulfoxide as 63 mg (100%) of a pale yellow oil. This oil was pyrolyzed directly using a gradient sublimator at 300 °C and under 0.02 mm pressure. The mixture, which collected on the cold finger, was chromatographed over silica gel using a 1:2 mixture of carbon tetrachloride–hexane for elution. The first fraction of eluate gave 1.3 mg (4%) of the pure anti isomer **9** as white crystals: mp 252 °C dec; NMR ($CDCl_3$) a doublet of doublets at τ 2.37 (4 H, J = 6.0, J' = 3.0 Hz, H_A), a singlet at 2.55 (4 H, $-CH{=}CH-$), a doublet of doublets at 2.63 (4 H, J = 6.0, J' = 3.0 Hz, H_B), and a singlet at 4.26 (4 H, H_C).

Anal. Calcd for $C_{24}H_{16}$: mol wt, 304.125. Found (high-resolution mass spectrum): mol wt, 304.124.

The second fraction of eluate gave 0.2 mg (0.6%) of white crystals: mp 200 °C dec; NMR ($CDCl_3$) a singlet at τ 2.36 (4 H, $-CH{=}CH-$), a doublet of doublets at 2.72 (4 H, J = 6.0, J' = 3.0 Hz, H_A), a doublet of doublets at 3.23 (4 H, J = 6.0, J' = 3.0 Hz, H_B), and a singlet at 3.28 (4 H, H_C).

Anal. Calcd for $C_{24}H_{16}$: mol wt, 304.125. Found (high-resolution mass spectrum): mol wt, 304.125.

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

Registry No.—**1**, 23284-44-3; **3**, 14724-91-5; **4**, 61158-76-7; **5**, 61216-66-8; **6**, 61158-81-4; **6** sulfoxide, 61247-61-8; **7**, 61216-68-0; **7** sulfoxide, 61158-82-5; **8**, 61158-77-8; **9**, 61216-67-9; 1,4-bis(bromomethyl)naphthalene, 58791-49-4; 1,4-bis(mercaptomethyl)-naphthalene, 59045-58-8; anthranilic acid, 118-92-3.

References and Notes

(1) D. J. Cram, C. K. Dalton, and G. R. Knox, *J. Am. Chem. Soc.*, **85**, 1088 (1963).
(2) G. W. Brown and F. Sondheimer, *J. Am. Chem. Soc.*, **89**, 7116 (1967).
(3) H. H. Wasserman and P. M. Keehn, *J. Am. Chem. Soc.*, **91**, 2374 (1969).
(4) T. Otsubo and V. Boekelheide, *Tetrahedron Lett.*, 3881 (1975).
(5) Henkel and Cie, British Patent, 807 720 (Jan 21, 1959); *Chem. Abstr.*, **54**, 413a (1960).
(6) R. H. Mitchell, T. Otsubo, and V. Boekelheide, *Tetrahedron Lett.*, 219 (1975).
(7) V. Boekelheide and R. A. Hollins, *J. Am. Chem. Soc.*, **95**, 3201 (1973).
(8) NMR measurements were made with a Varian XL-100-15 instrument and mass spectra were taken using a CEC-110-21b. Elemental and high-resolution mass spectral analyses were determined by Dr. R. A. Wielesek of the University of Oregon Microanalytical Laboratories.

Highly Stereoselective Synthesis of 9-*epi*-Prostaglandin $F_{2\alpha}$ and 11-*epi*-prostaglandin $F_{2\alpha}$ by the Aluminum Hydride Reduction of Prostaglandin E_2 and 11-*epi*-Prostaglandin E_2 Derivatives[1]

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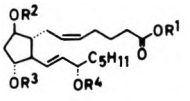
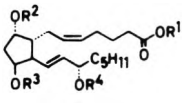
In connection with another study in progress in these laboratories, we required substantial quantities of 9-*epi*-prostaglandin $F_{2\alpha}$ ($PGF_{2\beta}$) (**1a**) and 11-*epi*-prostaglandin $F_{2\alpha}$ (**2a**). ($PGF_{2\beta}$) or derivatives thereof) has been obtained as one component of the mixtures formed on the sodium borohydride reduction[2-5] of PGE_2 (**3a**) (or analogues), or the aluminum amalgam[5,6] reduction of the mixed 10,11-α- and -β-epoxides of PGA_2 (or derivatives). Analogous procedures[5,6] have been utilized to prepare 11-*epi*-$PGF_{2\alpha}$, but the efficiency of these processes is very low (see Table I, for example). Weinshenker et al.[7] have described a synthesis of this compound (**2a**) the



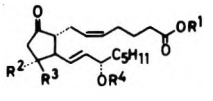
1

a) R^1, R^2, R^3, R^4 = H
b) R^1 = CH_3; R^2, R^3 = H; R^4 = CH_3CO
c) R^1 = CH_3; R^2, R^3, R^4 = H
d) R^1 = CH_3; R^2 = H; R^3, R^4 = THP



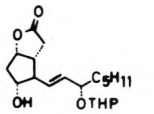
2

a) R^1, R^2, R^3, R^4 = H
b) R^1 = CH_3; R^2, R^3 = H; R^4 = CH_3CO
c) R^1 = CH_3; R^2, R^3, R^4 = H



3

a) R^1, R^3, R^4 = H; R^2 = OH
b) R^1, R^2, R^4 = H; R^3 = OH
c) R^1 = CH_3; R^2 = OH; R^3 = H; R^4 = CH_3CO
d) R^1 = CH_3; R^2 = H; R^3 = OH; R^4 = CH_3CO
e) R^1 = CH_3; R^2 = OTHP; R^3 = H; R^4 = THP
f) R^1, R^3, R^4 = H, R^2 = $OSi(CH_3)_3$
g) R^1 = CH_3; R^2 = H; R^3 = $OSi(CH_3)_3$; R^4 = CH_3CO



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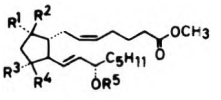

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a) R^1, R^3 = OH; R^2, R^4 = H; R^5 = CH_3CO
b) R^1, R^3 = H; R^2, R^4 = OH; R^5 = H or CH_3CO
c) R^1 = OH; R^2, R^4 = H; R^3 = OTHP; R^5 = THP

crucial aspect of which involved the nucleophilic inversion (tetraethylammonium formate on the tosylate) of the prostaglandin intermediate[8] **4**. Very recently, Corey and coworkers[9] have shown that both **1a** and **2a** were readily available by the stereospecific inversion of suitably protected 9- and 11-tosylates of $PGF_{2\alpha}$ with superoxide ion. This process, though useful, requires large amounts of the costly reagent 18-crown-6 to solubilize the potassium superoxide.

Table I. Reduction of PGE_2 and 11-*epi*-PGE_2 Derivatives

Registry no.	Substrate	Reducing agent	Group at C-11	Stereochemistry of reduction at C-9		Ref
				α	β	
363-24-6	PGE_2 (**3a**)	$NaBH_4$	α-OH	42	58	5
38310-90-6	11-*epi*-PGE_2 (**3b**)	$NaBH_4$	β-OH	21	79[a]	This work
37785-76-5	**3c**	AlH_3	α-OH	6	94[a]	This work
37785-77-6	**3d**	AlH_3	β-OH	100	0[a]	This work
54984-20-2	**3e**	AlH_3	α-THPO	40	60[a]	This work
61158-79-0	**3f**	$NaBH_4$	α-$(CH_3)_3SiO$	85	15	5
61218-48-2	**3g**	$NaBH_4$	β-$(CH_3)_3SiO$	0	100[a]	This work

[a] Ratio of isolated products.

Both PGE_2 and 11-*epi*-PGE_2 (**3b**) are easily prepared[5,6] from the corresponding 10,11-epoxides which in turn can be produced with a considerable degree of stereoselectivity from PGA_2.[10,11] It occurred to us that the transformation of **3a** and **3b** into **1a** and **2a** might be possible if a way could be devised to induce the hydroxyl moiety at C-11 to direct an intramolecular delivery[12] of hydride ion to the carbonyl group at C-9 without affecting other reducible groups in the substrate. For various reasons,[13] it was considered that aluminum hydride[14] would meet these requirements, and therefore an equimolar amount of Alane (aluminum hydride stabilized with triethylamine)[15] in benzene was added to a solution of PGE_2 methyl ester 15-acetate (**3c**) in tetrahydrofuran at −78 °C. Workup of the reaction after 15 min and separation of the mixture thus obtained by preparative thin layer chromatography (TLC) gave the starting material and three products **5a, 1b,** and **1c,** identified by direct comparison with authentic specimens, in a ratio of 20:4.5:26:49.5, respectively. Reduction from the α side had thus occurred with a selectivity greater than 94%! Reduction of 11-*epi*-PGE_2 methyl ester acetate (**3d**) in the same way gave the starting material, **2b,** and **2c** in a ratio of 15:54:31. No 9β,11β alcohol **5b** was formed and therefore hydride was introduced stereospecifically from the β face of the molecule. That a free hydroxyl group at C-11 was vital for the above stereochemical control was evident from the reduction of PGE_2 methyl ester bis(tetrahydropyranyl ether) (**3e**) in which case a 60:40 mixture of **1d** and **5c** was formed. This ratio was almost identical with that which has been reported[5] (see Table I) for the sodium borohydride reduction of PGE_2, but greatly different (15:85) from that which was obtained from the sodium borohydride reduction of the 11-trimethylsilyl ethers of PGE_2 derivatives.[5] Inasmuch as a bulky substituent at C-11 is known[5,16,17] to cause predominant or exclusive reduction with sodium borohydride to occur from the side opposite to this group (i.e., to give the cis-9,11 stereochemistry), the high proportion of the trans product formed in the reduction of **3e** with Alane is probably a reflection of a substantial intramolecular delivery of hydride even in the absence of a free hydroxyl group at C-11.

The alkaline hydrolysis of **1b, 1c, 2b,** and **2c** could be accomplished in yields exceeding 90%; thus $PGF_{2\beta}$ and 11-*epi*-$PGF_{2\alpha}$ were obtained in 76 and 86% overall yields (based on starting material consumed) from **3a** and **3b,** respectively.

The results described herein have a number of interesting and important implications of a mechanistic and synthetic nature.

Experimental Section

The melting points were determined in a Mel-Temp melting point apparatus and are not corrected. The rotations were measured with a Perkin-Elmer Model 141 polarimeter. The infrared spectra were recorded with a Perkin-Elmer Model 237 grating infrared spectrophotometer. The NMR spectra were obtained with a Varian T-60 spectrometer.

Aluminum Hydride Reduction of PGE_2 Methyl Ester 15-Acetate (3c). A solution of compound **3c** (0.500 g, 1.22 mmol) in anhydrous tetrahydrofuran (7.5 ml) was cooled to −70 °C in an atmosphere of argon. A 0.75 M solution (1.62 ml, 1.21 mmol) of Alane in benzene was mixed with anhydrous tetrahydrofuran (10.4 ml) and then added slowly with stirring, at −70 °C, to the solution of **3c.** Fifteen minutes after the addition was completed, water (5 ml) and 6 N hydrochloric acid (5 ml) were added at −70 °C. The product was extracted with ethyl acetate, and the extract was washed successively with saturated sodium bicarbonate and saturated sodium chloride solutions, and then dried over magnesium sulfate. The solvent was removed in vacuo and the mixture (0.480 g) thus obtained was separated by preparative TLC on silica gel (ethyl acetate–hexane; 60:40). In addition to the starting material (0.092 g), there was isolated a small amount (0.020 g, 5% based on starting material consumed) of $PGF_{2\alpha}$ methyl ester 15-acetate (**5a**), and the two major products $PGF_{2\beta}$ methyl ester 15-acetate (**1b,** 0.220 g, 54%) and $PGF_{2\beta}$ methyl ester (**1c,** 0.102 g, 28%).

Compound **5a** was an oil: $[\alpha]_D$ −5.3° ($CHCl_3$); IR ($CHCl_3$) 3615, 3485, 1733, 959 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (m, 3 H), 2.00 (s, 3 H), 2.28 (t, 2 H, J = 6.5 Hz), 3.60 (s, 3 H), 3.40 (m, 1 H), 4.08 (m, 1 H), 4.53–5.49 (m, 5 H). This substance was identical in all respects with an authentic specimen prepared as described by White.[5]

Compound **1b** also was an oil: $[\alpha]_D$ −30.0° (CH_3OH); IR ($CHCl_3$) 3615, 3485, 1734, 960 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (m, 3 H), 2.03 (s, 3 H), 2.28 (t, 2 H, J = 6.4 Hz), 3.62 (s, 3 H), 3.97 (m, 2 H), 4.87–5.62 (m, 5 H). This compound was identical in all of its properties with those of a sample prepared according to White.[5]

$PGF_{2\beta}$ methyl ester **1c** was a solid which after crystallization from ethyl acetate had mp 85–86 °C (lit.[18] 90–91 °C); $[\alpha]_D$ − 4.1° (CH_3OH); IR ($CHCl_3$) 3615, 3400, 1733, 957 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (m, 3 H), 2.32 (t, 2 H, J = 6.6 Hz), 3.67 (s, 3 H), 3.94 (m, 3 H), 5.42 (m, 4 H).

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.39; H, 9.91.

Aluminum Hydride Reduction of 11-*epi*-PGE_2 Methyl Ester 15-Acetate (3d). The reduction of **3d** was carried out in a manner identical with that described for **3c.** The crude mixture was separated by TLC on silica gel (ether–hexane, 60:40). In addition to the starting material (14%), there was isolated 11-*epi*-$PGF_{2\alpha}$ methyl ester 15-acetate (**2b,** 58% based on starting material consumed), and 11-*epi*-$PGF_{2\alpha}$ methyl ester (**2c,** 35%).

Compound **2b** was an oil: $[\alpha]_D$ + 31° ($CHCl_3$); IR ($CHCl_3$) 3625, 3535, 1732, 967 cm^{-1}; NMR ($CDCl_3$) δ 0.87 (m, 3 H), 2.02 (s, 3 H), 2.28 (t, 2 H, J = 6.7 Hz), 3.62 (s, 3 H), 4.30 (m, 2 H), 4.94–5.73 (m, 5 H). This compound was not characterized further; instead, it was directly hydrolysed to 11-*epi*-$PGF_{2\alpha}$ as described below.

Compound **2c** was a solid which, after crystallization from ethyl acetate, had mp 110–111°; $[\alpha]_D$ +84.4° (CH_3OH); IR ($CHCl_3$) 3610, 3425, 1734, 965 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (m, 3 H), 2.30 (t, 2 H, J = 6.8 Hz), 3.67 (s, 3 H), 4.17 (m, 3 H), 5.27–5.66 (m, 4 H).

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85. Found: C, 68.34; H, 9.85.

$PGF_{2\beta}$ (1a). A. Hydrolysis of $PGF_{2\beta}$ Methyl Ester 15-Acetate (1b). To a solution of **1b** (0.220 g, 0.534 mmol) in methanol (34 ml) was added water until turbidity was achieved and then potassium carbonate (0.220 g, 1.6 mmol) was added. The solution was left at room temperature for 53 h and then it was concentrated in vacuo to one-half the original volume. Water (5 ml) was added and the neutral materials were extracted with dichloromethane (10 ml). The aqueous phase was made acidic to ca. pH 2 with saturated aqueous oxalic acid solution and the product was extracted into ethyl acetate. The extract was washed with saturated sodium chloride solution, dried over magne-

sium sulfate, and evaporated in vacuo. The residual solid (0.175 g, 93%) had mp 94–95 °C (lit.[1] 96.5–97 °C), after crystallization from ethyl acetate, and was indistinguishable from an authentic specimen[3] of $PGF_{2\beta}$.

B. Hydrolysis of $PGF_{2\beta}$ Methyl Ester (1c). The hydrolysis of **1c** was effected in the same manner as described for **1b**, with the exception that the quantity of potassium carbonate was halved. $PGF_{2\beta}$ was obtained in 94% yield and had mp 93–95 °C after crystallization from ethyl acetate.

11-*epi*-$PGF_{2\alpha}$ (2a). The hydrolysis of **2b** or **2c** was accomplished in exactly the same way as described above for **1b** and **1c**. 11-*epi*-$PGF_{2\alpha}$ (**2a**) was thus obtained in 93% yield and had mp 117–118 °C (lit.[9] 117–119 °C) after crystallization from acetonitrile. This material was indistinguishable from an authentic sample prepared according to White.[5]

Registry No.—**1a**, 4510-16-1; **1b**, 58282-71-6; **1c**, 28977-26-6; **2a**, 38432-87-0; **2b**, 61158-80-3; **2c**, 58407-22-0; **5a**, 42161-56-8; aluminum hydride, 7784-21-6.

References and Notes

(1) Contribution No. 472 from the Syntex Institute of Organic Chemistry.
(2) S. Bergstrom, L. Krabisch, and J. Sjoval, *Acta Chem. Scand.*, **16**, 969 (1962).
(3) J. E. Pike, F. H. Lincoln, and W. P. Schneider, *J. Org. Chem.*, **34**, 3552 (1969).
(4) G. L. Bundy, W. P. Schneider, F. H. Lincoln, and J. E. Pike, *J. Am. Chem. Soc.*, **94**, 2123 (1972).
(5) D. R. White, U.S. Patent 3 745 178 (1973).
(6) J. E. Pike and W. P. Schneider, U.S. Patent 3 772 350 (1973).
(7) D. M. Floyd, G. A. Crosby, and N. M. Weinshenker, *Tetrahedron Lett.*, 3269 (1972).
(8) E. J. Corey, M. Albonico, V. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Am. Chem. Soc.*, **93**, 1491 (1971).
(9) E. J. Corey, K. C. Nicolaou, and M. Shibasaki, *J. Chem. Soc., Chem. Commun.*, 658 (1975).
(10) E. J. Corey and H. E. Ensley, *J. Org. Chem.*, **38**, 3187 (1973).
(11) See footnote 7 in ref 10.
(12) L. Angiolini and M. Tramontini, *J. Org. Chem.*, **39**, 2056 (1974); J. N. Labows and N. Landmesser, *ibid.*, **40**, 3798 (1975), and references cited therein.
(13) It was considered that the first equivalent of hydride ion would be consumed by the free hydroxyl group to give an alkoxyaluminohydride which would then transfer hydride to C-9 in an intramolecular manner to give a trans 9,11-diol. The aluminum species thus formed was not expected to effect reduction of the ester moieties in these molecules. Although some reduction of the 15-acetate did occur, the ester function at C-1 was not attacked under the specified conditions in any of the cases studied.
(14) H. C. Brown and N. M. Yoon, *J. Am. Chem. Soc.*, **88**, 1464 (1966).
(15) Purchased from Lithium Corporation of America, Bessemer City, N.C.
(16) A. Guzmán and J. M. Muchowski, *Tetrahedron Lett.*, 2053 (1975).
(17) W. P. Schneider, U.S. Patent 3 758 542 (1973).
(18) W. P. Schneider and H. C. Murray, *J. Org. Chem.*, **38**, 397 (1973).

Synthesis of 3-Substituted Furans

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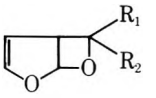
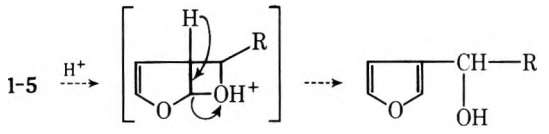
A considerable number of naturally occurring furans bear a substituent in position 3.[1] The synthetic access to them is usually not easy because of known difficulties in preparation of 3-furyl type synthons.[2] Although in recent years a number of methods for the synthesis of 3-substituted furans were reported,[3] there is still a need for further, possibly uncomplicated synthetic routes. We would like to present here a new synthesis of 3-substituted furans which is simple, does not require any special reagents or reaction conditions, and can be performed on a fairly large scale.

It is known since 1963 that carbonyl compounds can be photochemically added to furan furnishing in a remarkably regioselective reaction derivatives of 2,7-dioxabicyclo[3.2.0]-hept-3-ene.[4,5] The outcome of the photochemical cycloaddition is strongly dependent on the carbonyl compound used; the yields vary from 1% for acetophenone to 35% for benzaldehyde.[6] In this way oxetanes **1–7** were prepared (with the exception of **3**, cf. Experimental Section).



1, $R_1 = H$; $R_2 = CH_3$
2, $R_1 = H$; $R_2 = CO_2C_4H_9$
3, $R_1 = H$; $R_2 = CH_2OCOCH_3$
4, $R_1 = H$; $R_2 = CH_2CH_2CH(CH_3)_2$
5, $R_1 = H$; $R_2 = C_6H_5$
6, $R_1 = R_2 = CO_2C_2H_5$
7, $R_1 = H$; $R_2 = 2$-furyl

We have now found that oxetanes **1–5** can be isomerized in the presence of acids (e.g., *p*-toluenesulfonic acid) in aprotic solvents such as diethyl ether or carbon tetrachloride at room temperature to 3-furylmethanols **8–12** in good yields. There



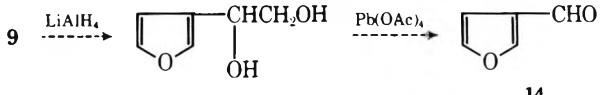
8, $R = CH_3$
9, $R = CO_2C_4H_9$
10, $R = CH_2OCOCH_3$
11, $R = CH_2CH_2CH(CH_3)_2$
12, $R = C_6H_5$

can be little doubt that the gain in stabilization on return to the furan system is the driving force of this isomerization. In Table I are shown the yields, boiling points, and analytical data of 3-furylmethanols obtained.

Table I. 3-Furylmethanols from Isomerization of 2,7-Dioxabicyclo[3.2.0]hept-3-enes

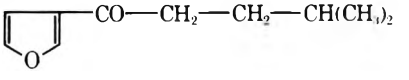
Compd	Yield, %	Bp, °C (mm)	Anal., % Calcd C	Calcd H	Found C	Found H
8	58	65–70 (0.2)	64.3	7.2	63.9	7.5
9	73	80–83 (0.15)	60.6	7.1	60.3	7.4
10	63	98–100 (0.2)	56.5	5.9	56.4	6.2
11	68	80–85 (0.2)	71.4	9.6	71.5	9.6
12	68	80–85 (0.2)	75.8	5.8	75.6	5.7

Compound **9** was reduced with lithium aluminum hydride to diol **13**, which, in turn, was cleaved with lead tetraacetate to 3-furylaldehyde **14** in 65% yield:



13 **14**

Compound **11** was oxidized with Sarett or Jones reagents to perilla ketone **15**.



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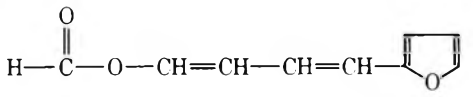
These examples show that 3-furylmethanols can be exploited in the synthesis of naturally occurring furans either directly by employing a suitable aldehyde for photocycloaddition or by means of convenient synthons, e.g., **9**, **13**, or **14**.

The behavior of oxetanes **6** and **7** toward acids was different from that of compounds **1–5**. Whereas oxetane **6** remained unchanged under the conditions employed, oxetane **7** was very unstable; the acidity of silica gel for chromatography was sufficient to convert **7** into a new compound for which the

constitution of the formate of 1-hydroxy-4-(2-furyl)-1,3-butadiene (**16**) was deduced from the spectral and analytical



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data. This is a new manner of oxetane ring cleavage in the 2,7-dioxabicyclo[3.2.0]hept-3-ene system.

Experimental Section

6-Carbobutoxy-2,7-dioxabicyclo[3.2.0]hept-3-ene (2). A solution of *n*-butyl glyoxylate (37.0 g) in furan (450 ml) was irradiated with a 400-W high-pressure mercury lamp under argon atmosphere in a Pyrex photochemical reactor. After 25 h the mixture was distilled and afforded 43.5 g (77.3%) of oxetane **2**: bp 86–88 °C (0.2 Torr); IR 1750, 1610 cm^{-1}; ^1H NMR (CCl_4) δ 6.59 (m, 1 H, $J_{1,3} = 1$, $J_{3,4} = 2.3$ Hz, H-3), 6.34 (d, 1 H, $J_{1,5} = 4.2$ Hz, H-1), 5.34 (t, 1 H, $J_{4,5} = 2.8$ Hz, H-4), 4.69 (d, 1 H, $J_{5,6} = 2.9$ Hz, H-6). 3.69 (m, 1 H, H-5), signals of the *n*-butoxy group at 4.13 (t, 2 H) and 1.1–1.8 (m, 7 H). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.6; H, 7.1. Found: C, 60.8; H, 7.1.

6-Acetoxymethyl-2,7-dioxabicyclo[3.2.0]hept-3-ene (3) was obtained from **2** by lithium aluminum hydride reduction followed by acetylation with acetic anhydride and pyridine in 53% overall yield: bp 83–86 °C (0.2 Torr); IR 1745, 1605 cm^{-1}; ^1H NMR (CCl_4) δ 6.65 (m, 1 H, $J_{3,4} = 3$, $J_{3,5} = 1.3$ Hz, H-3), 6.05 (d, 1 H, $J_{1,5} = 4.4$ Hz, H-1), 5.34 (t, 1 H, $J_{4,5} = 3$ Hz, H-4), 4.60 (pt, 1 H, $J_{5,6} = 2.9$ Hz, H-6), 4.23 (d, 2 H, CH_2OAc), 3.57 (m, 1 H, H-5), 2.08 (s, 3 H, OAc). Anal. Calcd for $C_8H_{10}O_4$: C, 56.5; H, 5.9. Found: C, 56.5; H, 6.2.

6-(3-Methylbutyl)-2,7-dioxabicyclo[3.2.0]hept-3-ene (4) was prepared in 66.4% yield from 4-methylpentanal and furan according to the method described for oxetane **2**: bp 135 °C (53 Torr); IR 1610 cm^{-1}; ^1H NMR (CCl_4) δ 6.60 (m, 1 H, $J_{3,4} = 2.8$ Hz, H-3), 6.21 (d, 1 H, $J_{1,5} = 4.5$ Hz, H-1), 5.27 (t, 1 H, $J_{4,5} = 3$ Hz, H-4), 4.45 (pt, 1 H, $J_{5,6} = 3.2$ Hz, H-6), 3.37 (m, 1 H, H-5), signals of the 3-methylbutyl group at 0.9–2.0 (m, 11 H). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.4; H, 9.6. Found: C, 71.6; H, 9.8.

6,6-Dicarbethoxy-2,7-dioxabicyclo[3.2.0]hept-3-ene (6) was obtained similarly in 30% yield from diethyl ketomalonate and furan. The crude product was purified by column chromatography: IR 1760, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.56 (m, 1 H, $J_{3,4} = 3$, $J_{3,5} = 1$ Hz, H-3), 6.33 (d, 1 H, $J_{1,5} = 4.2$ Hz, H-1), 5.18 (t, 1 H, $J_{4,5} = 2.5$ Hz, H-4), 4.26 (m, 5 H, H-5 and two CH_2O), 1.30 (t, 6 H, two CH_3). Anal. Calcd for $C_{11}H_{14}O_6$: C, 54.5; H, 5.8. Found: C, 54.6; H, 6.0.

Oxetanes **1**, **5** and **7** were prepared according to ref 5.

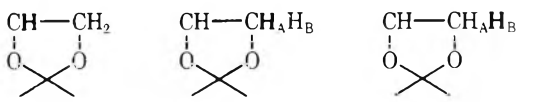
Isomerization of 6-Substituted 2,7-Dioxabicyclo[3.2.0]hept-3-enes. A 1% solution of oxetane **1** (or **2**–**5**) in diethyl ether or carbon tetrachloride was treated with 0.02–0.04% of *p*-toluenesulfonic acid and left at room temperature for 10–24 h. After neutralization with triethylamine the product was isolated by distillation. Yields, boiling points, and elemental analyses of 3-furylmethanols **8**–**12** are collected in Table I. All compounds exhibited ^1H NMR low-field signals at δ 7.3–7.4 (2 H) and 6.3–6.4 (1 H) typical for 3-monosubstituted furans. Also their IR spectra displayed bands specific for the furan ring at 1510 and 870–880 cm^{-1}.

Isomerization of 6-substituted 2,7-dioxabicyclo[3.2.0]hept-3-enes with higher concentration of catalyst led to retro cleavage; after addition of 5% *p*-toluenesulfonic acid to compound **5** only benzaldehyde could be detected after 10 h. From oxetane **1** tars were formed under similar conditions. On the other hand, oxetane **6** remained unchanged after standing with 1% hydrogen chloride for 140 h.

3-(1,2-Dihydroxyethyl)furan (13). Butyl 3-furylglycolate (**9**) was reduced with lithium aluminum hydride in ether solution at 0 °C. After typical workup 67% of diol **13** was obtained. The compound solidified after distillation at 110 °C (0.2 Torr): mp 54.5–55 °C; IR 3350, 1510, 875 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (m, 2 H, furan H-2 and H-5), 6.30 (s, 1 H, furan H-4), 4.70 (pd, 1 H, $J_{AX} = 4.2$, $J_{BX} = 6.8$ Hz, $CHOHCH_2OH$), 3.65 (m, 2 H, $CHOHCH_2OH$). Anal. Calcd for $C_6H_8O_3$: C, 56.2; H, 6.3. Found: C, 56.3; H, 6.6.

Oxidation of diol **13** with lead tetraacetate in benzene solution gave, after workup, 65% of 3-furylaldehyde, mp of phenylhydrazone 147.5 °C (lit.[7] 149.5°C).

1,2-*O*-Isopropylidene derivative of 3-(1,2-dihydroxyethyl)furan was obtained in 81% yield from **13** and acetone to which a catalytic amount of concentrated sulfuric acid was added: distilled at 45–50 °C (0.2 Torr); IR 1510, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (m, 2 H, furan H-2 and H-4), 6.36 (m, 1 H, furan H-4), 5.00 (pd, 1 H, $J_{AX} = 6.0$, $J_{BX} = 7.8$ Hz, fragment a), 4.16 (pd, 1 H, $J_{AB} = 7.7$ Hz, fragment b),



a b c

3.75 (t, 1 H, fragment c), 1.43 and 1.47 (two s, 6 H, two CH_3). Anal. Calcd for $C_9H_{12}O_3$: C, 64.3; H, 7.1. Found: C, 64.7; H, 7.4.

1-(3-Furyl)-4-methyl-1-pentanone (Perilla Ketone, 15). A solution of 1-(3-furyl)-4-methyl-1-pentanol (**11**, 100 mg) in 3 ml of acetone was treated with Jones reagent[8] until persistent yellow coloration. The excess of the oxidizing reagent was destroyed with a few drops of methanol whereupon the mixture was diluted with 2 ml of water and extracted several times with chloroform. Evaporation of the dried ($MgSO_4$) chloroform solution and distillation of the remaining liquid at 60–70 °C (10 Torr) afforded 61 mg (61.7%) of the perilla ketone: mp of 2,4-dinitrophenylhydrazone 149.5 °C (lit.[9] 149.5 °C); IR 1680, 1570, 1520, 875 cm^{-1}; ^1H NMR (CCl_4) δ 8.67, 7.83, and 6.81 (three m, 3 H, furan H-2, H-4, and H-5), 2.69 (t, 2 H, $J_{2,3} = 7.6$ Hz, $COCH_2$–), signals of the 2-methylpropyl group at 0.93–1.8 (m, 9 H). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.3; H, 8.5. Found: C, 72.5; H, 8.7.

Essentially the same result was obtained on oxidation of **11** with Sarett reagent.

Formate of 1-Hydroxy-4-(2-furyl)-1,3-butadiene (16). 6-(2-Furyl)-2,7-dioxabicyclo[3.2.0]hept-3-ene (**7**, 1 g) was chromatographed on a silica gel (Merck) column in a mixture of light petroleum (bp 60–80 °C) and benzene (10:3 v/v). The main fraction (0.63 g) was distilled at 80 °C (0.02 Torr): IR 1730, 1640, 1625, 1555, 1220, 1150, 970, 925, 885, and 738 cm^{-1}; ^1H NMR (CCl_4) δ 8.12 (s, 1 H, HCOO–), 5.43–7.53 (m, 7 H, vinylic and furan H); UV (cyclohexane) λ_{max} 293 nm (ϵ 36 100), 304.5 (45 500), and 317.5 (34 200). Anal. Calcd for $C_9H_8O_3$: C, 65.9; H, 4.9. Found: C, 65.8; H, 4.8.

Registry No.—**1**, 7555-25-1; **2**, 61063-39-6; **3**, 61063-40-9; **4**, 61063-41-0; **5**, 1915-16-8; **6**, 61063-42-1; **7**, 7555-27-3; **8**, 13129-26-5; **9**, 61063-43-2; **10**, 61063-44-3; **11**, 60122-21-6; **12**, 40358-49-4; **13**, 61063-45-4; **13** 1,2-*O*-isopropylidene derivative, 61063-46-5; **14**, 498-60-2; **15**, 553-84-4; **16**, 61063-47-6; *n*-butyl glyoxylate, 6295-06-3; furan, 110-00-9; 4-methylpentanal, 1119-16-0; diethyl ketomalonate, 609-09-6; acetone, 67-64-1.

References and Notes

(1) F. M. Dean, "Naturally Occurring Oxygen Ring Compounds", Butterworths, London, 1963, p 1.
(2) (a) P. Bosshard and C. H. Eugster, *Adv. Heterocycl. Chem.*, **7** 411 (1966); (b) A. Pelter, *MTP Int. Rev. Sci.: Org. Chem., Ser. One*, **4**, 204 (1973).
(3) C. Botteghi, L. Lardicci, and R. Menicagli, *J. Org. Chem.*, **38**, 2361 (1973); M. E. Garst and T. A. Spencer, *J. Am. Chem. Soc.*, **95**, 250 (1973); K. Kondo and M. Matsumoto, *Chem. Lett.*, 701 (1974); Y. Nakahara, M. Matsui, and K. Mori, *Agric. Biol. Chem.*, **38**, 2243 (1974); K. Kondo and M. Matsumoto, *Tetrahedron Lett.*, 391 (1976); T. Jaworski and T. Mizerski, *Rocz. Chem.*, **50**, 359 (1976).
(4) G. O. Schenck, W. Hartmann, and R. Steinmetz, *Chem. Ber.*, **96**, 498 (1963).
(5) S. Toki, K. Shima, and H. Sakurai, *Bull. Chem. Soc. Jpn.*, **38**, 760 (1965); K. Shima and H. Sakurai, *ibid.*, **39**, 1806 (1966).
(6) Calculated for the carbonyl compound used. Yields based on the aldehyde consumed are in the range of 73–88%.[5] The unreacted aldehyde can usually be recovered by distillation.
(7) H. Gilman and R. R. Burtner, *J. Am. Chem. Soc.*, **55**, 2908 (1933).
(8) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, p 142.
(9) T. Ueda and J. Fujita, *Chem. Ind. (London)*, 1618 (1962).

Anodic and Chemical Oxidation of 1-Benzyl-3-isochromanone and 1-Benzyl-1,4-dihydro-3(2*H*)-isoquinolone Derivatives

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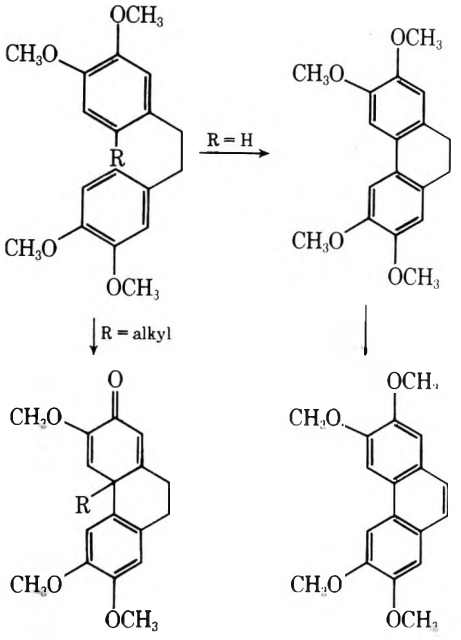
Electrochemical oxidation is a useful method for biaryl coupling of phenols and phenol eithers. These laboratory reactions offer attractive synthetic procedures that parallel a wide range of important biosynthetic processes. Simple me-

thoxy derivatives of bibenzyl undergo intramolecular coupling to afford either dihydrophenanthrenes or the completely aromatic compounds in good yield by electrolysis;[1] but from alkoxybibenzyl compounds with an electron-donating substituent ortho to the ethylene link and para to a methoxy group the principal products have been dienones[2,3] (Scheme I). Several examples are on record in which 1-benzylisoquinoline alkaloids have been converted to morphinandienones by anodic oxidation.[4]

Scheme I



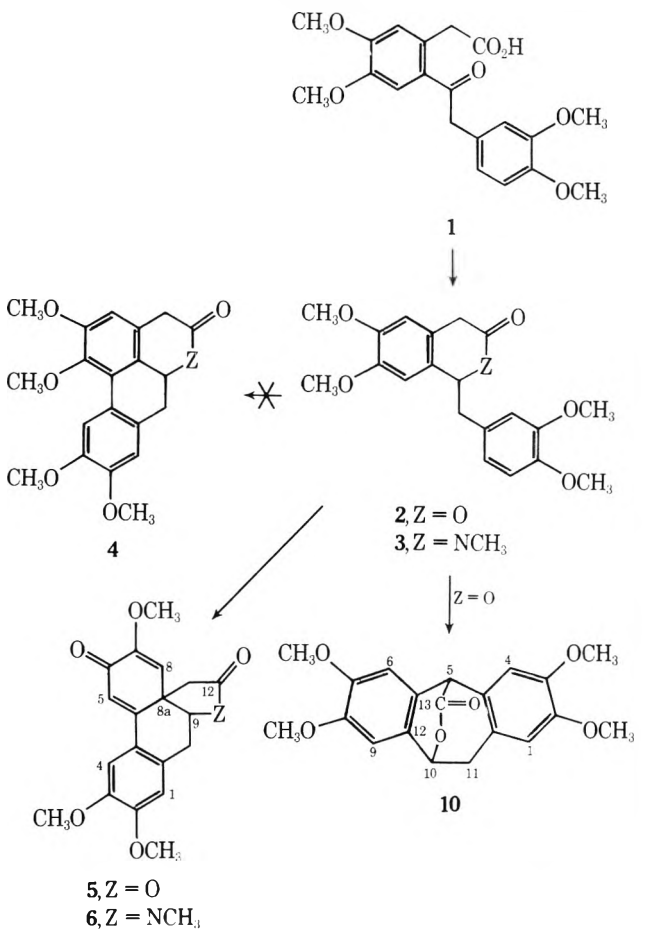
In an earlier communication the keto acid **1** was proposed as a starting compound for a series of isoquinoline alkaloids biogenetically derived from the 1-benzylisoquinolines,[5] and tetrahydropapverine and laudanosine were prepared from **1**. In this study 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3-isochromanone (**2**) and 1-(3,4-dimethoxybenzyl)-2-methyl-6,7-dimethoxy-1,4-dihydro-3(2*H*)-isoquinolone (**3**), both prepared from the keto acid **1**, were oxidized electrochemically and also with the chemical oxidant vanadium oxyfluoride. When this work was initiated we supposed that on anodic oxidation of **2** or **3** a simple biaryl coupling would occur with formation of compounds with the aporphine skeleton (**4**).[6] The actual results reported here are more complex than we originally proposed (Scheme II).

The lactone **2** was used as a model compound in these oxidations since the lactone is more easily prepared from the keto acid **1** than the lactam **3**. Anodic oxidation of the lactone **2** has afforded at least two distinct products depending in part on the solvent (and pH) used. Electrolysis of **2** in dichloromethane–trifluoroacetic acid (DCM–TFA)[1] with tetrabutylammonium tetrafluoroborate as supporting electrolyte gave 6,12-dioxo-2,3,7-trimethoxy-6,8a,9,10-tetrahydro-9,8a-epoxyethanophenanthrene (**5**) as the main product in 33% yield. The same spirodienone **5** was isolated in 59% yield from the oxidation of **2** by vanadium oxyfluoride in DCM–TFA solution.

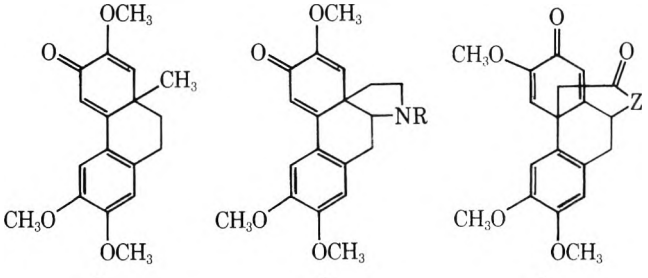
An analogous dienone **6** (6,12-dioxo-2,3,7-trimethoxy-6,8a,9,10-tetrahydro-9,8a-iminoethanophenanthrene) was obtained in approximately 40% yield from the lactam **3**, either by anodic oxidation or vanadium oxyfluoride, when the solvent system DCM–TFA was used.

The constitutions **5** and **6** are supported by elemental composition and spectral data. In both cases the infrared spectra show bands characteristic of the dienone system (1660–1650 and 1630 cm^{-1}); moreover, the positions of the acyl

Scheme II



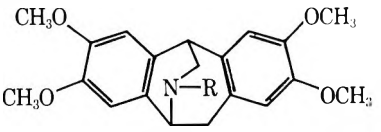
carbonyl bands are shifted to higher wavenumbers in going from **2** to **5** (1740 to 1760 cm^{-1}) or from **3** to **6** (1640 to 1690 cm^{-1}) corresponding to a change from a six- to a five-membered ring in the lactone or lactam, respectively. The NMR spectra are in agreement with the assigned structures, and the UV spectra are helpful in establishing the patterns of conjugation. Compounds **5** and **6** exhibit a similar series of absorption bands in the UV, and the spectra of both compounds correspond closely to those reported for a pair of structurally related conjugated dienones (7[3] and 8[7]). The alternative possibility that **5** or **6** possess a morphinandienone structure (**9**) can be excluded on the basis of the very different UV spectrum described for salutaridine.[8]



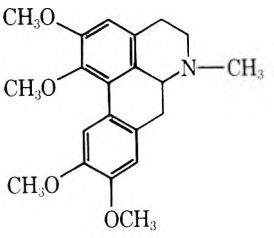
When the isochromanone derivative **2** was oxidized electrolytically in acetonitrile with quaternary ammonium salts, a different product was obtained in 20% yield which is assigned the bridged lactone structure **10**. The formulation of this product as 2,3,7,8-tetramethoxy-13-oxo-10,5-(epoxymethano)dibenzo[*a*,*d*]cycloheptadiene (**10**) rather than a biphenyl derivative (**4**, Z = O) is based on the NMR and UV spectra. In the aromatic region there are three bands at δ 6.77 (1 H), 6.71 (2 H), and 6.48 (1 H) for a total of four hydrogens. In addition to the complex pattern, from interaction of the methylene

hydrogens with the adjacent carbinol hydrogen, that would be present in either **10** or **4** there is a singlet corresponding to one hydrogen at δ 4.41 that can be attributed only to the hydrogen at position 10 in **10**. In the NMR spectrum of the starting lactone **2** there is a singlet for two hydrogens at δ 3.19, and the same spectral feature should persist in the oxidation product if the correct structure were **4** and not **10**; no such band appears in the NMR of the actual product.

When the UV spectrum of the product assigned structure **10** (λ_{max} 289 nm, log ϵ 3.90) is compared with those of *N*-acetylisopavine (**11a**, λ_{max} 287 nm, log ϵ 3.95)[9] and glaucine (**12**, λ_{max} 281 and 302 nm, log ϵ 4.15 and 4.16, respectively)[10]



11a, R = $COCH_3$
b, R = CH_3

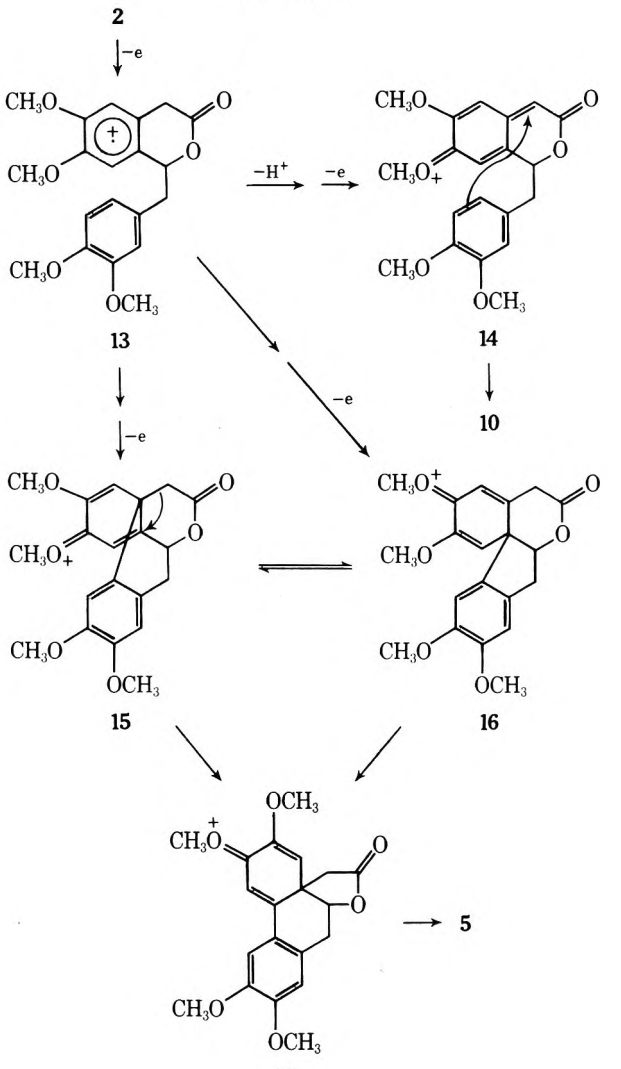


12

the choice is clearly in favor of the constitution with two isolated dimethoxybenzene rings rather than the tetramethoxybiphenyl system.

The mode of oxidative coupling represented by **10** has not been reported previously from either chemical or electrochemical oxidations of substituted bibenzyls (cf. Scheme I), and this new structural type provides a lactonic analogue of the alkaloid isopavine (**11b**). Although the lactam **3** has also been subjected to anodic oxidation in acetonitrile solution, no nitrogenous product similar to **10** has yet been isolated. We have not established the mechanisms for these reactions, but the formation of **10** from **2** can be rationalized by assuming that a cation radical **13** is generated from **2**, and in neutral or basic solution, and with activation of the adjacent carbonyl group, **13** loses a proton from the 4 position of the isochromanone ring. A second stage of oxidation of the resulting radical would afford the cation **14** which can then serve as an electrophile toward the veratryl ring, leading to **10** (Scheme III). The same intermediate **13** can be invoked to explain the formation of the spirodienone **5**. In acidic solution the loss of a proton would be repressed, and alternatively intramolecular coupling followed by a second oxidation step could occur to give either **15** or **16**, which as a long-lived cation in DCM–TFA[1] could rearrange to the same conjugated dienone **17**; subsequent hydrolysis of **17** would afford **5**.

Scheme III



Experimental Section

General. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory. IR and UV spectra were recorded respectively on Perkin-Elmer 337 and Cary 14 spectrophotometers. NMR spectra were obtained on Varian A-60 and HA-100 MHz spectrometers. Electrochemical reactions were carried out in a H-type cell with a sintered glass disk separating the anode and cathode compartments; a Princeton Applied Research Model 173 potentiostat/galvanostat equipped with a Model 176 current-to-voltage converter was the power supply. The working and auxillary electrodes were platinum, and silver wire was used as the reference electrode.

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-3-isochromanone (2). The keto acid (**1**, 1 g) in ethanol (20 ml) was treated with $NaBH_4$ (0.4 g). After 0.5 h the mixture was heated on a water bath for 10 min, diluted with water (50 ml), and cooled. Addition of 20% HCl to pH 3 and heating quickly gave a colorless solid (0.8 g): mp 174–175 °C (from EtOH); IR 1740 cm^{-1}; *m/e* (M^+) 358; NMR ($CDCl_3$) δ 6775–6.30 (m, 5, ArH), 5.58 (t, 1, *J* = 5 Hz, ArC**H**RO–), 3.78 (s, 9, OCH_3), 3.62 (s, 3, OCH_3), 3.38–2.48 (m, 4, Ar**CH**$_2$), 3.19 (s, 2 Ar**CH**$_2$CO).

Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19. Found: C, 67.04; H, 6.28.

6,12-Dioxo-2,3,7-trimethoxy-6,8a,9,10-tetrahydro-9,8a-epoxyethanophenanthrene (5). A. By Anodic Oxidation. The electrolysis vessel was filled with a 4:1 solution of DCM–TFA containing tetrabutylammonium tetrafluoroborate (4.5 g). The lactone (**2**, 0.72 g) was dissolved in the anode compartment, and a potential of 1.3 V was applied for 2.5 h. A deep purple color developed quickly around the anode. The anolyte was stirred for 15 min with Zn dust, but there was no perceptible change in color. The organic solvents were evaporated under reduced pressure, and the residual golden foam was washed with aqueous Na_2CO_3 and then with water. The solid was dissolved in $CHCl_3$–EtOH, and on cooling the spirodienone (**5**) was deposited as a pale yellow solid (0.23 g): mp 286–288 °C; IR 1760 C=O for γ-lactone), 1640, 1630 cm^{-1}; UV max (95% EtOH) 238 nm (log ϵ 4.02), 2.64 (4.12), 290 (3.92), and 357 (3.93); NMR δ 6.96 (s, β H in α, β-unsaturated ketone), 6.76 (s, 1, ArH), 6.49 (s, 1, ArH), 6.03 (s, α H in α,β-unsaturated ketone), 5.05 (t, 1, *J* = 3.5 Hz, CHO–), 3.95 (s, 6, Ar**OCH**$_3$), 3.78 (s, 3, vinyl OCH_3), 3.08 (d, 2, *J* = 3.5 Hz, Ar**CH**$_2$), 2.72 (s, 2, Ar**CH**$_2CO_2$).

Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.69; H, 5.22.

B. By Vanadium Oxyfluoride Oxidation. To a stirred solution of the lactone (**2**, 3.6 g) in DCM (100 ml)–TFA (5 ml) at 0 °C was added a slurry of VOF_3 (5.5 g) in TFA (30 ml). The reaction mixture immediately became dark purple in color. After 5 h the solution was poured into water (400 ml) containing citric acid (12 g). The organic layer was separated, washed with water, and concentrated to afford a red-brown solid. The product **5** was obtained by recrystallization from $CHCl_3$ as ivory crystals, 2.0 g, mp 286–288 °C. This product

proved to be identical with 5 from part A by superimposing the IR spectra.

6,12-Dioxo-2,3,7-trimethoxy-11-methyl-6,8a,9,10-tetrahydro-9,8a-iminoethanophenanthrene (6). A. By Anodic Oxidation. The lactam (**3**, 1.6 g) was electrochemically oxidized in DCM–TFA solution at a constant potential of 1.8 V over a period of 2.5 h. The purple anolyte was treated with Zn dust, filtered, and washed with water (2 × 150 ml), followed by aqueous $NaHCO_3$ (2 × 150 ml). The organic layer was dried (Na_2CO_3), and the solvent was evaporated to leave a brown oil that was redissolved in hot EtOAc–$CHCl_3$. From this solution the lactam spirodienone (**6**) crystallized as a pale yellow solid: 0.6 g; mp 252–254 °C; IR (Nujol) 1690 (C=O for γ-lactam), 1660, 1650 cm^{-1}; UV max (95% EtOH) 239 nm (log ε 4.04), 265 (4.10), 293 (3.92), and 356 (3.89); *m/e* (M^+) 355; NMR δ 6.86 (s, β H in α,β-unsaturated ketone), 6.65 (s, 1, ArH), 6.41 (s, 1, ArH), 5.95 (s, α H in α,β-unsaturated ketone), 3.92 (m, 1, ArCHN), 3.84 (s, 6, OCH_3), 3.67 (s, 3, vinyl OCH_3), 2.91 (s, 3, NCH_3), 2.81 (s, 2, $ArCH_2CO$), 2.78–2.43 (m, 2, $ArCH_2$).

Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.72; H, 6.15; N, 4.17.

B. By Vanadium Oxyfluoride Oxidation of 3. A solution of the lactam **3** (3.6 g) in DCM (100 ml) was cooled to 0 °C and treated with a suspension of VOF_3 (5.5 g) in TFA (30 ml). The red-purple solution was stirred for 4 h and then poured into water (400 ml) containing citric acid (12 g). The organic layer was separated and washed with water, dried (Na_2CO_3), and evaporated. The residue (3.6 g was dissolved in MeOH (40 ml)–$CHCl_3$ (15 ml), an the first crop of crystals, 1.4 g, mp 253–255 °C, was identical with the dienone **6** from anodic oxidation of the lactam **3** by infrared spectral comparison.

2,3,7,8-Tetramethoxy-13-oxo-10,5-(epoxymethano)dibenzo[*a,d*]cycloheptadiene (10). A solution of MeCN (230 ml) containing tetrabutylammonium hydrogen sulfate (10 g) was divided between the compartments of the electrolytic cell. The lactone (**2**, 1.79 g) was dissolved in the anolyte. Electrolysis at 1.3 V (vs. Ag reference electrode) for 4 h gave a red-brown solution. The anode solution was evaporated, and the residual brown oil was washed with water to afford an orange solid that was recrystallized from MeOH as colorless crystals: 0.4 g; mp 242–243 °C; IR spectrum (Nujol) 1740 cm^{-1}; UV max (95% EtOH) 285 nm inflection (log ε 3.89), 288 (3.90), 290 (3.89); NMR δ 6.77 (s, 1, ArH), 6.71 (s, 2, ArH), 6.48 (s, 1, ArH), 5.53 (dd, 1, *J* = 7.0, 1.6 Hz, ArCHO–), 4.41 (s, 1, $Ar_2CHC=O$), 3.82 and 372 (2 s, 12, OCH_3), 3.62 (dd, 1, *J* = 24, 4.6 Hz), and 3.21 (dd, 1, *J* = 20, 3 Hz); mass spectrum *m/e* (M^+) 356.

Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66; O, 26.94. Found: C, 67.64; H, 5.92; O, 26.99.

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Registry No.—**1**, 26954-85-8; **2**, 61140-40-7; **3**, 61140-41-8; **5**, 61140-42-9; **6**, 61140-43-0; **10**, 61140-44-1.

References and Notes

(1) (a) A. Ronlán, O. Hammerich, and V. D. Parker, *J. Am. Chem. Soc.*, 95, 7132 (1973); V. D. Parker and A. Ronlán, *ibid.*, **97**, 4714 (1975); (c) A. Ronlán, K. Bechgaard and V. D. Parker, *Acta Chem. Scand.*, **27**, 2375 (1973).
(2) (a) M. Sainsbury and R. F. Schinazi, *J. Chem. Soc., Chem. Commun.*, 718 (1972); M. Sainsbury and J. Wyatt, *J. Chem. Soc., Perkin Trans. 1*, 661 (1976). U. Palmquist, A. Nilsson, V. D. Parker, and A. Ronlán, *J. Am. Chem. Soc.*, **98**, 2571 (1976).
(3) J. R. Falck, L. L. Miller, and F. R. Stermitz, *J. Am. Chem. Soc.*, **96**, 2981 (1974).
(4) (a) L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Am. Chem. Soc.*, **93**, 5941 (1971); (b) *ibid.*, **95**, 2651 (1973); J. R. Falck, L. L. Miller, and F. R. Stermitz, *Tetrahedron*, **30**, 931 (1974); (d) E. Kotani and S. Tobinaga, *Tetrahedron Lett.*, 4759 (1973).
(5) I. W. Elliott, *J. Heterocycl. Chem.*, **7**, 1229 (1970); **9**, 453 (1972).
(6) The constitution **4** (Z = O) was originally proposed for product **5**: I. W. Elliott, Abstracts of Papers, 5th International Congress of Heterocyclic Chemistry, Ljubljana, Yugoslavia, 1975, p 93; H. L. Johnson, M. A. Thesis, Fisk University, Nashville, Tenn., 1972.
(7) S. M. Kupchan, A. J. Liepa, V. Kameswaren, and R. F. Bryan, *J. Am. Chem. Soc.*, **95**, 6861 (1973).
(8) D. H. R. Barton, G. W. Kirby, W. Steglich, G. M. Thomas, A. R. Battersby, T. A. Dobson, and H. Ramuz, *J. Chem. Soc.*, **2423** (1965).
(9) A. R. Battersby and D. A. Yeowell, *J. Chem. Soc.*, 1988 (1958).
(10) A. H. Jackson and J. A. Martin, *J. Chem. Soc. C*, 2061 (1966).

Baeyer–Villiger-Type Oxidation of an Isoindolo[1,2-*b*][3]benzazepine Derivative

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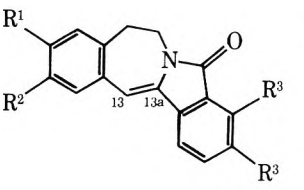
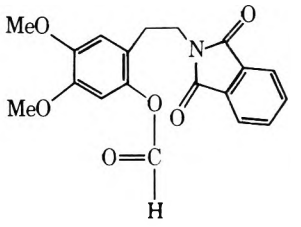
During the course of our work with isoindolo[1,2-*b*][3]-benzazepine derivatives **1a–c**, prepared by a new photo-



1a, $R^1 = R^2 = OMe$; $R^3 = H$
b, $R^1 + R^2 = OCH_2O$; $R^3 = OMe$
c, $R^1 = R^2 = R^3 = OMe$

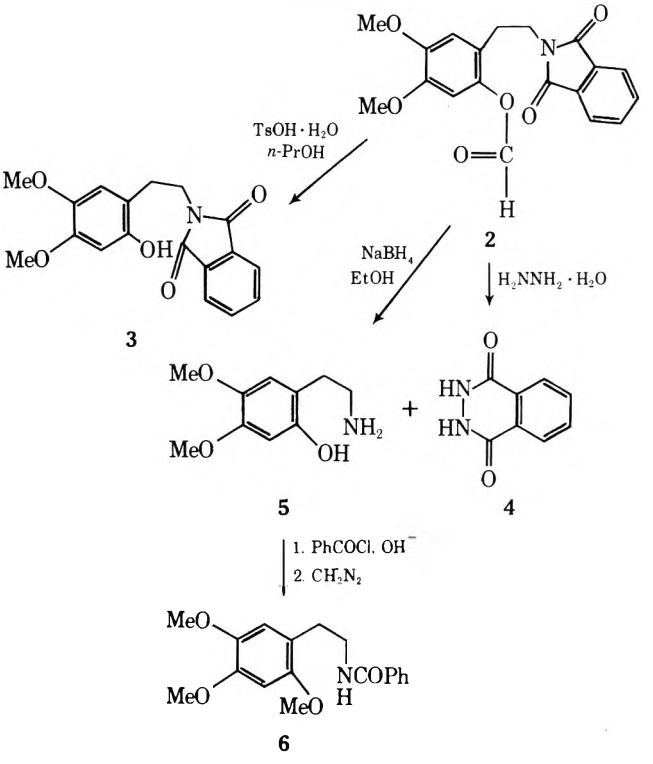


2

chemical method and correlated with rearrangement products of protoberberine and papaverrubine alkaloids,[3] we investigated routes to C-13–C-13a functionalized derivatives of **1a**. We report on the *m*-chloroperbenzoic acid (MCPBA) oxidation of **1a** to the phthalimide derivative **2**, a reaction which, in sum, is the result of oxidative double bond cleavage and Baeyer–Villiger reaction.

Attempts to prepare the epoxide of **1a** using 1 equiv of MCPBA[4] as well as basic,[5] acidic,[6] and neutral[7] conditions were unsuccessful (see Experimental Section). However, treatment of **1a** with 3 equiv of MCPBA resulted in the formation of **2** in 60% yield. The product showed the molecular formula $C_{19}H_{17}NO_6$ indicating incorporation of three oxygen atoms into compound **1a**. Its IR spectrum showed absorption at 1735 and at 1760 and 1710 cm^{-1} consistent with the presence of formyl ester and phthalimide functionality, respectively. The NMR spectrum exhibited a one-proton singlet at

Scheme I



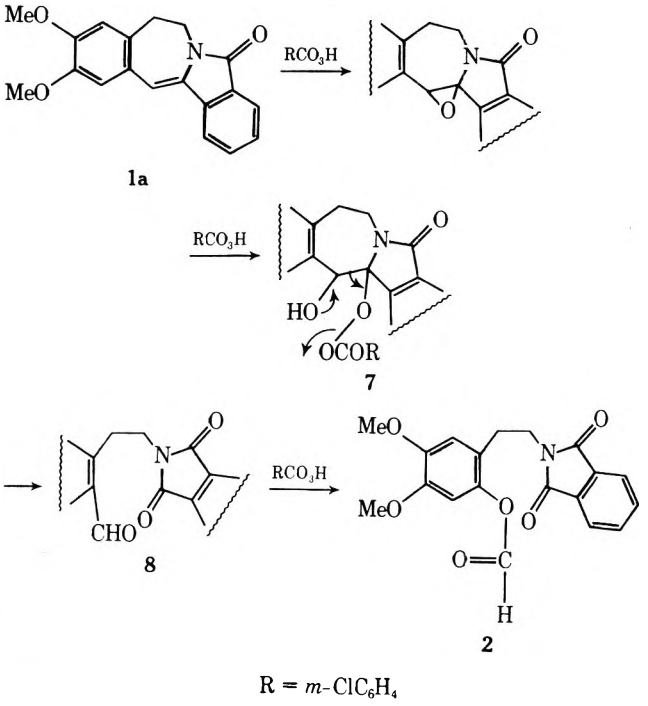
3 **2** **5** **4** **6**

τ 1.59 confirming the presence of a formyl function. The remaining absorptions were fully compatible with the assigned structure (see Experimental Section). Finally, the mass spectrum of **2** showed, besides the correct parent ion at *m/e* 355, a base peak at *m/e* 327 ($M^+ - CO$) indicating facile decarbonylation as may be expected from phenyl formate derivatives.[8]

Structure **2** was confirmed by acid-catalyzed deformylation to **3** and by conversion with NH_2NH_2 to phthalhydrazide and the amino phenol **5**. Compound **5** was obtained in better yield by sodium borohydride reduction of **2**. The structure of **5**[9] is based on spectral evidence (see Experimental Section) and on its transformation into the known **6** by successive benzoylation and methylation.

A plausible mechanism for the MCPBA-promoted rearrangement of **1a** into **2** (Scheme II) incorporates, as the salient

Scheme II



features, the fragmentation (**7** → **8**) and Baeyer–Villiger[10] steps **8** → **2**. Baeyer–Villiger oxidation products have been previously encountered in attempted epoxidations of α,β-unsaturated ketones,[5] α-amino-α,β-unsaturated ketones,[10] enol ethers,[12] and enamides.[13] The proposed mechanism for the oxidative rearrangement of **1a** by MCPBA has analogy in the work of Bagli and Immer.[12] A related rearrangement has been observed in the case of iminium salts.[14]

Experimental Section[15]

Reaction of 7,8-Dihydro-10,11-dimethoxy-5*H*-isoindolo[1,2-*b*][3]benzazepin-5-one (1a) with MCPBA. To a stirred solution of 50 mg (0.16 mmol) of compound **1a** in 20 ml of dry methylene chloride was added 90 mg (0.52 mmol) of 98% *m*-chloroperbenzoic acid and the solution was stirred at room temperature under nitrogen for 6.5 h after which time TLC (silica gel, ethyl acetate–methylene chloride, 1:1) showed the absence of the highly fluorescent spot due to starting material and the potassium iodide–starch test showed the absence of MCPBA. The solution was washed successively with 5% aqueous sodium bicarbonate, dried (Na_2SO_4), and evaporated to dryness. The resulting pale yellow oil solidified upon standing. Recrystallization from 2-propanol gave 35 mg (60%) of **2**: mp 163–164.5 °C; IR 1760, 1735 (OCHO), 1710 cm^{-1}; UV 298 nm (ϵ 2600), 285 (5200), 235 (sh, 15 200); NMR ($CDCl_3$) τ 1.59 (s, 1, OCHO), 2.1–2.3 (m, 4, ArH), 3.20 (s, 1, H-3), 3.35 (s, 1, H-6), 6.06 (t, 2, J = 7 Hz, CH_2N), 6.16 and 6.20 (2 s, 6, 2 OCH_3), 7.13 (t, 2, J = 7 Hz, CH_2CH_2N); mass spectrum *m/e* (rel intensity) 355 (M^+, 8), 327 (100), 180 (67), 167 (96), 160 (30), 149 (30).

Anal. Calcd for $C_{19}H_{17}NO_6$: C, 64.22; H, 4.82; N, 3.93. Found: C, 64.29; H, 4.74; N, 3.87.

When the above reaction was carried out with 1 equiv of MCPBA for 14 days, TLC (EtOH–PhH, 5:95) showed only starting material (major, R_f 0.49), trace amounts of two other components (R_f 0.31 and 0.22), and the absence of compound **2**. The minor components were in insufficient amounts for characterization.

When the above reaction was carried out at room temperature using hydrogen peroxide under basic,[5] acidic,[6] and neutral[7] conditions only starting material (>80%) was recovered. Under acidic conditions[6] at 100 °C for 30 min, there was obtained compound **2** (60%) which was shown to be identical by UV and NMR spectral comparison with a sample obtained above.

***N*-[β-(2-Hydroxy-4,5-dimethoxyphenethyl)]phthalimide (3).** A solution of 35 mg (0.10 mmol) of compound **2** in 5 ml of 1-propanol containing a catalytic amount of *p*-toluenesulfonic acid hydrate was refluxed for 5 h and evaporated to dryness. The residue was taken up in chloroform and the solution was extracted with $NaHCO_3$ solution. The organic layer was evaporated to dryness to give 25 mg (78%) of compound **3**. Recrystallization from ethyl acetate gave an analytical sample: mp 214–215 °C; IR 1760, 1705 cm^{-1}; NMR (acetone-d_6) τ 1.97 (br s, 4, ArH), 2.04 (s, 1, exchangeable with D_2O, OH), 3.13 (s, 1, H-6), 3.33 (s, 1, H-3), 5.93 (t, 2, J = 7 Hz, CH_2N), 6.15 and 6.27 (2 s, 6, 2 OCH_3), 6.93 (t, 2, J = 7 Hz, CH_2CH_2N); mass spectrum *m/e* (rel intensity) 327 (M^+, 39), 180 (26), 167 (100), 160 (29), 149 (29).

Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 65.67; H, 5.41; N, 4.00.

The acetate of **3** was prepared under standard conditions using acetic anhydride in pyridine. Recrystallization from ethyl acetate gave an analytical sample: mp 188.5 °C; IR 1755 (ester and imide CO), 1720 cm^{-1} (imide CO); NMR($CDCl_3$) τ 2.1–2.3 (m, 4, ArH), 3.18 (s, 1, H-3), 3.39 (s, 1, H-6), 6.15 (t, 2, J = 7 Hz, CH_2N), 6.15 and 6.18 (2 s, 6, 2 OCH_3), 7.20 (t, 2, CH_2CH_2N), 7.82 (s, 3, $OCOCH_3$); mass spectrum *m/e* (rel intensity) 369 (M^+, 10), 327 (70), 180 (34), 167 (100).

Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 65.04; H, 5.14; N, 3.74.

Reaction of Compound 2 with Hydrazine Hydrate. A solution of 50 mg (0.14 mmol) of **2** and 25 mg of hydrazine hydrate (85%) in 2 ml of 95% ethanol was refluxed for 2 h according to an established literature procedure.[16] Normal workup gave 6 mg (27%) of **phthalhydrazide (4)**, identical by melting point and mixture melting point with an authentic sample[17] and 7 mg (26%) of **2-(2-aminoethyl)-4,5-dimethoxyphenol (5)** which was shown to be identical by TLC and NMR with the $NaBH_4$ reduction product of **2** described below.

Sodium Borohydride Reduction of Compound 2. A solution of 50 mg (0.14 mmol) of **2** and 100 mg of sodium borohydride in 10 ml of dry ethanol was refluxed for 7.5 h and evaporated to dryness. The residue was partitioned in methylene chloride–water and the organic layer was separated, dried (Na_2SO_4), and evaporated to give 21 mg (76%) of **2-(2-aminoethyl)-4,5-dimethoxyphenol (5)**: mp 123–126 °C; NMR ($CDCl_3$) τ 3.45 (br s, 2, ArH), 4.96 (br s, 3, exchangeable with D_2O, OH and NH_2), 6.20 and 6.24 (2 s, 6, 2 OCH_3), 6.95 (t, 2, J = 5.5 Hz, CH_2N), 7.34 (t, 2, J = 5.5 Hz, CH_2CH_2N); mass spectrum *m/e* (rel intensity) 197 (M^+, 80), 180 (65), 168 (97), 167 (100), 163 (25), 153 (59). Compound **5** was further characterized as described below.

***N*-Benzoyl-β (2,4,5-trimethoxyphenethyl)amine (6).** Compound **5** (21 mg, 0.11 mmol) was benzoylated according to Senoh and Witkop[18] to give 21 mg (65%) of ***N*-benzoyl-β-(4,5-dimethoxy-2-hydroxyphenethylamine,** NMR ($CDCl_3$) τ 1.7–1.9 (m, 2, ArH), 2.1–2.6 (m, 4, ArH and OH, exchangeable with D_2O), 2.7–2.95 (br s, 1, exchangeable with D_2O, NH), 3.35 and 3.40 (2 s, 2, H-3 and H-6), 6.20 (s, 6, 2 OCH_3), 6.28 (t, 2, J = 7 Hz, CH_2N), 7.08 (t, 2, J = 7 Hz, CH_2CH_2N), which, without purification, was subjected to reaction with an excess of diazomethane in ether–methanol. Normal workup followed by PLC on silica gel (benzene–methanol–acetone, 8:1:1) gave a sample of **6** which was recrystallized from aqueous methanol: mp 106–107 °C (lit.[18] 106 °C); IR 3350 (NH), 1655 cm^{-1}; (CO); NMR ($CDCl_3$) τ 1.7–1.9 (m, 2, ArH), 2.1–2.6 (m, 3, ArH), 2.7–2.95 (br s, 1, exchangeable with D_2O, NH), 3.40 and 3.43 (2 s, 2, H-3 and H-6), 6.16, 6.19, and 6.22 (3 s, 9, 3 OCH_3), 6.33 (t, 2, J = 7 Hz, CH_2N), 7.12 (t, 2, J = 7 Hz, CH_2CH_2N).

Acknowledgments. We thank the National Research Council of Canada for support by way of an operating grant and a Scholarship to H.O.B. We also wish to express our gratitude to Professor R. Rodrigo, whose critical examination of the Ph.D. Thesis of H.O.B. first brought to light the correct structure **2**.

Registry No.—**1a**, 35611-54-2; **2**, 61177-89-7; **3**, 61177-90-0; **3** acetate, 61177-91-1; **4**, 1445-69-8; **5**, 61177-92-2; **6**, 61177-93-3; *N*-benzoyl-β-(4,5-dimethoxy-2-hydroxy)phenethylamine, 61177-94-4.

References and Notes

(1) National Research Council of Canada Scholar, 1970–1971.
(2) Ontario Graduate Fellowship holder, 1976–present.
(3) H. O. Bernhard and V. Snieckus, *Tetrahedron Lett.*, 4867 (1971).
(4) Other workers have noted the great resistance of an acyl enamine to undergo epoxidation with MCPBA: P. K. Martin, H. Rapoport, H. W. Smith, and J. L. Wong, *J. Org. Chem.*, **34**, 1359 (1969); J. D. White, W. E. Haefliger, and M. J. Dimsdale, *Tetrahedron*, **26**, 233 (1970).
(5) A. Padwa and R. Hartman, *J. Am. Chem. Soc.*, **88**, 1518 (1966).
(6) E. T. Roe, J. T. Scanlan, and D. Swern, *J. Am. Chem. Soc.*, **71**, 2219 (1949).
(7) Y. Ogata and Y. Sawaki, *Bull. Chem. Soc. Jpn.*, **38**, 194 (1965).
(8) F. W. McLafferty, "Interpretation of Mass Spectra", 2d ed, W. A. Benjamin, Reading, Mass., 1973, p 135.
(9) Compound **5** is a derivative of 6-hydroxydopamine which has been recently implicated in the inhibition of biogenic amine uptake in rat brain: R. Heikkila and G. Cohen, *Science*, **172**, 1257 (1971).
(10) This step is well documented for methoxylated benzaldehyde derivatives; see C. H. Hassall, *Org. React.*, **9**, 74 (1957). We thank a referee for this reference.
(11) D. L. Coffen and D. G. Korzan, *J. Org. Chem.*, **36**, 390 (1971).
(12) J. F. Bagli and H. Immer, *Can. J. Chem.*, **46**, 3115 (1968); H. Immer and J. F. Bagli, *J. Org. Chem.*, **33**, 2457 (1968).
(13) J. F. Bagli and H. Immer, *J. Org. Chem.*, **35**, 3499 (1970).
(14) H. Ishi and T. Ishikawa, *Tetrahedron Lett.*, 1203 (1976). See, however, P. Milliet, A. Picot, and X. Lusinichi, *ibid.*, 1573 (1976).
(15) Microanalysis was performed by Microtech Laboratories, Inc., Skokie, Ill.; Dr. F. Pascher, Bonn, West Germany; and Organic Microanalysis, Montreal, Canada. Melting points (uncorrected) were measured on a Fisher-Johns apparatus. IR spectra were determined on a Beckman IR-5A in CH_2Cl_2 solution. UV spectra were recorded on a Cary Model 14 spectrophotometer in EtOH solution. NMR spectra were obtained with a Varian T-60 spectrometer using Me_4Si as an internal standard. Mass spectra were determined with a Hitachi Perkin-Elmer RMU-6E spectrometer. TLC was performed using Merck GF-254 silica gel. All evaporations were conducted in vacuo under water aspirator pressures.
(16) L. I. Smith and O. H. Emerson, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 151.
(17) H. D. K. Drew and H. H. Hatt, *J. Chem. Soc.*, 19 (1937).
(18) S. Senoh and B. Witkop, *J. Am. Chem. Soc.*, **81**, 6222 (1959).

Nitrogen-15 Nuclear Magnetic Resonance. Structure of Sulfaguanidine[1]

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Contribution No. 5155 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California 91125

Received August 16, 1976

Sulfaguanidine (**1**)[2] is unusual compared to the many derivatives of sulfanilamide (4-aminobenzenesulfonamide) that contain the grouping $-SO_2HN-$ in being insoluble in aqueous alkali. Its 4-amino group is comparably basic to the other sulfanilamides (pK_B = 11.25) but its guanidino group is only very weakly basic (pK_B = 13.52).[3] The nonacidic character of the compound caused Schwenker[4] to investigate its infrared and ^1H NMR spectra and, by comparison of the infrared spectra in KBr pellets with those of several model compounds, it appeared that **1** had no infrared absorption which could be ascribed to the N–H bond of an $-SO_2NH-$ group. The ^1H NMR spectrum in dimethyl sulfoxide solution was less decisive because of serious overlap of the downfield N–H resonances with the resonances of the aromatic ring, but nonetheless, there appeared to be no evidence for the three different kinds of $-SO_2NHC(=NH)NH_2$ proton resonances predicted for the conventional guanidine structure. It was concluded therefore that the correct structure for sulfaguanidine is not **1a**, but instead the tautomer **1b**. Schwenker's work seems to have been largely, if not totally, ignored, and as recently as 1975, a ^{13}C investigation[5] formulates sulfaguanidine as **1a** in accord with the standard reference works.[6]

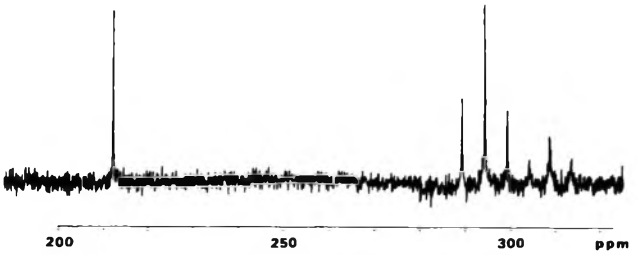
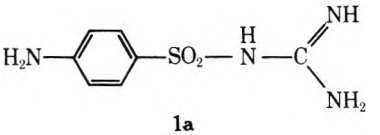
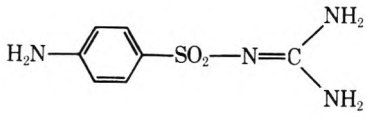


Figure 1. Natural-abundance ^{15}N NMR spectrum of sulfaguanidine in dimethyl sulfoxide with no proton decoupling. The chemical shifts are in parts per million upfield of $D^{15}NO_3/D_2O$.



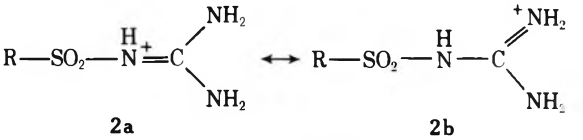
1a



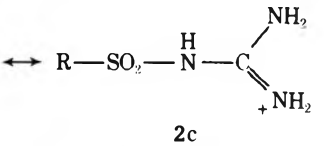
1b

Because the structure of **1** may not be the same in solution as it is in the solid, we have taken the natural-abundance ^{15}N spectrum with a Bruker WH-180 spectrometer at 18.23 MHz (8 g of **1** in 18 ml of dimethyl sulfoxide) *without* proton decoupling, using a 65° flip angle, a repetition rate of 20 s, and an accumulation time of 12 h. The upfield portion (Figure 1) of the resulting spectrum showed two triplet resonances, one over twice the intensity of the other, consistent with a structure having three $-NH_2$ groups. The lower intensity triplet (309.3 ppm upfield of $D^{15}NO_3$) arises from the 4-amino group and the larger intensity triplet (295.0 ppm) from the $=C(NH_2)_2$ amino groups of **1b**. The N–H coupling constants for the two triplets were 85 and 91 Hz, respectively. A downfield singlet resonance at 212.3 ppm upfield of $D^{15}NO_3$ corresponded to the $-SO_2N=C<$ nitrogen.

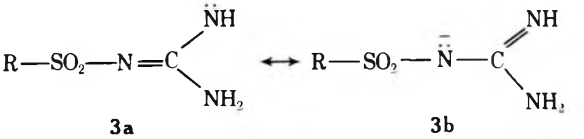
Why does structure **1b** correspond to a substance with a weakly basic and weakly acidic guanidine group? One can write the usual resonance forms for both the conjugate acid, **2**, and the conjugate base, **3**, of **1b**. To be sure, **2a** will be rendered less favorable by the close proximity of the RSO_2^- group to the positively charged nitrogen, but **2b** and **2c** should be



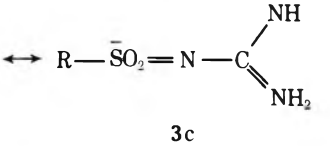
2a **2b**



2c



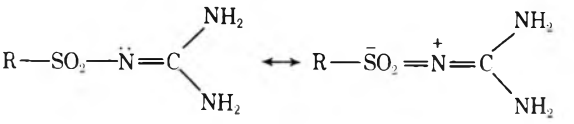
3a **3b**



3c

reasonably comparable to structures usually written for amidinium ions.[6] The resonance forms **3a–c** would appear, if anything, to enhance the acidity of **1b** by charge delocalization. However, there is a possibility that failure of **1** to dissolve in alkali, when other sulfa derivatives are soluble, could be ascribed to a very much lower water solubility of **1**. However, this cannot be the case, because, in fact, **1** is substantially more soluble in neutral water than the other sulfa derivatives.[2]

The only reasonable explanation for low basicity and acidity of **1b** vs. what might otherwise be expected seems to be through some special stabilizing characteristic of **1b** which is not shared to the same extent by **2** or **3** (or by the corresponding conjugate bases). One such possibility is delocalization of the lone pair on nitrogen to sulfur, as expressed by **4**. The fact that the two $-NH_2$ groups of the guanidine have



4

no appreciable chemical-shift difference is in accord with an important contribution of **4**.[8]

Registry No.—**1b**, 61116-95-8.

References and Notes

(1) Supported by the Public Health Service, Research Grant 11072 from the Division of General Medical Sciences, and by the National Science Foundation.
(2) R. O. Roblin, Jr., J. H. Williams, P. S. Winnek, and J. P. English, *J. Am. Chem. Soc.*, **62**, 2002 (1940).
(3) P. H. Bell and R. O. Roblin, Jr., *J. Am. Chem. Soc.*, **64**, 2905 (1942).
(4) G. Schwenker, *Arch. Pharm. (Weinheim, Ger.)*, **295**, 753 (1962).
(5) C. Chang and H. C. Floss, *J. Med. Chem.*, **18**, 505 (1975).
(6) For example, "The Merck Index", Merck and Co., 1968, p. 995.
(7) G. W. Wheland, "Resonance in Organic Chemistry", Wiley, New York, N.Y., 1955, pp 357–361.
(8) **Note Added in Proof.** A very recent x-ray study shows that structure **1b** is also correct for the solid: M. Alléaume, A. Gulko, F. H. Herbstein, M. Kapon, and R. E. Maroh, *Acta Crystallogr.*, **B32**, 669 (1976).

"Abnormal" Displacement in the Reaction of 2-(*N*-Methylpyrrolyl)methyltrimethylammonium Salts with Sodium Cyanide

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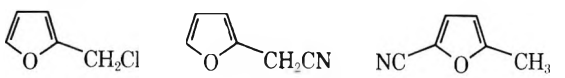
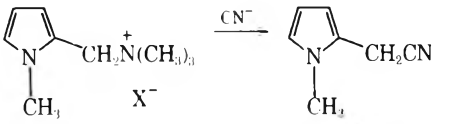
Received September 1, 1976

It has been known for some time that the reaction of 2-(chloromethyl)furan (**1**) with metal cyanides can proceed in two directions, "normal" displacement to afford **2**, as well as "abnormal" substitution to afford **3**,[1] whereas the reaction of



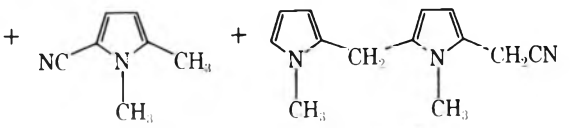
1 **2** **3**

benzyl halides with cyanide occurs with direct substitution. Although much attention has been focused on this process in the chemistry of furans,[2] no intensive studies have been performed on cyanide displacement with corresponding pyrrole derivatives. We wish to report on the reaction of 2-pyrrolylmethylammonium salts (**4**) with sodium cyanide. Under a variety of conditions, this operation produces not only *N*-methylpyrrole-2-acetonitrile (**5**), as reported earlier by others,[3]



4a, X = I
b, X = OSO_2OCH_3
c, X = OSO_2-4-$CH_3C_6H_4$
d, X = Cl
e, X = OSO_2CF_3

5



6 **7**

but also significant amounts of heretofore unrecognized, "abnormal" nitrile (**6**). Furthermore, thorough analysis of the reaction mixtures revealed minor dipyrrolylmethane byproducts, **7** and **8**, signaling the participation of an ion-pair process in the cyanolysis.

When quaternary ammonium salts[4] **4** were heated in solution with sodium (or potassium) cyanide, trimethylamine was evolved. Temperatures of 80–95 °C afforded a reasonable reaction rate, with total reaction times of 1.5–3 h. GLC analysis of a crude organic product from the reaction of **4d** (xylene/water) revealed that three volatile substances were generated. Distillation of the product mixture provided in 78% yield a fraction composed of isomeric (mol wt 120) nitriles (GLC/MS, IR) in a ratio of ca. 9:1, assigned structures **5** and **6**, respectively (vide infra). Kugelrohr distillation of the residue furnished a yellow solid (mol wt 213) nitrile (MS, IR) in 8% yield, leaving behind some dark tar.

A mixture of the isomeric nitriles was resolved by fractional distillation to provide a sample of pure **5** (mp 28–29 °C) and a fraction highly enriched in **6**; recrystallization (CH_3OH) supplied a sample of pure **6** (mp 53–55 °C). The higher boiling nitrile was recrystallized (Et_2O) to give a pure sample of **7** (mp 88–89 °C). Full spectral data, which support these structural assignments, are provided in the Experimental Section.

Five salts differing in their counterion were investigated under various circumstances. In every case, a mixture of isomeric products **5** and **6** was formed. Compound **7** was generally a minor product (1–8%), although slightly higher yields of **7** (10–15%) were obtained when the reaction was conducted in aqueous solution under comparatively dilute conditions. Results of some representative experiments are presented in Table I. The data indicate that the amount of "abnormal" substitution, ranging from 10 to 40%, is greatly dependent on the reaction medium (cf., e.g., entries 2, 7, 11, 12, 15, and 16; 4, 9, 13, and 14) and, to a lesser extent, on the counterion of substrate **4** (cf. entries 1–5; 6–10). No conditions have yet been discovered where the "abnormal" reaction mode is absent, or for that matter, reduced below a minimum level of 8–10%.[5] In contrast to the solvent dependence observed here, 2-(chloromethyl)furan (**1**) yields predominantly "abnormal" product **3** in polar, protic media and "normal" product **2** in dipolar, aprotic media.[2b]

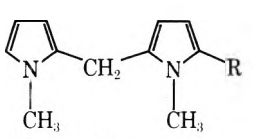
Salt **4b** decomposed in water in less than 3 h at 90 °C (but decomposed slowly at 50 °C). Subsequent addition of sodium cyanide to the decomposed material (in situ) did not generate any **5** or **6**. Of eight volatile substances detected (GLC) in the tarry product derived from the thermal degradation experiment, the three major ones were identified (MS) as **8a–c**. This suggests the possible existence of an electrophilic intermediate such as **9**, which combines in situ with *N*-methylpyrrole originating from **4**, presumably via a demethylation/retro-Mannich reaction sequence.[6] Similarly, the source of dipyrrolylmethane **7** may be explained in terms of the interception

Table I. Results for the Reaction of 4 with Sodium Cyanide[a]

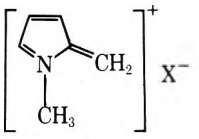
Entry	Compd	$[CN]_0$[b]	Medium	Temp, °C	% 5 and 6[c]	% 6 in 5 and 6[c]
1	**4a**	12.5	Xylene/water	Reflux[d]	57	16
2	**4b**	12.5	Xylene/water	Reflux[d]	87	12.5
3	**4c**	12.5	Xylene/water	Reflux[d]	69	11.5
4	**4d**	12.5	Xylene/water	Reflux[d]	89	10
5	**4e**	12.5	Xylene/water	Reflux[d]	68	23.5
6[e]	**4a**	6.25	Me_2SO	85, 80	91, 92	31, 34
7[e]	**4b**	6.25	Me_2SO	80	86, 75	35, 36
8	**4c**	6.25	Me_2SO	85	82	33
9[e]	**4d**	6.25	Me_2SO	80	86, 69	40, 40
10	**4e**	6.25	Me_2SO	80	80	34
11	**4b**	12.5	Water	80	60	13
12	**4b**	6.25	Water	80	49	11
13	**4d**	12.5	Water	80	68	12
14	**4d**	6.25	Water	80	52	10
15	**4b**	11.5	*f*	80	88	22
16	**4b**	satd[g]	C_2H_5OH	Reflux	70	31

[a] Reactions were carried out using a NaCN/4 ratio of 2.5 to 1. [b] Initial molar concentration of cyanide. [c] Yields of **5** and **6** were determined by GLC using an internal reference (added during workup) and detector response factors. Standard error in the analytical data is estimated to be at most ±2%. [d] Approximately 94 °C (azeotrope). [e] Results presented for two reactions (respectively). [f] Ethylene glycol/water, 8:1. [g] Reaction arranged to have initial concentration of 3.0 M, but NaCN did not appear to dissolve completely, even at boiling point of solvent.

of azafulvalenium intermediate **9** by nitrile **5**.[7] Deliberate decomposition of **4b** at 90 °C in the presence of **5** (2 molar equiv) produced **7** in 28% yield (purified).



8a, R = H
b, R = *N*-methyl-2-pyrrolylmethyl
c, R = 5-(*N*′-methyl-2-pyrrolylmethyl)-*N*-methyl-2-pyrrolylmethyl



9

The cyanolysis of **4** may entail bimolecular (S_N2/S_N2'), unimolecular (S_N1), or combination mechanisms. By-product **7**, together with the thermal decomposition results, suggests that this reaction may proceed, at least in part, by an S_N1 process involving ion pair **9**. The fact that the counterion of **4** has an influence on the product distribution supports this view.

In conclusion, we wish to point out that this work indicates a greater generality for "abnormal" displacement in substitution reactions of five-membered-ring heteroarylmethyl compounds.

Experimental Section

Boiling points are uncorrected; melting points are corrected. ^1H NMR spectra were recorded on a Perkin-Elmer R-32 instrument at 90 MHz, and chemical shifts are reported in parts per million downfield from tetramethylsilane (internal reference). IR spectra were determined on a Perkin-Elmer 521 spectrophotometer; UV spectra were obtained on a Cary 14 instrument; mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6 spectrometer at an ionizing energy of 70 eV. GLC analyses were performed on a Perkin-Elmer Model 3920 gas chromatograph, connected to a Hewlett-Packard 3352 data system, using a 6 ft × 0.125 in., 1.35% OV-17 on Chromosorb W AW/DMS column.

Quaternary Ammonium Salts. A stirred solution of newly distilled 2-dimethylaminomethyl-*N*-methylpyrrole[3a] in dry benzene, in a flask immersed in a water bath at ambient temperature, was treated with a solution of the appropriate methylating agent (1 molar equiv) in dry benzene. After addition, the reaction mixture was stirred for an additional 1 h. The solid which separated was collected by filtration, rinsed with dry ether, and dried in vacuo at room temperature for 2–3 h. The salts, characterized and assayed by ^1H NMR, were >98% pure (2% limit to the analytical procedure). All of the salts were thermally unstable and decomposed slowly even at room temperature. Attempted recrystallization of **4c** and **4d** resulted in some decomposition (and darkening). The products were stored unchanged at −20 °C for over 1 year. The triflate salt **4e** appeared to be the most thermally stable of the five salts and a satisfactory elemental analysis was obtained on this material, isolated directly from the methylation reaction (mp 103–104 °C, turned pink).

General Cyanolysis. Sodium cyanide and the appropriate reaction medium were heated at the desired temperature and the ammonium salt was added. The reaction mixture was heated until the amount of product nitriles was no longer increasing. The mixture was diluted with toluene and water, an internal reference was mixed in (α-naphthol, hexadecane, or bibenzyl), and the organic layer was separated. Control experiments with pure nitriles and the internal reference served to validate the assay procedure.

Isolation of 5, 6, and 7. The organic phase from a 0.1-mol experiment with **4d** in xylene/water was concentrated to an oil. The oil was distilled [bp 65–72 °C (1.0 Torr)] to give a 78% yield of **5** and **6**, in a ratio of ca. 9:1, respectively. Separation of **5** and **6** was generally effected by fractional distillation of mixtures largely enriched in **5** using a 1.5-ft column packed with porcelain saddles. Pure **5** had bp 60–61 °C (0.005 Torr) [mp 28–29 °C; IR (neat) ν_{max} 3105, 2950, 2250 (CN), 1490, 1410, 1312, 1290, 1196, 1086, 715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.49, 3.53 (pair of s, 5 H, 1-CH_3 and CH_2CN, respectively), 6.03 (m, 2 H), 6.55 (t, 1 H, J = ca. 2 Hz, 5-H); UV (CH_3OH) λ_{max} (ε) 217 nm (7350); MS *m/e* (rel abundance) 120 (100), 119 (93), 94 (93), 93 (46), 92 (36), 51 (32), 44 (86)] and a fraction highly enriched in **6** had bp 39–41 °C (0.005 Torr). A sample of pure **6**, obtained by recrystallization from methanol, had mp 53–55 °C [IR (KBr) ν_{max} 3120, 2915, 2200 (conjugated CN), 1460, 1430, 1393, 1380, 1315, 1173, 1028, 773 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.23 (s, 3 H, $W_{1/2}$ = ca. 1.5 Hz, 5-CH_3), 3.61 (sharp s, 3 H, 1-CH_3), 5.90 (broadened d, 1 H, J = ca. 4 Hz, 4-H), 6.66 (sharp d, 1 H, J = ca. 4 Hz, 3-H); UV (CH_3OH) λ_{max} (ε) 227 (5860), 258 nm (15 400); MS *m/e* (rel abundance) 120 (72), 119 (83), 44 (100), 40 (83)]. Compound **7** was typically isolated from the pot residue of the initial distillation by flash distillation (Kugelrohr). A sample of pure **7**, obtained by recrystallization from dry ether, had mp 88–89 °C [IR (KBr) ν_{max} 3105, 2895, 2250 (CN), 1490, 1455, 1415, 1312, 1290, 1199, 1019, 1006, 770, 760, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.44, 3.49 (pair of s, 6 H, 1-CH_3 and 1′-CH_3), 3.61 (s, 2 H), 3.83 (s, 2 H), 5.78 (m, 2 H), 6.03 (m, 2 H), 6.54 (m, 1 H); UV (CH_3OH) λ_{max} (ε) 223 nm (15 200); MS *m/e* (rel abundance) 213 (100), 212 (58), 173 (81), 132 (50), 94 (92), 93 (54)]. Satisfactory elemental analyses (C, H, N) were obtained for the new substances, **6** and **7**.

Acknowledgment. We thank the analytical section of the Chemical Research Department for services rendered to this work.

Registry No.—**4a**, 54828-80-7; **4b**, 61076-05-9; **4c**, 61076-06-0; **4d**, 61076-07-1; **4e**, 61076-08-2; **5**, 24437-41-0; **6**, 56341-36-7; **7**, 61076-09-3; 2-dimethylaminomethyl-*N*-methylpyrrole, 56139-76-5; sodium cyanide, 143-33-9.

References and Notes

(1) M. M. Runde, E. W. Scott, and J. R. Johnson, *J. Am. Chem. Soc.*, **52**, 1284 (1930); T. Reichstein, *Chem. Ber.*, **63**, 749 (1930).

(2) (a) S. Divald, M. C. Chun, and M. M. Joullié, *Tetrahedron Lett.*, 777 (1970). (b) S. Divald, Ph.D. Dissertation, University of Pennsylvania, 1969, and references cited therein. (c) T. M. Cresp and M. V. Sargent, *Aust. J. Chem.*, **27**, 905 (1974); F. Yamamoto, H. Morita, and S. Oae, *Heterocycles*, **3**, 1 (1975); S. Divald, M. C. Chun, and M. M. Joullié, *J. Org. Chem.*, **41**, 2835 (1976). 2-Furylmethyltrimethylammonium iodide was caused to react with cyanide, under special conditions, to yield a mixture of **2** (27%) and **3** (5%): E. L. Eliel and P. E. Peckham, *J. Am. Chem. Soc.*, **76**, 1209 (1950).

(3) (a) W. Herz and J. L. Rodgers, *J. Am. Chem. Soc.*, **73**, 4921 (1951); (b) W. Herz, *ibid.*, **75**, 483 (1953); W. Orth, L. Rappen, and G. Busse, U.S. Patent 3 523 952 (1970).

(4) Prepared by methylation of 2-dimethylaminomethyl-*N*-methylpyrrole[3a] using a suitable reagent.

(5) This fact raises the question as to whether other reported reactions of N-substituted pyrrolylmethylammonium salts actually produced only the "unrearranged" (or "normal") nitrile: see ref 3a; W. Herz and R. L. Settine, *J. Org. Chem.*, **24**, 201 (1959).

(6) Carbon–carbon bond cleavages of this type are not unprecedented in pyrrole chemistry; see, e.g., W. M. Quattlebaum, Jr., and A. H. Corwin, *J. Am. Chem. Soc.*, **64**, 922 (1942).

(7) Azafulvalenium ions may be implicated in various aspects of pyrrole chemistry,[8a,8c] and two examples of isolable salts from NH pyrroles have been reported.[8b,8c]

(8) (a) E.g., R. M. Silverstein, E. E. Ryskiewicz, C. Willard, and R. C. Koehler, *J. Org. Chem.*, **20**, 668 (1955); D. Klamann, P. Weyerstahl, and H. Dujmovits, *Justus Liebigs Ann. Chem.*, **714**, 76 (1968); (b) P. E. Sonnet, *J. Heterocycl. Chem.*, **7**, 1101 (1970), and references cited therein; (c) K. Hafner and K. Pfeiffer, *Tetrahedron Lett.*, 4311 (1968).

Carbon–Carbon Reductive Cleavage during Metal–Ammonia Reaction

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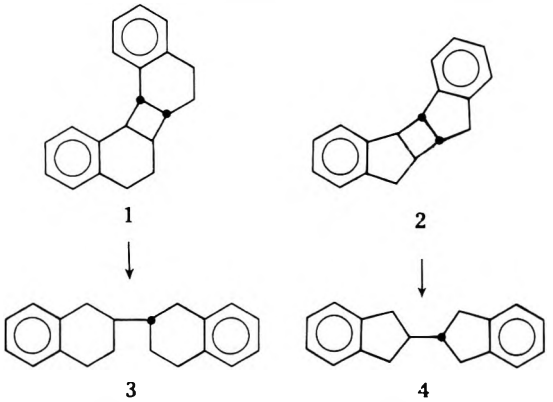
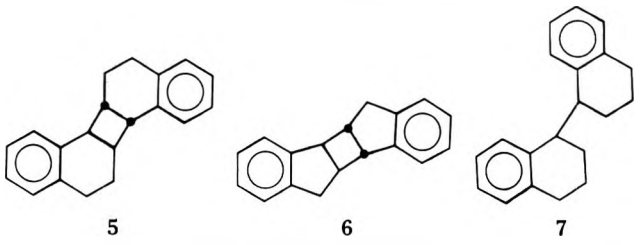
The majority of metal–ammonia reactions (Birch reductions) do not involve carbon–carbon bond cleavage.[2] We have recently observed that the photodimers **1**[3] and **2**[4] are selectively cleaved to hydrocarbons **3**[5] and **4**,[6] respectively, on



treatment with lithium or sodium in ether–ammonia. Hydrocarbons **1** and **2** react rapidly and a permanent blue color is not observed until after addition of 2 equiv of metal.

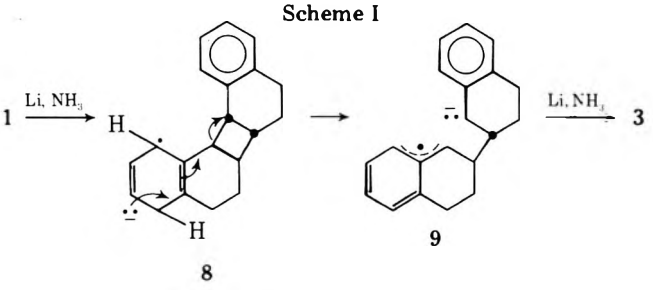
In contrast, hydrocarbons **5**[7] and **6**,[4] isomers of **1** and **2**, respectively, are totally inert to the lithium–ammonia cleavage reaction under comparable conditions. We attribute this spectacular difference in reactivity to a combination of steric strain and contiguous benzylic positions in **1** and **2**. We have recently obtained an x-ray crystallographic analysis[3] of hydrocarbon **1**, which shows that the four-membered ring is planar and has an elongated bond (1.579 Å). Interestingly, it is this bond which is cleaved during the lithium–ammonia reduction. We have also determined that **7**[8a] is inert to Na–



NH_3 reductive cleavage. Comparison of structures **1**, **5**, and **7** suggests that relief of steric strain is involved in the reductive cleavage of **1**.

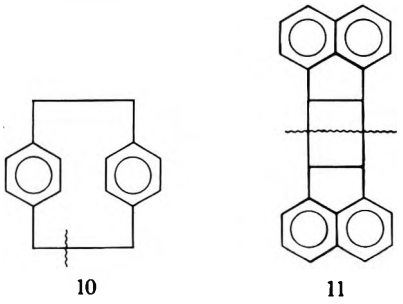
We offer the rationalization shown in Scheme I as an ex-

Scheme I



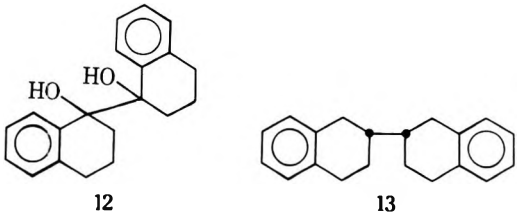
planation for the process and feel that while relief of steric strain is important, the availability of a benzylic position to stabilize the anion in structure **9** is an essential factor. Base-induced cleavage of **1** and **2** without the assistance of a reductive process is unlikely, since these hydrocarbons are stable to strong anhydrous base.[8b]

Recent reviews provide a few examples of carbon–carbon reductive cleavage.[2] The major structural features responsible for this effect are vicinal benzylic positions and/or relief of strain, as implied above. Whereas 1,2-diarylethanes appear to be stable to reduction,[9] tri- and tetraarylethanes are known to cleave.[10] If **10** is considered to be a diarylethane, it should



be stable. However, cleavage of the carbon–carbon bond as shown indicates that relief of steric strain must be essential.[11] Cleavage of the cyclobutane ring of **11** with sodium to the radical anion of acenaphthalene has been established by ESR studies.[12]

It is of interest that while hydrocarbon **7** is unaffected by the Li–NH_3 reaction, the diol **12**[13] is cleaved to tetralin in



approximately 25% yield. However, the cleavage of **12** could result from a retro-pinacol reaction,[2b] and hence this may be an unfair comparison. Nevertheless, it serves as a good reminder that predictions of reductive cleavage must be made cautiously.

While the reductive cleavage described for **1** and **2** is useful in distinguishing head-to-head and head-to-tail dimers of the type shown by **1, 2, 5,** and **6,** it is also useful as a stereospecific synthesis of β,β′-linked hydrocarbon types illustrated by **3** and **4,** which are otherwise difficult to obtain as pure hydrocarbons. Since a single product was obtained in the preparation of **3,** we assume that the positions β to the aromatic rings of **1** are not involved. This permits the stereochemical assignment shown for **3,** mp 84–85 °C,[5] and hence suggests the meso configuration for hydrocarbon **13,** mp 118–119 °C.[14]

Experimental Section

Li–NH_3 Reductive Cleavage of *cis,anti,cis*-5,6,6a,-6b,7,8,12b,12c-Octahydrodibenzo[*a,i*]biphenylene (1) to 1,1′,-2,2′,3,3′,4,4′-Octahydro-2,2′-binaphthyl (3). To a solution of 2.0 g (7.2×10^{-3} mol) of **1**,[5] mp 71–72 °C, in 10 ml of dry ether and 50 ml of ammonia was added 0.11 g (1.57×10^{-2} g-atom) of lithium in small pieces. After addition, the blue color persisted. After 1 h, the reaction was quenched with anhydrous ammonium chloride, ammonia was allowed to evaporate, and 200 ml of water was added to the residue. The reaction mixture was extracted (ether, 3 × 100 ml) and the organic layer was washed with 50-ml portions of 10% sulfuric acid, Claisen's alkali,[16] and water. The ether layer was dried ($MgSO_4$) and concentrated to give 1.95 g of a crystalline product, mp 73–78 °C. GC analysis[17a] of the product showed less than 2% of unreacted **1** and a major peak corresponding to **3**.[5b] Recrystallization of the crude product from isohexane gave 1.2 g (60% yield) of white needles, mp 84.5–85 °C. A second crop of 0.5 g of less pure material was obtained by concentration of the mother liquor. The total yield was 85%. The product had an identical ^1H NMR spectrum and undepressed melting point on mixing with a known sample of **3**.[5b]

Li–NH_3 Reductive Cleavage of 4bβ,4cα,9,9aα,9bβ,10-Hexahydrocyclobuta[1,2-*a*:4,3-*a*′]diindene (2) to 2,2′-Biindanyl (4). To a solution of 1.0 g (4.3×10^{-3} mol) of the photodimer **2**,[4] mp 110 °C, in 10 ml of ether and 50 ml of ammonia was added 0.65 g (9.3×10^{-3} g-atom) of lithium. The reaction and product isolation was carried out as described above to give 1.0 g of a solid. GC analysis[17b] of this solid showed a major peak and no unreacted **2.** Recrystallization of the product from acetone gave 0.8 g (80% yield) of white crystals of **4**: mp 165–167 °C (lit.[6a] mp 165–166.5 °C); ^1H NMR ($CDCl_3$) δ 7.10 (m, 8, ArH), 3.20–2.90 (m, 4, $ArCH_2$), 2.83–2.30 (m, 6, $ArCH_2CH$); mass spectrum (70 eV) *m/e* 234.

Hydrogenation of 1,1′,2,2′,3,3′,4,4′-Octahydro-1,1′-binaphthyl-1,1′-diol (12) to 1,1′,2,2′,3,3′,4,4′-Octahydro-1,1′-binaphthyl (7). A solution of 15 g (0.051 mol) of the pinacol **12**[13] in 500 ml of acetic acid and 1.5 g of 10% Pd/C was shaken in a Parr hydrogenation vessel under a 50-psig hydrogen atmosphere at 60–70 °C for 43 h. The reaction mixture was filtered and concentrated under reduced pressure. The crude hydrogenation product was purified by chromatography on basic alumina using isohexane. The combined hydrocarbon fractions were distilled using a Kugelrohr apparatus at 160–170 °C (0.2 mm) to give 3.5 g (0.013 mol, 26% yield) of a clear, colorless oil:[8a,17c] ^1H NMR ($CDCl_3$) δ 7.31–6.86 (m, 8, ArH), 3.72–3.20 (m, 2, ArCH), 2.65 (t, 4, $ArCH_2$), J = 4 Hz, and 2.13–1.04 (m, 8, $ArCH_2CH_2CH_2$); mass spectrum (70 eV) *m/e* 262.

Reaction of 12 with Sodium–Ammonia. A solution of 0.8 g (0.0027 mol) of **12,** mp 185–189 °C (lit.[13] mp 191 °C), in 50 ml of THF was added to a solution of 50 ml of ammonia and 0.5 g (0.22 g-atom) of sodium. After 1 h, the reaction was quenched by addition of solid ammonium chloride and the products isolated as previously described. The resulting oil was analyzed by GC[17c] and shown to contain 25% tetralin.

Acknowledgments. We thank the Contraceptive Development Branch, Center for Population Research, National Institute of Child Health and Human Development (Contract No. N01-HD-2846), for partial support. We also thank Continental Oil Co. for some financial assistance.

Registry No.—**1,** 42182-84-3; **2,** 23358-17-0; **3,** 61158-73-4; **4,** 39060-95-2; **7,** 1154-13-8; **12,** 3073-53-8; tetralin, 119-64-2; lithium, 7439-93-2; ammonia, 7664-41-7; sodium, 7440-23-5.

References and Notes

(1) (a) Research Associate, Oklahoma State University; (b) Graduate Research Assistant, Oklahoma State University; (c) Graduate Research Assistant, Oklahoma State University, and Continental Oil Co. Fellow, 1975; (d) Department of Chemistry, University of Oklahoma; (e) Department of Chemistry, Oklahoma State University.
(2) (a) R. L. Augustine, Ed., "Reduction", Marcel Dekker, New York, N.Y., 1968; (b) A. J. Birch and G. Subba Rao, *Adv. Org. Chem.*, **8,** 1–65 (1972).
(3) J. E. Burks, Jr., D. van der Helm, T. K. Dobbs, L. L. Ansell, P. H. Ruehle, and E. J. Eisenbraun, *Acta Crystallogr.*, submitted.
(4) (a) W. Metzner and D. Windisch, *Justus Liebigs Ann. Chem.*, **730,** 111 (1970); (b) J. Bowyer and Q. N. Porter, *Aust. J. Chem.*, **19,** 1455 (1966).
(5) (a) L. Reggel, H. W. Sternberg, and I. Wender, *Nature (London)*, **190,** 81 (1961); (b) E. J. Eisenbraun, R. C. Bansal, D. V. Hertzler, and W. P. Duncan, *J. Org. Chem.*, **35,** 1265 (1970).
(6) (a) W. Lüttke and J. Grussdorf, *Chem. Ber.*, **98,** 140 (1965); (b) F. Fichter and H. Stenzl, *Helv. Chim. Acta*, **22,** 425 (1939).
(7) (a) J. Dekker and T. G. Dekker, *J. S. Afr. Chem. Inst.*, **28,** 122 (1975); (b) Alternate synthesis this laboratory.
(8) (a) Unpublished work, this laboratory. We assume to have a mixture of meso and *dl* isomers. (b) Hydrocarbons **1** and **2** were separately treated with potassium *tert*-butoxide in anhydrous dimethyl sulfoxide at room temperature for 2.5 h and recovered unchanged.
(9) C. B. Wooster and J. F. Ryan, *J. Am. Chem. Soc.*, **56,** 1133 (1934).
(10) Reference 2a, p 106.
(11) J. L. Marshall and T. K. Folsom, *Tetrahedron Lett.*, 757 (1971).
(12) von F. Gerson and B. Weidmann, *Helv. Chim. Acta*, **49,** 1837 (1966).
(13) E. B. Barnett and C. A. Lawrence, *J. Chem. Soc.*, 1104 (1935).
(14) (a) W. Hückel and M. Wartini, *Justus Liebigs Ann. Chem.*, **686,** 40 (1965); (b) R. C. Bansal, Ph.D. Thesis, Oklahoma State University, 1966; (c) P. Markov, D. Lasarov, and C. Ivanov, *Justus Liebigs Ann. Chem.*, **704,** 126 (1967).
(15) ^1H NMR spectra were obtained on a XL-100 Varian instrument. GC analyses for the hydrocarbons were obtained with a Hewlett-Packard Model 5750 apparatus fitted with a hydrogen-flame detector using helium as carrier gas. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and were uncorrected.
(16) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. I, Wiley, New York, N.Y., 1967, p 153.
(17) (a) An 8 ft × 0.25 in. column of 80–100 mesh Chromosorb G coated with 7% UC W-98 at 230 °C was used; (b) ref 17a at 190 °C; (c) a 6 ft × 0.25 in. column of 80–100 mesh, AW-DMCS-treated Chromosorb G coated with 3.5% *N,N*′-bis(*p*-methoxybenzylidine)-α,α′-bitoluidine at 220 °C was used.

Reactions of Enones with the New Organocuprates, $LiCu_2(CH_3)_3$, $Li_2Cu_3(CH_3)_5$, and $Li_2Cu(CH_3)_3$

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It has been reported that a mixture of $(CH_3)Li$ and $LiCu(CH_3)_2$ provides unusually stereoselective methylation of 4-*tert*-butylcyclohexanone compared to CH_3Li alone.[1] It was suggested that a highly reactive cuprate having the stoichiometry $Li_2Cu(CH_3)_3$ or $Li_3Cu(CH_3)_4$ is formed when CH_3Li and $LiCu(CH_3)_2$ are allowed to react and that reaction of these species with the ketone would explain the observed results. We have recently obtained direct evidence for the existence of $LiCu_2(CH_3)_3$ and $Li_2Cu(CH_3)_3$ in both dimethyl ether and tetrahydrofuran and indirect evidence for the species $Li_2Cu_3(CH_3)_5$ and $Li_2Cu(CH_3)_3$ in diethyl ether by low-temperature NMR.[2] All of the cuprates appear to be single species in solution except $Li_2Cu(CH_3)_3$ which has been shown to exist as an equilibrium mixture. Since $LiCu(CH_3)_2$ has proven to be an excellent conjugate methylating agent for α,β-unsaturated carbonyl compounds, it was considered to be important to evaluate these new cuprates as conjugate methylating agents.

$$LiCu(CH_3)_2 + CH_3Li \rightleftharpoons Li_2Cu(CH_3)_3 \quad (1)$$

Six enones (I–VI) were chosen to react with $LiCu(CH_3)_2$, $LiCu_2(CH_3)_3$, and $Li_2Cu(CH_3)_3$ in THF and $LiCu(CH_3)_2$, $Li_2Cu_3(CH_3)_5$, and $Li_2Cu(CH_3)_3$ in Et_2O solvent. The results of these reactions are shown in Tables I and II. In THF solvent

Table I. Methylation of Enones with $LiCu(CH_3)_2$, $LiCu_2(CH_3)_3$, and $Li_2Cu(CH_3)_3$[a] in THF at Room Temperature

Expt	Cuprate reagent[b]	Enone[c]	Molar ratio of reagent to enone	Reaction time, h	Enone recovered, %	Product, % 1,4 methylation	Product, % 1,2 methylation
1	$LiCu(CH_3)_2$	*t*-BuCH=CHC(=O)Bu-*t* (*trans*) (I)	3:1	3	5	95[d]	0
2	$LiCu_2(CH_3)_3$	(I)	3:1	3	20	82	0
3	$Li_2Cu(CH_3)_3$	(I)	2:1	3	0	108	0
4	$LiCu(CH_3)_2$	CH_3CH=$CHCCH_3$ (II)	3:1	3	7	93[e]	0
5	$LiCu_2(CH_3)_3$	(II)	3:1	3	11	90	0
6	$Li_2Cu(CH_3)_3$	(II)	2:1	3	11	93	0
7	$LiCu(CH_3)_2$	CH_3CH=$C(CH_3)CCH_3$ (III)	3:1	3	44	56[f]	0
8	$LiCu_2(CH_3)_2$	(III)	3:1	3	95	0	0
9	$Li_2Cu(CH_3)_3$	(III)	2:1	3	48	52	0
10	$LiCu(CH_3)_2$	$(CH_3)_2C$=$CHCCH_3$ (IV)	3:1	3	49	51[g]	0
11	$LiCu_2(CH_3)_3$	(IV)	3:1	3	66	30	0
12	$Li_2Cu(CH_3)_3$	(IV)	2:1	5	30	8	59[i]
13	$LiCu(CH_3)_2$	 (V)	3:1	3	0	100[h]	0
14	$LiCu_2(CH_3)_3$	(V)	3:1	3	0	103	0
15	$Li_2Cu(CH_3)_3$	(V)	2:1	3	0	95	0
16	$LiCu(CH_3)_2$	 (VI)	3:1	5	100	0	0
17	$LiCu_2(CH_3)_3$	(VI)	3:1	5	100	0	0
18	$Li_2Cu(CH_3)_3$	(VI)	2:1	5	100	0	0

[a] $Li_2Cu(CH_3)_3$ is in equilibrium with $LiCu(CH_3)_2$ and CH_3Li. [b] Registry no.: $LiCu(CH_3)_2$, 15681-48-8; $LiCu_2(CH_3)_3$, 61303-82-0; $Li_2Cu(CH_3)_3$, 61278-42-0. [c] Registry no.: I, 20859-13-6; II, 625-33-2; III, 565-62-8; IV, 141-79-7; V, 930-68-7; VI, 78-59-1. [d] Registry no., 61267-93-4. [e] Registry no., 61267-94-5. [f] Registry no., 61267-95-6. [g] Registry no., 61267-96-7. [h] Registry no., 61267-97-8. [i] Registry no., 21981-08-8.

Table II. Methylation of Enones with $LiCu(CH_3)_2$ and $Li_2Cu(CH_3)_3$ in Et_2O at Room Temperature

Expt	Cuprate reagent	Enone	Molar ratio of reagent:enone	Reaction time, min	Enone recovered, %	Product, % 1,4 methylation	Product, % 1,2 methylation
19	$LiCu(CH_3)_2$	I	1:1	10	37	63	0
20	$LiCu(CH_3)_2$	I	3:1	10	0	100	0
21	$Li_2Cu_3(CH_3)_5$	I	1:1	10	0	105	0
22	$Li_2Cu(CH_3)_3$	I	2:3	10	0	53	47[a]
23	$LiCu(CH_3)_2$	II	3:1	10	3	97	0
24	$Li_2Cu_3(CH_3)_5$	II	1:1	10	0	108	0
25	$Li_2Cu(CH_3)_3$	II	2:1	10	0	96	3[b]
26	$LiCu(CH_3)_2$	III	3:1	10	6	94	0
27	$Li_2Cu_3(CH_3)_5$	III	1:1	10	0	95	0
28	$Li_2Cu(CH_3)_3$	III	2:1	10	0.5	14	86[c]
29	$LiCu(CH_3)_2$	IV	3:1	10	17	82	1
30	$Li_2Cu_3(CH_3)_5$	IV	1:1	10	6	96	0
31	$Li_2Cu(CH_3)_3$	IV	2:1	10	2	19	79
32	$LiCu(CH_3)_2$	V	1:1	1	9	91	0
33	$Li_2Cu_3(CH_3)_5$	V	1:1	10	0	95	0
34	$Li_2Cu(CH_3)_3$	V	2:3	1	0	100	0
35	$LiCu(CH_3)_2$	VI	3:1	10	0	100	0
36	$Li_2Cu_3(CH_3)_5$	VI	1:1	10	0	94	0
37	$Li_2Cu(CH_3)_3$	VI	2:1	10	0	3[d]	93[e]

[a] Registry no., 61267-98-9. [b] Registry no., 61267-99-0. [c] Registry no., 61268-00-6. [d] Registry no., 61268-01-7. [e] Registry no., 61268-02-8.

(Table I), $LiCu_2(CH_3)_3$ reacted with enones in the same fashion as $LiCu(CH_3)_2$ to give 100% 1,4-regioselective methylation, but at a slower rate (expt 2, 5, and 11). When the enone was substituted in the α position (enone III), $LiCu_2(CH_3)_3$ did not react under the conditions that $LiCu(CH_3)_2$ gave a 56% yield. On the other hand, $Li_2Cu(CH_3)_3$ has a reaction rate similar to that of $LiCu(CH_3)_2$ in the reactions of β-monosubstituted enones (I, II, III, and V) but gives mostly 1,2 methylation for β-disubstituted enones such as IV (expt 12). Although all three cuprate reagents gave quantitative conjugate alkylation with cyclohexenone (V), none of the three reagents reacted with isophorone (VI).

In Et_2O solvent (Table II), the reactions are much faster than in THF solvent. $Li_2Cu_3(CH_3)_5$ is more reactive than $LiCu(CH_3)_2$ and also provides 100% 1,4 regioselectivity in each case studied as does $LiCu(CH_3)_2$. $Li_2Cu(CH_3)_3$ gives 100% conjugate alkylation for cyclohexenone (V) whereas $LiCu(CH_3)_2$ under the same conditions results in some recovered reactant. However, in diethyl ether, $Li_2Cu(CH_3)_3$ is in general less regioselective than $LiCu(CH_3)_2$. Clearly in the case of $Li_2Cu(CH_3)_3$, CH_3Li is reacting in diethyl ether to form 1,2-addition product.

It appears that the relative rates of $LiCu(CH_3)_2$, $LiCu_2(CH_3)_3$, $Li_2Cu_3(CH_3)_5$, and $Li_2Cu(CH_3)_3$ reaction with enones depends on the steric requirement of the particular enone. When the enone is disubstituted (either β,β or α,β), reaction is much slower than for a monosubstituted enone. For example, $LiCu_2(CH_3)_3$ does not react with III (an α,β-disubstituted enone) in THF whereas $LiCu(CH_3)_2$ effects conjugate addition in 56% yield (expt 7 and 8). On the other hand, $LiCu_2(CH_3)_3$ and $LiCu(CH_3)_2$ react with II (β-monosubstituted enone) in THF at about the same rate (expt 4 and 5). Clearly all of the cuprates react with cyclohexenone (V) at a rapid rate compared to the other enones whereas isophorone (VI) (a β,β-disubstituted enone) does not react with any of the cuprates.

When $Li_2Cu(CH_3)_3$ was allowed to react with IV (a β,β-disubstituted enone) in THF, the reaction involving conjugate addition is apparently slowed down so much that 1,2 addition by the equilibrium concentration of CH_3Li becomes the major reaction. The same phenomenon is observed in diethyl ether (Table II). $Li_2Cu(CH_3)_3$ is affected much more than $LiCu(CH_3)_2$ by disubstitution in the enone. For example, with the least substituted enones (II and V), $Li_2Cu(CH_3)_3$ gives conjugate addition in high yield, whereas with the more sterically hindered enones (I, III, IV, and VI), substantial 1,2 addition takes place.[3,4]

In conclusion, the new organocuprates, $LiCu_2(CH_3)_3$ and $Li_2Cu(CH_3)_3$ in THF and $Li_2Cu(CH_3)_3$ and $Li_2Cu_3(CH_3)_5$ in Et_2O, react with enones in a similar manner compared to $LiCu(CH_3)_2$. Except in the cases of disubstituted enones, $Li_2Cu(CH_3)_3$ gives quantitative conjugate methylation of the enones studied at a comparable or greater rate than $LiCu(CH_3)_2$ provided that the reaction is carried out in THF. On the other hand, poor regioselectivity was observed in diethyl ether. $LiCu_2(CH_3)_3$ gave quantitative regioselectivity in THF and reacted in general more slowly than $LiCu(CH_3)_2$. Since $LiCu_2(CH_3)_3$ is insoluble in diethyl ether, studies were not carried out in this solvent. $Li_2Cu_3(CH_3)_5$ in ether gave excellent results with all of the enones and appeared to react somewhat more rapidly compared to $LiCu(CH_3)_2$.

Experimental Section

Apparatus. Reactions were performed under nitrogen at the bench using Schlenk tube techniques.[5] Other manipulations were carried out in a glove box equipped with a recirculating system using manganese oxide columns to remove oxygen and dry ice–acetone to remove solvent vapors.[6] ^1H NMR spectra were obtained at 60 MHz using a Varian A-60 NMR spectrometer.

Analytical. Active CH_3 group analysis was carried out by hydrolyzing samples with hydrochloric acid on a standard vacuum line and collecting the evolved methane with a Toepler pump.[3] Lithium was determined by flame photometry. Iodide was determined by the Volhard procedure. Copper was determined by electrolytic deposition on a Pt electrode.

Materials. Tetrahydrofuran (Fisher Certified reagent grade) was distilled under nitrogen over $NaAlH_4$ and diethyl ether (Fisher reagent) over $LiAlH_4$ prior to use. Methyllithium in THF and Et_2O was prepared by the reaction of $(CH_3)_2Hg$ with excess lithium metal. Both solutions were stored at −78 °C until ready to use. Cuprous iodide was purified by precipitating from an aqueous KI–CuI solution.[7] The precipitated solid was washed with water, ethanol, and diethyl ether and then dried at room temperature under reduced pressure.

Preparation of Reagents in THF. $LiCu_2(CH_3)_3$. Cuprous iodide (1.53 g, 8.05 mmol) was weighed into a 50-ml round-bottom flask in the drybox, then the flask fitted with a rubber septum. The flask was removed from the drybox, connected by means of a needle to a nitrogen bubbler, and 15 ml of THF added to slurry the solid. The slurry was cooled to −78 °C and 15.1 ml of a 0.802 M solution of methyllithium (12.1 mmol) in THF was added to the flask. Within 5 min all the solid had dissolved and a clear, brown solution was present. ^1H NMR at −96 °C showed the solution to contain only $LiCu_2(CH_3)_3$.[2] Analysis of the solution showed Li, Cu, CH_3, and I to be present in a ratio of 1.49:1.00:1.50:1.02.

$LiCu(CH_3)_2$. Cuprous iodide (1.26 g, 6.62 mmol) was allowed to react with 16.5 ml of 0.802 M methyllithium (13.2 mmol) in THF using the same procedure as was used to prepare $LiCu_2(CH_3)_3$ (see above). All the solid dissolved within 1 min to yield a clear, light brown solution. ^1H NMR at −96 °C showed only one signal at δ −15.7, which corresponded to $LiCu(CH_3)_2$. An analysis of the solution showed Li, Cu, CH_3, and I to be present in a ratio of 2.00:1.00:2.12:0.98.

$Li_2Cu(CH_3)_3$. Cuprous iodide (0.80 g, 4.23 mmol) was allowed to react with 19.0 ml of 0.802 M methyllithium (16.9 mmol) in THF using the above procedure for making $LiCu_2(CH_3)_3$. All the solid dissolved within 1 min to yield a clear, colorless solution. ^1H NMR at −96 °C showed the presence of $Li_2Cu(CH_3)_3$ in equilibrium with $LiCu(CH_3)_2$, and CH_3Li [four signals at δ −1.40, −1.57, −1.73, and −2.08 are observed; signals at δ −1.57 and −2.08 are due to $LiCu(CH_3)_2$ and CH_3Li, respectively, while those at δ −1.40 and −1.73 are due to $Li_2Cu(CH_3)_3$]. An analysis of the solution showed Li, Cu, CH_3, and I to be present in a ratio of 3.82:1.00:3.62:0.94.

Preparation of Reagent in Et_2O. $LiCu(CH_3)_2$. Cuprous iodide (0.53 g, 2.79 mmol) was weighed into a 50-ml round-bottom flask in the drybox, then the flask fitted with a rubber spetum. The flask was removed from the drybox and connected by means of a needle to a nitrogen bubbler, and 5 ml of Et_2O added to slurry the solid. The slurry was cooled to −78 °C and 4.4 ml of 1.27 M solution of methyllithium (5.58 mmol) in Et_2O was added to the flask. All the solid dissolved immediately and a clear, colorless solution formed. ^1H NMR at −96 °C showed only $LiCu(CH_3)_2$ to be present. An analysis of the solution showed Li, Cu, CH_3, and I to be present in a ratio of 1.97:1.00:.96:0.95.

$Li_2Cu_3(CH_3)_5$. Cuprous iodide (0.380 g, 2.0 mmol) was allowed to react with 3.5 ml of 0.95 M solution of methyllithium (3.3 mmol) in Et_2O using the same procedure as was used to prepare $LiCu(CH_3)_2$ (see above). Most of the solids dissolved immediately to give a clear, light pink solution, but a small amount of a yellow solid (methylcopper) remained. An analysis of the solution showed Li, Cu, CH_3, and I to be present in a ratio of 5.21:3.00:5.09:3.03. If all of the iodide is assumed to be present as LiI, then the organocopper species would have a Li:Cu:CH_3 ratio of 2.18:3.00:5.09. This indicates the presence of the complex $Li_2Cu_3(CH_3)_5$. This compound was indeed shown to be present by NMR studies.[2]

$Li_2Cu(CH_3)_3$. Cuprous iodide (0.57 g, 2.97 mmol) was allowed to react with 9.36 ml of 1.27 M solution of methyllithium (11.9 mmol) in Et_2O using the same procedure as was used to prepare $LiCu(CH_3)_2$ (see above). All the solid dissolved immediately and a clear, colorless solution remained. ^1H NMR at −96 °C showed $Li_2Cu(CH_3)_3$, $LiCu(CH_3)_2$, and CH_3Li to be present.[2] An Analysis of the solution a showed Li, Cu, CH_3, and I to be present in a ratio of 3.82:1.00:3.88:1.02.

General Reactions of Enones. A 10-ml Erlenmeyer flask with a Teflon-coated magnetic stirring bar was dried in an oven and allowed to cool under nitrogen flush, then sealed with a rubber septum and connected by means of a needle to a nitrogen-filled manifold equipped with a mineral oil filled bubbler. The cuprate reagent (ca. 0.1–0.5 mmol) was syringed into the flask, then the calculated amount of enone (in THF or Et_2O solvent with internal standard, n-$C_{12}H_{26}$ or n-$C_{14}H_{30}$) was added to the stirred reagent. After the designated reaction time, the reaction was quenched by H_2O slowly and dried by $MgSO_4$. A 10-ft 5% Carbowax 20M on Chromosorb W column was used to separate the 1,4 and 1,2 methylation products of enone I (120 °C), enone II (90 °C), enone III (100 °C), enone IV (100 °C), enone V (100 °C), and enone VI (100 °C). Authentic samples of 1,2-addition products were prepared by reaction of the enone with MeLi. The yield percent for each reaction with $LiCu(CH_3)_2$ was normalized by 100% yield = enone recovery % + 1,2 product % + 1,4 product %. The yield percents for other reactions were based on the $LiCu(CH_3)_2$ reaction.

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References and Notes

(1) T. L. Macdonald and W. C. Still, *J. Am. Chem. Soc.*, **97**, 5280 (1975).
(2) E. C. Ashby and J. J. Watkins, *J. Chem. Soc., Chem. Commun.*, in press.
(3) Professor Still has informed us that the reference to low-temperature 1,4 addition of cuprates to isophorone was erroneously included and should be ignored.
(4) W. C. Still and T. L. Macdonald, *Tetrahedron Lett.*, 2659 (1976).
(5) D. F. Shriver, "The Manipulation of Air-Sensitive Compounds", McGraw-Hill, New York, N.Y., 1969.
(6) E. C. Ashby and R. D. Schwartz, *J. Chem. Educ.*, **51**, 65 (1974).
(7) G. B. Kauffman and L. A. Teter, *Inorg. Synth.*, **7**, 9 (1963).

A Synthesis of 3,7-Dimethylpentadec-2-yl Acetate. The Sex Pheromone of the Pine Sawfly *Neodiprion lecontei*[1]

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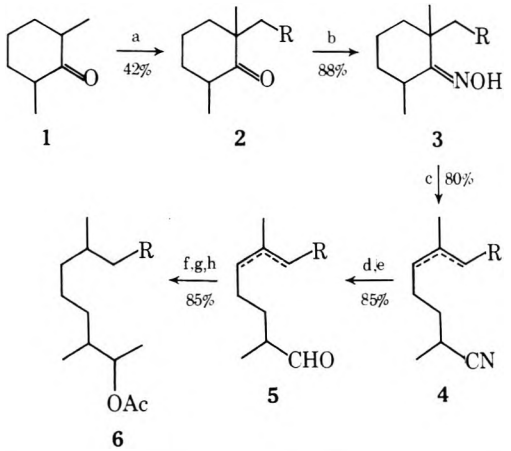
The sawflies are ubiquitous in North America and include in their host selection a great diversity of plant groups. Many species (e.g., *Diprion hercyniae* and *Neodiprion lecontei*) are among the worst defoliators of spruce and pine forests as a result of feeding by the caterpillar-like larvae on coniferous needles.[2] Recently Coppel and co-workers[3] identified 3,7-dimethylpentadec-2-yl acetate (**6**) as the major component of the sex pheromone produced by female *Neodiprion lecontei*. We report below a facile synthesis of racemic **6** starting with commercial 2,6-dimethylcyclohexanone (**1**).

In the synthesis outlined in Scheme I (R = *n*-heptyl), the

Scheme I



a, NaH, n-$C_8H_{17}I$/THF; b, NH_2OH·HCl, NaOAc/EtOH; c, p-TsCl/pyridine, reflux; d, DiBALH/hexane, −78°C; e, H_3O^+; f, MeMgI/Et_2O; g, Ac_2O; h, PtO_2/HOAc, H_2.

key step, a Beckmann fragmentation of the oxime **3**[4] to the isomeric olefinic nitriles **4**, proceeded in 90% yield when **3** reacted with 2 equiv of p-TsCl in refluxing pyridine.[5] The synthesis was completed by standard procedures as shown to give the acetate **6** in 59% overall yield from the ketone **2**.

Experimental Section

2,6-Dimethyl-2-*n*-octylcyclohexanone (2). A flame-dried 250-ml three-neck flask fitted with a magnetic stirrer, condenser, addition funnel, nitrogen inlet, and gas bubbler was charged with 4.5 g (90 mmol) of 50% NaH. After the mineral oil was removed with 2 × 20 ml of ether, 90 ml of THF (freshly distilled from Na) and 10 ml of DMF was added. The mixture was heated to reflux and 9.45 g (75 mmol) of 2,6-dimethylcyclohexanone was added dropwise. When hydrogen evolution had ceased, the mixture was cooled to 25 °C and 17.5 g (73 mmol) of 1-iodooctane added in one portion. After stirring at ambient temperature for 1 h, the mixture was refluxed for a further 1 h whereupon 50 ml of 3 M H_2SO_4 was added and refluxing continued for 3.5 h. After cooling, the organic layer was separated, diluted with 100 ml of ether, and washed with 2 × 100 ml of H_2O. After drying over $MgSO_4$, the solvent was removed in vacuo and the residue distilled via short path to give 3.34 g (36%) of the starting ketone **1** and 7.31 g (42%) of **2**: bp 117–120 °C (0.1 mm); IR (CCl_4) 1710 cm^{-1}; NMR (CCl_4) δ 0.85 (distorted t, 3 H), 0.92 (d, 3 H, J = 7 Hz), 0.92, 1.08 (2 sharp singlets, 3 H), 1.26 (br s, 14 H), 1.0–2.0 (br, 7 H); *m/e* (rel intensity) 238 (M^+, 22), 126 (100).

2,6-Dimethyl-2-*n*-octylcyclohexanone Oxime (3). A mixture of 5.96 g (25 mmol) of ketone **2**, 10.4 g (150 mmol) of NH_2OH·HCl, 20.6 g (150 mmol) of NaOAc·$3H_2O$, and 20 ml of EtOH was refluxed for 48 h. After 150 ml of H_2O was added, the product was extracted into 2 × 40 ml of ether, dried over $MgSO_4$, and concentrated in vacuo. Methanol (15 ml) was added and the mixture refrigerated overnight. The crystalline product was collected by suction filtration and washed with cold methanol to give 2.05 g of oxime, mp 79–81 °C. The filtrate and washings were combined and concentrated in vacuo and the resultant oil was distilled via short path to give 3.51 g of the oxime as a colorless, viscous oil, bp 127–130 °C (0.1 mm). The combined yield of oximes was 5.56 g (88%). The data for the crystalline oxime are presented below: IR (CCl_4) 3400 cm^{-1}; (broad); NMR (CCl_4) δ 9.9 (s, 1 H), 1.3 (br s, 14 H superimposed on d, 3 H), 1.1 (s, 3 H), 0.9 (distorted t, 3 H), 1.2–2.0 (br, 7 H); *m/e* (rel intensity) 253 (M^+, 6), 236 (5), 141 (100), 126 (22).

Beckmann Fragmentation of Oximes 3. A mixture of 4.00 g (15.8 mmol) of the crystalline oxime **3** and 6.83 g (35.6 mmol) of p-toluenesulfonyl chloride in 10 ml of pyridine was refluxed for 2.5 h. After cooling to 25 °C, 1 ml of H_2O was added and the mixture stirred for 10 min whereupon the dark brown solution was poured into 100 ml of water and extracted with 3 × 25 ml of hexane. The combined hexane layers were washed with 2 × 25 ml of H_2O, dried over $MgSO_4$, and concentrated in vacuo. The resultant brown oil was distilled via Kugelrohr to give 3.35 g (90%) of the isomeric olefinic nitriles **4**: bp 125–130 °C (bath) (0.1 mm); IR (CCl_4) 2240 cm^{-1}; NMR (CCl_4) δ 5.0 (m, 1 H), 2.4 (sextet, 1 H), 2.0 (m, 2 H), 2.0 (m, 2 H), 1.65 (br s, 3 H), 1.0–1.7 (br, 6 H), 1.3 (br s, 10 H, superimposed on d, 3 H), 0.85 (distorted t, 3 H); *m/e* (rel intensity) 235 (M^+, 51), 220 (33), 207 (80), 150 (79), 126 (64), 107 (100).

Reduction of the Nitriles 4 to the Aldehydes 5. To a magnetically stirred solution of 3.35 g (14.2 mmol) of the nitriles **4** in 20 ml of hexane was added dropwise at −78 °C 2.80 ml (2.22 g, 15.6 mmol) of DiBALH in 3 ml of hexane. After stirring at −78 °C for an additional 30 min, the cooling bath was removed and stirring continued at ambient temperature for 2 h. The mixture was carefully poured into 35 ml of rapidly stirred 3 M H_2SO_4. After 1 h, the organic layer was washed with 2 × 25 ml of H_2O, dried over $MgSO_4$, and concentrated in vacuo and the residue was distilled via Kugelrohr to give 2.86 g (85%) of the aldehydes **5** as a colorless oil: bp 110–115 °C (bath)(0.1 mm); IR (CCl_4) 2820, 2720, 1720, 1640 cm^{-1}; NMR (CCl_4) δ 9.5 (d, 1 H, J = 2 Hz), 5.0 (m, 1 H), 2.2 (sextet, 1 H), 2.0 (distorted t, 2 H), 1.6 (br s, 3 H), 1.25 (br s, 10 H), 1.05 (d, 3 H, J = 7 Hz), 0.85 (distorted t, 3 H); *m/e* (rel intensity) 238 (M^+, 27), 180 (100), 126 (45).

3,7-Dimethylpentadec-2-yl Acetate (6). To a magnetically stirred solution of MeMgI [prepared from 1.42 g (10.0 mmol) of MeI and 0.36 g (15.0 g-atoms) of Mg in 10 ml of Et_2O] was added 1.70 g (7.15 mmol) of aldehyde **5** in 3 ml of Et_2O. After stirring at 0 °C for 10 min, 2.00 g (20 mmol) of Ac_2O was added dropwise. After addition was compete, stirring was continued for 15 min, whereupon 20 ml of aqueous NH_4Cl was added. The organic layer was washed with 2 × 10 ml of H_2O, dried over $MgSO_4$, and concentrated in vacuo.

The crude product from above in 15 ml of HOAc was reduced over Pt (15 mg of PtO_2) at 15 psi H_2. The catalyst was removed by filtration and the solvent removed in vacuo. The residue was distilled via Kugelrohr to give 1.88 g (88%) of **6** as a colorless oil: bp 130–135 °C (bath)(0.1 mm); IR (CCl_4) 1740, 1240 cm^{-1}; NMR (CCl_4) δ 4.8 (m, 1 H), 1.95 (s, 3 H), 1.25 (br s, 18 H), 1.0–1.5 (m with Me doublets superimposed, 13 H), 0.9 (distorted t, 3 H); MS^3 *m/e* (rel intensity) 298 (M^+, 13), 238 (100).

The distilled product showed one major component (>95%) by VPC analysis on a 4 ft × 0.25 in. 10% SE-30/Chromosorb P column at 180 °C. The VPC retention time, IR, and mass spectra of **6** as prepared above were identical with those of an authentic sample kindly provided by Professor Coppel.[3]

Acknowledgment. We wish to thank the Research Corporation and State University of New York at Binghamton (Biomedical Research Support Grant) for generous financial support. We also thank Jon Stickles and John Soderquist for technical assistance.

Registry No.—1, 2816-57-1; 2, 61259-60-7; 3, 61288-74-2; 4 (5-ene), 61259-61-8; 4 (6-ene), 61259-62-9; 5 (5-ene), 61259-63-0; 5 (6-ene), 61259-64-1; 6, 59056-74-5; 1-iodooctane, 629-27-6; MeI, 74-88-4; Ac_2O, 108-24-7.

References and Notes

(1) Part V of a series on pheromone synthesis.
(2) H. H. Ross, "A Textbook of Entomology", 3d ed, Wiley, New York, N.Y., 1965, pp 301–304.
(3) D. M. Jewett, F. Matsumura, and H. C. Coppel, *Science*, **192**, 51 (1976).
(4) A mixture of syn and anti oximes was obtained which could be separated by TLC on silica gel using CH_2Cl_2 as eluent. Separation was not necessary since the yield in the fragmentation did not appear to be a function of oxime stereochemistry.
(5) J. A. Marshall, N. H. Anderson, and J. A. Schlicher, *J. Org. Chem.*, **35**, 858 (1970).

A Facile Internal Dilactonization of 1,6-Dialkyl-7,8-diphenyltricyclo[4.2.1.$0^{2,5}$]non-7-en-9-one-*endo*-2,5-dicarboxylic Acids

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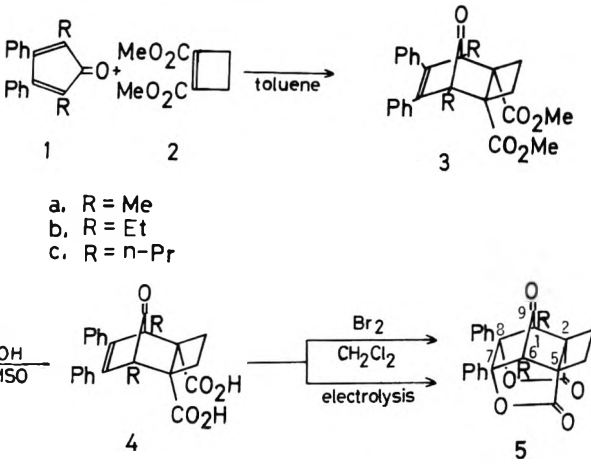
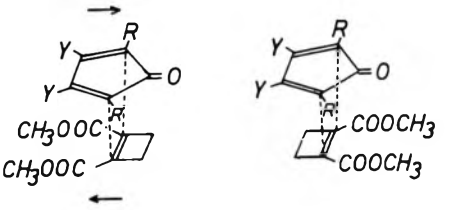
Although electrophile-induced monolactonization of 2-*endo*-norbornenecarboxylic acid and related compounds is well known,[1] examples involving formation of dilactone are rare.[2] The present note describe the facile formation of dilactones **5** from 1,6-dialkyl-7,8-diphenyltricyclo[4.2.1.$0^{2,5}$]-non-7-en-9-one-*endo*-2,5-dicarboxylic acids (**4**) which were obtained by Diels–Alder reactions[3] of 2,5-dialkyl-3,4-diphenylcyclopentadienones (**1**)[4] with dimethyl Δ^1-cyclobutene-1,2-dicarboxylate (**2**),[5] followed by hydrolysis.



Reaction of **1** with two equimolar amounts of **2** in refluxing toluene for 3–4 days produced the single products in 42–93% yields. The analytical and spectral data are compatible with the 1:1 adduct structure of **3** (see Tables I and II). The ^1H ester methyl resonances which appear at 3.61–3.62 ppm for these adducts are in accord with the *endo*-carbomethoxy assignment.[1c] The endo stereoselectivity can be predicted on the basis of the secondary orbital interactions[6] between carbomethoxy groups and diene systems, as well as the dipole–



dipole interactions[7] between reactants in the transition state of the [4 + 2] cycloaddition.

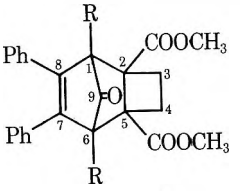
The dimethyl esters **3** were converted by alkaline hydrolysis in dimethyl sulfoxide at 80 °C to the corresponding dicarboxylic acids **4**, which, on treatment with excess bromine in dichloromethane at room temperature, afforded the corresponding dilactones **5** in 22–26% yields (from **3**). The struc-

Table I. Cycloadducts 3 Derived from Cyclopentadienones 1 and Dimethyl Δ^1-Cyclobutene-1,2-dicarboxylate (2)

Registry no.	Compd[b]	R	Time,[a] days	Yield, %	Mp, °C	IR (KBr), cm^{-1}, $\nu_{C=O}$	^1H NMR, δ ($CDCl_3$) $-COOCH_3$	^1H NMR, δ ($CDCl_3$) Others
61202-87-7	**3a**	Me	3	42	142–144.5	1726 1749 1778	3.62	1.33 (s, 6 H, CH_3) 1.66–2.87 (m, 4 H, $-CH_2CH_2-$) 6.88–7.19 (m, 10 H, aromatic)
61202-88-8	**3b**	Et	3.5	93	126–128.7	1724 1750 1773	3.61	0.77 (t, J = 8 Hz, 6 H, CH_3) 2.05 (q, J = 8 Hz, 4 H, $-CH_2-$) 1.95–2.72 (m, 4 H, $-CH_2CH_2-$) 6.89–7.20 (m, 10 H, aromatic)
61202-89-9	**3c**	*n*-Pr	4	59	120–122	1720 1742 1763	3.62	0.7–2.8 (m, 18 H, *n*-$CH_3CH_2CH_2-$) 6.63–7.37 (m, 10 H, aromatic)

[a] Time of disappearance of 1, monitored by TLC. [b] Satisfactory analytical data (±0.4% for C, H) for all compounds were submitted for review.

Table II. ^{13}C NMR Spectral Data of 3[a]



Compd	R	C-1, 6 (s)	C-2, 5[b] (s)	C-3, 4 (t)	C-7, 8 (s)	C-9 (s)	–CO– (s)	$-OCH_3$ (q)	CH_3- (q)	$-CH_2-$ (t)	$-CH_2-$ (t)
3a	Me	59.74	58.92	21.10	142.85	200.31	172.39	51.94	6.98		
3b	Et	62.98	59.09	21.75	142.60	201.12	172.72	51.78	9.74	16.07	
3c	*n*-Pr	62.82	59.09	21.75	142.52	221.25	172.72	51.78	15.10	18.34	25.49

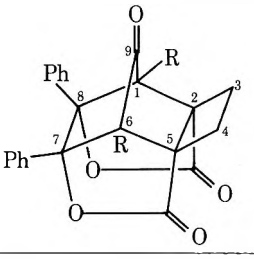
[a] In parts per million, from internal Me_4Si in $CDCl_3$. Parentheses indicate splitting patterns in the partial proton decoupling measurements. [b] Assigned from comparison with the corresponding ^{13}C chemical shifts of the adducts from 1 and dimethyl maleate and dimethyl fumarate.

Table III. 1,6-Dialkyl-7,8-diphenyltricyclo[4.2.1.$0^{2,5}$]nonan-9-one-2,8:5,7-dicarbolactone (5)

Registry no.	R[b] (no.)	Yield, % method[a] A	B	Mp, °C	M^+, *m/e*	$\nu_{C=O}$ (KBr disk), cm^{-1}	^1H NMR, δ, ppm (in $CDCl_3$)
61202-90-2	Me (5a)	26	21	284–285	400	1810 1783 1772	1.18 (s, 6 H, CH_3) 1.94–2.96 (m, 4 H, CH_2) 6.99 (s, 10 H, Ph)
61202-91-3	Et (5b)	23	58	264–266	428	1808 1781 1774	0.53 (t, 6 H, CH_3) 1.74–3.02 (m, 8 H, CH_2) 7.02 (s, 10 H, Ph)
61202-92-4	*n*-Pr (5c)	22	35	231–232	456	1803 1778 1769	0.58–1.24 (m, 14 H, *n*-Pr) 1.57–2.00 2.01–2.98 (m, 4 H, ring CH_2) 6.99 (s, 10 H, Ph)

[a] Method A: treatments of the dicarboxylic acids 4 with excess bromine in dichloromethane. Yields from the methyl ester 3. Method B: electrolysis of the dicarboxylic acids 4 under Kolbe condition. Yields from 4. [b] Satisfactory analytical data (±0.3% for C, H) for all compounds were submitted for review.

Table IV. ^{13}C NMR Spectral Data of 5[a]



R (no.)	C-2, 5 (s)	C-1, 6 (s)	C-3, 4 (t)	C-7, 8 (s)	–COO– (s)	C-9 (s)	CH_3- (q)	$-CH_2-$ (t)	$-CH_2-$ (t)
Me (5a)	55.84	59.57	16.56	92.69	170.93	207.29	6.17		
Et (5b)	54.87	63.11	16.49	92.26	170.00	207.90	7.92	15.26	
n-Pr (5c)	55.11	62.82	16.56	92.36	172.07	207.94	14.61	16.88	24.59

[a] In parts per million, from internal Me_4Si in $CDCl_3$. Parentheses indicate splitting patterns in the partial proton decoupling measurements.

tures of 5 were confirmed by NMR (^{13}C and ^1H), IR, mass spectra, and elemental analysis. The results are summarized in Tables III and IV.

Recently, benzocyclobutene derivatives have been prepared by the Diels–Alder addition of 2 to an appropriate diene and subsequent bisdecarboxylation and aromatization of the resulting six-membered ring.[8] An attempted decarbonylative bisdecarboxylation of 4 by electrolysis under Kolbe condition[1b,9] was unsuccessful, giving 5 in 21–58% yields (Table III). No benzocyclobutene derivatives or bisdecarboxylated compounds[1b,9] were detected. The other electrophilic reagents such as lead(IV) acetate and thallium(III) acetate were ineffective under usual conditions[1a,8a,10] so far in our hands.

The facile formation of dilactone may be ascribed to the close proximity of the double bond to the carboxyl groups.[2a,b]

Experimental Section

General. Melting points were taken on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared spectra were obtained on a Jasco IR-G or a Hitachi EPI-G3 spectrometer. ^{1}H NMR spectra were measured on a JEOL C-60HL or a JEOL 4H-100 instrument and are reported in parts per million downfield from internal Me_4Si. ^{13}C NMR spectra were recorded on a JEOL FX-60 pulsed Fourier transform nuclear magnetic resonance spectrometer operating at 15.030 MHz. Samples were observed in 10-mm o.d. tubes, at 0.1–0.2 M solutions in chloroform-*d* at 30 °C. Chemical shifts are given in parts per million downfield from Me_4Si as zero. Partial proton decoupling was used to distinguish between individual carbon atoms. Mass spectra were obtained on a JEOL 01SG-2 mass spectrometer.

General Procedure for Reaction of 1 with 2. A stirred solution of **1** (3 mmol) and **2** (6 mmol) in dry toluene (25 ml) was refluxed under nitrogen until **1** was consumed. The reaction was followed by NMR and TLC. Toluene was evaporated from the solution and the residue was recrystallized from ethanol to afford colorless crystals of **3** (Tables I and II).

General Procedure for Hydrolysis and Dilactonization of 3. The dimethyl ester **3** (4 mmol) in 95% aqueous dimethyl sulfoxide (150 ml) containing potassium hydroxide (0.8 g) was stirred at 80 °C in a water bath for 5 h. The reaction mixture was poured into ice–water (ca. 1.5 l.) and acidified carefully with dilute hydrochloric acid. The white solid formed was filtered and dried. Without further purification, the hydrolysis product was treated with excess bromine (6 mmol) in dichloromethane (20 ml) with stirring at room temperature for 7 h, and the solution was concentrated under reduced pressure. The residue was recrystallized from ethanol, forming colorless prisms of **5** (Tables III and IV).

General Procedure for Electrolysis of 4. The diacid **4** (1 mmol) was dissolved in a solution of 90% aqueous pyridine (50 ml) and triethylamine (0.7 ml). This stirred mixture was electrolyzed under nitrogen between two platinium plate electrodes at 100–200 V (dc) with a current of 0.5 A for 7 h, during which time the mixture was cooled with an ice water bath. The dark brown mixture was concentrated under reduced pressure. To the residue was added 10% aqueous solution of sodium hydrogen carbonate and the mixture was extracted with benzene and ether, washed with water, and then dried ($MgSO_4$). After evaporation of the solvents, the residue was crystallized from ethanol to yield **5** (Table III).

Acknowledgment. We are grateful to Professor Kazuhiro Maruyama (Faculty of Science, Kyoto University) for his interest and encouragement. This work has been supported in part by a Research Grant (to K.M. and T.U.) from the Ministry of Education, Japan.

Registry No.—**1a**, 26307-17-5; **1b**, 51932-77-5; **1c**, 61202-93-5; **2**, 1128-10-5; **4a**, 61202-94-6; **4b**, 61202-95-7; **4c**, 61202-96-8.

References and Notes

(1) (a) A. McKillop, M. E. Ford, and E. C. Taylor, *J. Org. Chem.*, **39**, 2434 (1974), and references cited therein; (b) H. H. Westberg and H. J. Dauben, Jr., *Tetrahedron Lett.*, 5123 (1968); (c) K. N. Houk and L. J. Luskus, *J. Am. Chem. Soc.*, **93**, 4606 (1971).
(2) (a) C. M. Cimarusti and J. Wolinsky, *J. Am. Chem. Soc.*, **90**, 113 (1968); (b) R. Criegee, H. Kristinsson, D. Seebach, and F. Zanker, *Chem. Ber.*, **98**, 2331 (1965); (c) the first example of this type of dilactonization was reported by K. Alder and S. Schneider, *Justus Liebigs Ann. Chem.*, **524**, 189 (1936). We are grateful to a referee for calling our attention to the latter two references.
(3) K. Matsumoto, T. Uchida, and K. Maruyama, *Chem. Lett.*, 877 (1974).
(4) C. F. H. Allen and J. A. VanAllan, *J. Am. Chem. Soc.*, **64**, 1260 (1942); **72**, 5165 (1952); *J. Org. Chem.*, **17**, 845 (1952).
(5) R. N. MacDonald and R. R. Reitz, *J. Org. Chem.*, **37**, 2418 (1972).
(6) R. Hoffmann and R. B. Woodward, *J. Am. Chem. Soc.*, **87**, 4388 (1965); K. N. Houk, *Tetrahedron Lett.*, 2621 (1970).
(7) J. A. Berson, Z. Hamlet, and W. A. Mueller, *J. Am. Chem. Soc.*, **84**, 297 (1962); P. B. Sargent, *ibid.*, **91**, 3061 (1969); K. L. Williamson, Y. L. Hsu, R. Lacko, and C. H. Youn, *ibid.*, **91**, 6129 (1969); K. L. Williamson and Y. L. Hsu, *ibid.*, **92**, 7385 (1970); P. L. Watson and R. N. Warrener, *Aust. J. Chem.*, **26**, 1725 (1973).
(8) R. P. Thummel, *J. Chem. Soc., Chem. Commun.*, 899 (1974); R. P. Thummel, *J. Am. Chem. Soc.*, **98**, 628 (1976).
(9) (a) H. Plieninger and W. Lehnert, *Chem. Ber.*, **100**, 2427 (1967); (b) P. Radlick, R. Klem, S. Spurlock, J. J. Sims, E. E. van Tamelen, and T. Whitesides, *Tetrahedron Lett.*, 5117 (1968).
(10) R. N. MacDonald and C. E. Reineke, *J. Org. Chem.*, **32**, 1878 (1967); E. E. van Tamelen and S. P. Pappas, *J. Am. Chem. Soc.*, **85**, 3297 (1963); N. B. Chapman, S. Sotheeswaran, and K. J. Toyne, *Chem. Commun.*, 214 (1965).

1-Methyl-1-dihalomethylcyclohexane Derivatives[1]

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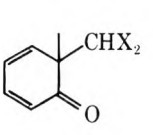
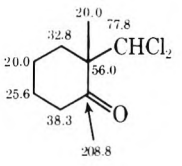
Two projects of terpene synthesis required the use of dihalomethylcyclohexadienones, derived from Reimer–Tiemann reactions of *o*- and *p*-cresols, as starting materials. In this connection it became important to determine the stereochemistry and conformation of the cyclohexanic substances encountered in early steps of the reaction sequences, a task accomplished in part by ^{13}C NMR spectroscopy.

Whereas dichloromethylcyclohexadienones are common Reimer–Tiemann products, their dibromomethyl equivalents have been reported only rarely.[2,3] Treatment of *o*-cresol with bromoform and base yielded dienone **1b**, whose hydrogenation produced ketone **4**. Dehydrobromination of the latter with potassium *tert*-butoxide led to bicycle **5**. These three reactions parallel the earlier **1a** → **2** → **3** sequence[4] and have the same



1a, X = Cl
b, X = Br



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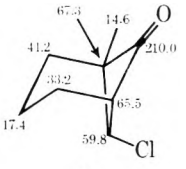

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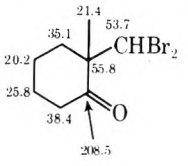

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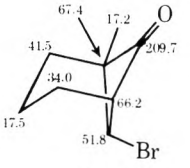
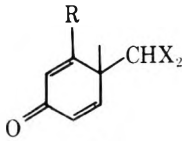


5

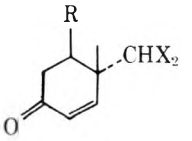
stereochemical consequence, as shown by the ^{13}C NMR analysis of bicycles **3** and **5**.

The *p*-cresol-based dienone **6b**[3] and its hydrogenation product **8b**[3] as well as the comparable dichloro compounds **6a**,[5] **7a**,[6] **8a**,[7] and the product (**9a**) of the sodium borohydride reaction of **8a** tosylhydrazone, were analyzed by ^{13}C NMR



6

a, R = H; X = Cl
b, R = H; X = Br
c, R = Me; X = Cl
d, R = Me; X = Br



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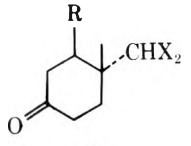

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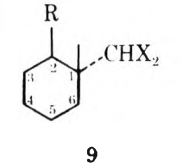

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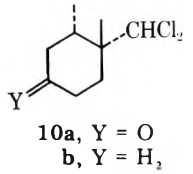


10a, Y = O
b, Y = H_2

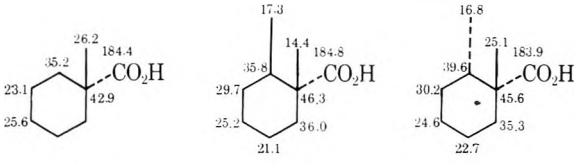
Table I. Carbon Shifts of 1-Methyl-1-dihalomethylcyclohexane Derivatives[a,e]

	6a[b]	6b	6c	7a	7c	7d	8a	8b	8c	8d	9a	9c	9d	10a	10b
C(1)	47.3	47.4	50.4	44.2	47.3	46.6	41.3	40.6	43.8	43.0	41.9	44.5	44.0	43.2	43.6
C(2)	148.3	149.1	157.5	30.2	33.6	34.4	33.3	34.0	36.3	36.7	34.4	35.8	36.5	38.2	34.8
C(3)	130.3	130.3	129.4	33.3	41.6	42.0	36.3	36.6	45.3	45.4	21.7	30.9	31.4[c]	44.8	29.7[d]
C(4)	184.3	184.5	184.7	197.4	197.5	197.5	209.9	209.7	209.5	209.4	25.7	25.6	25.7	209.8	19.5
C(5)	130.3	130.3	130.6	129.2	129.4	129.4	36.3	36.6	36.8	37.1	21.7	21.3	21.6	36.5	21.8[d]
C(6)	148.3	149.1	147.6	151.3	150.8	152.3	33.3	34.0	29.4	31.4	34.4	29.5	31.7[c]	29.9	29.3
1-Me	22.6	24.5	23.5	20.7	16.8	18.4	18.2	19.8	15.8	16.6	18.0	16.3	17.0	16.2	16.1
2-Me			18.7		14.8	15.1			15.2	15.8		15.1	15.1	14.7	13.7
X_2CH	76.4	49.9	75.8	79.8	78.7	55.4	82.0	59.0	81.5	59.4	84.0	83.5	63.2	81.6	83.6

[a] The δ values are in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] Cf. R. Hollenstein and W. von Philipsborn, *Helv. Chim. Acta*, 55, 2030 (1972). [c] Signals may be reversed. [d] Determined by deuteration of **10a**. [e] Registry no.: **6a**, 6611-78-5; **6b**, 17746-79-1; **6c**, 14789-74-3; **7a**, 38510-80-4; **7c**, 61279-00-3; **7d**, 61279-01-4; **8a**, 24463-33-0; **8b**, 49783-23-5; **8c**, 42374-15-2; **8d**, 61279-02-5; **9a**, 24147-13-5; **9c**, 61279-03-6; **9d**, 61279-04-7; **10a**, 42374-18-5; **10b**, 61279-05-8.

spectroscopy. The carbon shifts, listed in Table I, facilitated the general structure analysis of methylated derivatives of **6**–**9** (vide infra).

The reaction of dienone **6a** with lithium dimethylcuprate produced a methylated enone of unknown stereochemistry. Its hydrogenation product had to be either **8c** or **10a** and was identical with the minor component of the ca. 4:1 isomer mixture from a hydrogenation of dienone **6c**.[8] Treatment of **6b** with lithium dimethylcuprate, followed by hydrogenation, led to an enone and anone, respectively, with stereochemical features identical with the products of the two-reaction sequence emanating from **6a**, as evidenced by ^{13}C NMR analysis. In order to determine the relative configuration of the various chloro compounds, they were converted into 1,2-dimethylcyclohexanecarboxylic acids of known constitution. Sodium borohydride reduction of the tosylhydrazone of the **6a**-derived cyclohexanone gave a 1-dichloromethyl-1,2-dimethylcyclohexane whose treatment with sodio ethyleneglycolate,[7] followed by acid hydrolysis of the resultant ethylene acetal and chromic acid oxidation,[7] yielded a carboxylic acid identical with the product of the Diels–Alder reaction of butadiene and tiglic acid followed by hydrogenation.[9] In view of the structure of the latter product being **12** the methylation

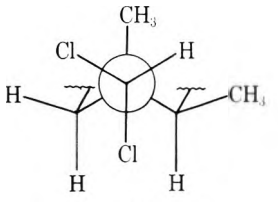


11 12 13

products of **6a** and **6b** are **7c** and **7d**, respectively, their dihydro derivatives **8c** and **8d**, respectively, and the deoxo compounds **9c** and **9d**, respectively. Furthermore, the major product of the hydrogenation of **6c** possesses structure **10a**.

Both cyclohexanone **8a** and the mixture of ketones **8c** and **10a** could be deoxygenated by successive treatments with tosylhydrazine and sodium borohydride and the resultant 1-dichloromethyl-1-methylcyclohexane (**9a**)[7] and the mixture of cyclohexanes **9c** and **10b**, respectively, were transformed into 1-methylcyclohexanecarboxylic acid (**11**) and the mixture of acids **12** and **13**, respectively, for ^{13}C NMR analysis (cf. shifts portrayed on formulas **11**, **12**, and **13**). The acid **13** was identical with the product of the reaction of 1,2-dimethylcyclohexanol with formic and sulfuric acids.[10,11]

The chemical shifts of the carbons β to the carbonyl group in the cyclohexanones **8c** and **10a** (cf. Table I) are interpreted most readily on the basis of the presence of equatorial dichloromethyl groups with preferred rotamer populations **14** and **15**, respectively. The same conformations appear to predominate in the cyclohexanes **9c** and **10b**, respectively.[12] The



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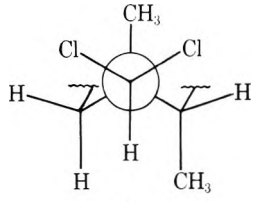

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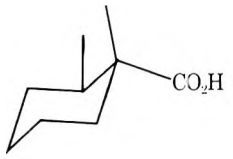

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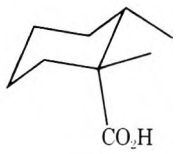

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1-methyl shifts of the acids **12** and **13** reveal these compounds to possess conformations **16** and **17**, respectively.

Experimental Section

Melting points were determined on a Reichert micro hot stage and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 167 spectrophotometer. ^1H NMR spectra of $CDCl_3$ solutions (Me_4Si, δ 0 ppm) were recorded on a Varian A-56/60A spectrometer, while the ^{13}C NMR spectra were produced on a Varian XL-100-15 spectrometer operating at 25.2 MHz in the Fourier transform mode. The δ values denoted on formulas **2**, **3**, **4**, **5**, **11**, **12**, and **13** refer to $CDCl_3$ solutions.

6-Dibromomethyl-6-methyl-2,4-cyclohexadienone (1b). A solution of 200 g of NaOH in 500 ml of H_2O was added dropwise over a 1.5-h period to a vigorously stirring solution of 233 g of freshly distilled *o*-cresol in 546 g of $CHBr_3$ and the stirring continued at room temperature for 48 h. The mixture was diluted with 2 l. of H_2O, the layers separated, and the aqueous phase extracted with 1 l. of pentane. The extract was dried (Na_2SO_4), evaporated to 250 ml, and combined with the $CHBr_3$ phase. The organic solution was washed with H_2O (500 ml), cold Claisen alkali (360 ml), H_2O (300 ml) again, and saturated brine solution. It then was dried (Na_2SO_4) and evaporated (30 °C, 1 Torr). The residue, 38.4 g, was chromatographed on alumina (activity 1) and eluted with chloroform, yielding 35 g of dienone **1b**: mp 51–52 °C; IR ($CHCl_3$) C=O 6.03 (s), C=C 6.10 μ (s); ^1H NMR δ 1.30 (s, 3, Me), 5.95 (s, 1, BrCH), 6.08 (dd, 1, J = 10, 2 Hz, H-2), 6.42 (dd, 1, J = 10, 6 Hz, H-4), 6.73 (ddd, 1, J = 10, 2, 1 Hz, H-5), 7.07 (ddd, 1, J = 10, 6, 2 Hz, H-3).

Anal. Calcd for $C_8H_8OBr_2$: C, 34.32; H, 2.88. Found: C, 34.12; H, 2.95.

2-Dibromomethyl-2-methylcyclohexanone (4). A mixture of 12.05 g of **1b** and 1.20 g of 10% Pd/C in 90 ml of EtOH was hydrogenated at room temperature and atmospheric pressure for 6 h. It then was filtered and the filtrate concentrated to 30 ml, diluted with 150 ml of H_2O, and extracted with 200 ml of hexane. The extract was dried (Na_2SO_4) and evaporated. The residue, 11 g, was chromatographed on SiO_2 and eluted with 30:1 hexane–ether, yielding 8.85 g of oily ketone **4**: IR ($CHCl_3$) C=O 5.84 μ (s); ^1H NMR δ 1.27 (s, 3, Me), 6.28 (s, 1, BrCH).

Anal. Calcd for $C_8H_{12}OBr_2$: C, 33.83; H, 4.26. Found: C, 33.98; H, 4.23.

***syn*-7-Bromo-1-methylbicyclo[3.1.1]heptan-6-one (5).** A solution of 7.0 g of **4** in 35 ml of dry Me_3COH was added dropwise over a 2-h period to a solution of 7 g of $KOCMe_3$ in 100 ml of Me_3COH under nitrogen at room temperature and the mixture then stirred at 65 °C for 3 h. It was concentrated to 75 ml, 120 ml of 5% aqueous $NaHCO_3$ solution added, and the mixture extracted with 200 ml of hexane. The extract was washed with H_2O (160 ml), dried (Na_2SO_4), and evaporated. Chromatography of the residue, 4.83 g, on SiO_2 and elution with hexane gave 220 mg of an exo–endo mixture of *tert*-butyl 1-methylbicyclo[3.1.0]hexane carboxylates. Elution with 30:1 hexane–ether gave 2.2 g of liquid ketone **5**: IR ($CHCl_3$) C=O 5.60 μ (s); ^{1}H NMR δ 1.18 (s, 3, Me), 3.38 (t, 1, J = 3 Hz, COCH), 4.20 (s, 1, BrCH).

Anal. Calcd for $C_8H_{11}OBr$: C, 47.31; H, 5.46. Found: C, 47.45; H, 5.28.

Cyclohexenones 7c and 7d. A solution of 1.44 g of dienone **6a** in 15 ml of dry ether was added over a 20-min period to a freshly prepared 0.22 M ethereal $LiCuMe_2$ solution (50 ml) kept under N_2 at −5 °C and the mixture stirred at −5 °C for 3 h. It then was poured into 120 ml of 2 N HCl and extracted with ether (250 ml). The extract was washed with H_2O and saturated $NaHCO_3$ and NaCl solutions, decolorized (activated charcoal), dried ($MgSO_4$), and evaporated. Crystallization of the residual solid (1.57 g) from hexane gave colorless crystals of ketone **7c**: mp 62–64 °C; IR (CCl_4) C=O 5.92 (s), C=C 6.04 μ (m); ^{1}H NMR δ 1.00 (d, 3, J = 7 Hz, 5-Me), 1.24 (s, 3, 4-Me), 5.91 (s, 1, ClCH), 6.08 (d, 1, J = 10 Hz, H-2), 7.08 (d, 1, J = 10 Hz, H-3).

Anal. Calcd for $C_9H_{12}OCl_2$: C, 52.20; H, 5.84; Cl, 34.24. Found; C, 52.39, H, 5.94; Cl, 34.08.

A like reaction between dienone **6b** (1.01 g in 10 ml of ether) and $LiCuMe_2$ (50 ml of 0.10 M ethereal solution) led to 0.98 g of solid whose crystallization from hexane yielded crystalline ketone **7d**: mp 72–74 °C; IR (CCl_4) C=O 5.94 (s), C=C 6.04 μ (m); ^{1}H NMR δ 1.01 (d, 3, J = 7 Hz, 5-Me), 1.32 (s, 3, 4-Me), 6.06 (s, 1, BrCH), 6.25 (d, 1, J = 10 Hz, H-2), 7.26 (d, 1, J = 10 Hz, H-3).

Anal. Calcd for $C_9H_{12}OBr_2$: C, 36.52; H, 4.09. Found: C, 36.76; H, 4.14.

Cyclohexanones 8c, 8d, and 10a. A mixture of 630 mg of **7c** and 100 mg of 10% Pd/C in 100 ml of EtOAc was hydrogenated at room temperature and atmospheric pressure and then filtered. Evaporation of the filtrate yielded 620 mg of ketone **8c**: IR (CCl_4) C=O 5.82 μ (s); ^{1}H NMR δ 0.93 (d, 3, J = 6 Hz, 3-Me), 1.22 (s, 3, 4-Me), 5.97 (s, 1, ClCH); spectral properties identical with literature values.[8]

Similar hydrogenation of **7d** (150 mg of **7d**, 20 mg of 10% Pd/C, and 20 ml of EtOAc) yielded ketone **8d** (150 mg): mp 88–91 °C; IR (CCl_4) C=O 5.78 μ (s); ^{1}H NMR δ 0.94 (d, 3, J = 7 Hz, 3-Me), 1.08 (s, 3, 4-Me), 6.14 (s, 1, BrCH); *m/e* (calcd for $C_9H_{14}OBr_2$; 295.941) 295.931.

Repetition of the hydrogenation of dienone **6c** according to the literature procedure[8] as well as in EtOAc as above gave a 41:9 mixture of **10a** and **8c**, respectively, with spectral properties identical with those recorded.[8]

Cyclohexanes 9a, 9c, 9d, and 10b. A solution of 1.00 g of **8a** and 1.86 g of *p*-toluenesulfonylhydrazine in 100 ml of MeOH was refluxed for 2 h, whereupon it was cooled, 1.90 g of $NaBH_4$ added in small portions, and the mixture refluxed for 4 h.[13] It then was poured into 150 ml of H_2O and extracted with 300 ml of pentane. The extract was washed with H_2O and saturated NaCl solution, dried (Na_2SO_4), and evaporated. A pentane solution of the residue was filtered through an alumina column and evaporated, yielding 0.77 g of liquid dichloride **9a**, identical in all respects with an authentic sample.[7]

A Caglioti reduction of **8c** under the above conditions (595 mg of **8c**, 970 mg of $TsNHNH_2$, and 65 ml of MeOH; 1.1 g of $NaBH_4$) led to 455 mg of liquid dichloride **9c** [^{1}H NMR δ 0.85 (d, 3, J = 7 Hz, 2-Me), 1.00 (s, 3, 1-Me), 5.88 (s, 1, ClCH)] which was used without purification in the acetalation–oxidation (vide infra).

A Caglioti reduction of the mixture of ketones **8c** and **10a** under the aforementioned conditions (1.64 g of **8c** and **10a**, 2.68 g of $TsNHNH_2$, and 140 ml of MeOH; 3.03 g of $NaBH_4$) yielded 1.05 g of a 41:9 mixture of dichlorides **10b** [^{1}H NMR δ 0.99 (d, 3, J = 7 Hz, 2-Me), 1.21 (s, 3, 1-Me), 5.68 (s, 1, ClCH)] and **9c**, respectively, which was utilized without further purification in the acetalation–oxidation (vide infra).

A Caglioti reduction of **8d** under the above conditions (98 mg of **8d**, 120 mg of $TsNHNH_2$, and 10 ml of MeOH; 150 mg of $NaBH_4$) yielded 52 mg of liquid dibromide **9d**: ^{1}H NMR δ 0.80 (d, 3, J = 7 Hz, 2-Me), 1.04 (s, 3, 1-Me), 6.10 (s, 1, BrCH); *m/e* (calcd for $C_9H_{16}Br_2$, 281.962) 281.944.

1,2-Dimethyl-1-cyclohexanecarboxylic Acids 12 and 13. A mixture of 455 mg of **9c** and sodium ethyleneglycolate (from 1.20 g of Na) in 20 ml of distilled ethylene glycol was refluxed under N_2 for 26 h.[7,14] It then was poured into 50 ml of H_2O and extracted with 150 ml of pentane. The extract was washed with H_2O and saturated NaCl solution, dried (Na_2SO_4), and evaporated. A mixture of the residue, 425 mg of ethylene acetal [^{1}H NMR δ 0.85 (s, 3, 1-Me), 0.85 (d, 3, J = 6 Hz, 2-Me), 3.83 (s, 4, OCH_2), 4.68 (s, 1, O_2CH)], and 15 ml of 10% H_2SO_4 in 1.5 ml of EtOH was stirred at room temperature for 12 h. Water (50 ml) was added and the mixture extracted with pentane. The extract was washed with H_2O and saturated NaCl solution, dried (Na_2SO_4), and evaporated. A solution of the residual aldehyde [^{1}H NMR δ 0.76 (d, 3, J = 7 Hz, 2-Me), 0.88 (s, 3, 1-Me), 9.37 (s, 1, CHO)] in 20 ml of acetone was treated at 0 °C with enough Jones reagent (26 g of CrO_3, 23 ml of concentrated H_2SO_4, and 100 ml of H_2O) to produce a persistent brown color, whereupon it was permitted to warm to room temperature. After the addition of H_2O the mixture was extracted with ether. The extract was washed with H_2O and saturated brine and extracted with 10% KOH solution. The aqueous extract was acidified with 2 M H_2SO_4 and reextracted into ether. The organic solution was washed with H_2O and brine, dried, and evaporated, yielding 250 mg of acid **12**, identical in all respects with an authentic sample.[9]

The same three-reaction sequence on the dichloride mixture **9c** and **10b** (582 mg of dichlorides, 1.3 g of Na, and 20 ml of ethylene glycol) led successively to a 23:27 mixture (215 mg) of acetals [^{1}H NMR δ (**10b** derived) 4.75 (s, 1, O_2CH)] (corresponding to a 100 and 25% acetalation of **9c** and **10b**, respectively), aldehydes [^{1}H NMR δ (**10b** derived) 1.07 (s, 3, 1-Me), 9.71 (s, 1, CHO)] and acids (115 mg) **12** and **13**, identical in all respects with authentic samples.[9,10]

Registry No.—**1b**, 61279-06-9; **4**, 61279-07-0; **5**, 61279-08-1; **9c** ethylene acetal, 61279-09-2; **9c** aldehyde, 13036-68-5; **10b** ethylene acetal, 61279-10-5; **10b** aldehyde, 23668-50-0; **12**, 13277-92-4; **13**, 61279-11-6; o-cresol, 95-48-7.

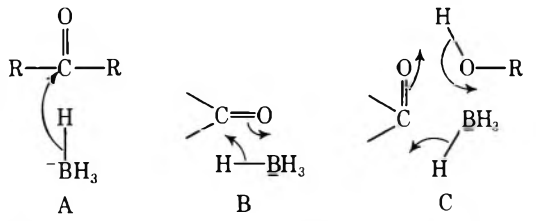
References and Notes

(1) The work in Perugia was supported by NATO Research Grant 1040.
(2) K. Auwers, *Ber.* **18**, 2665 (1885); H. Yamaguchi and T. Okamoto, *Chem. Pharm. Bull.*, **23**, 2907 (1975), and references cited therein.
(3) E. Raviña, J. M. Montañés, M. T. Cobreros, and F. Tato, *Chim. Ther.*, **8**, 290 (1973).
(4) E. Wenkert, P. Bakuzis, R. J. Baumgarten, D. Doddrell, P. W. Jeffs, C. L. Leicht; R. A. Mueller, and A. Yoshikoshi, *J. Am. Chem. Soc.*, **92**, 1617 (1970).
(5) E. Wenkert, F. Haviv, and A. Zeitlin, *J. Am. Chem. Soc.*, **91**, 2299 (1969).
(6) Produced by partial hydrogenation of **6a**.
(7) E. Wenkert, P. Bakuzis, and F. Haviv, *J. Org. Chem.*, **35**, 2092 (1970).
(8) E. Raviña, J. M. Montañés, and M. T. Cobreros, *An. Quim.*, **69**, 657 (1973).
(9) G. Stork and I. J. Borowitz, *J. Am. Chem. Soc.*, **82**, 4307 (1960).
(10) H. O. House and W. F. Gilmore, *J. Am. Chem. Soc.*, **83**, 3980 (1961).
(11) The present study corrects the previous misassignment of the stereochemistry of the products of hydrogenation of dienone **6c**.[8]
(12) The same argument applies to the bromo compounds **8d** and **9d** whose conformational preferences are equivalent to **14**.
(13) L. Caglioti, *Tetrahedron*, **22**, 487 (1966).
(14) P. J. Beeby and S. Sternhell, *Aust. J. Chem.*, **23**, 1005 (1970); cf. also R. Riemschneider, I. Ahrlé, W. Cohnen, and E. Heilmann, *Chem. Ber.*, **92**, 900 (1959).

The Kinetic Role of Hydroxylic Solvent in the Reduction of Ketones by Sodium Borohydride. New Proposals for Mechanism, Transition State Geometry, and a Comment on the Origin of Stereoselectivity

Summary: The kinetic order with respect to 2-propanol in the reduction of cyclohexanone by sodium borohydride is found to be 1.5, and an acyclic mechanism is proposed; in consequence of this mechanism a purely steric rationalization of stereoselectivity is suggested, in which the axial hydrogen at C-4 plays a crucial role.

Sir: In a recent communication,[1] we have shown that the four-center transition state mechanism (B) is of no significance in the nonphotochemical borohydride reduction of ketones in 2-propanol. In order to make distinction between the two other most probable mechanisms[2]—the six-membered cyclic (C) and the linear acyclic (A)—knowledge of the kinetic



A B C

role of hydroxylic solvent was clearly of crucial importance. Although it has been known since 1961 that hydroxylic solvent is required in these reductions,[3] such a kinetic study has not yet been reported. No measurable reduction of cyclohexanone occurs in pure, dry diglyme,[3,4] and, therefore, we have measured the pseudo-second-order rate constants of reduction[5] as a function of 2-propanol concentration in the range 0.2 M and higher. The results, shown graphically in Figure 1, clearly show the surprising result that, in this concentration range,[6] the order with respect to 2-propanol is neither first nor second, but ½. Thus the overall process for sodium borohydride reduction of cyclohexanone in 2-propanol is rate = k[ketone][BH_4^-][Pr-i-OH]$^{3/2}$ with an overall kinetic order of 7/2 and a rate constant of $k = 9.7 \times 10^{-4}$ l.$^{5/2}$ mol$^{-5/2}$ s^{-1} at 25 °C.

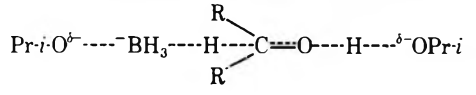
This order with respect to solvent is clearly inconsistent with the six-center mechanism (C) incorporating one molecule of solvent, and places severe constraints on other possible mechanisms. We wish to put forward what appears to be the simplest interpretation of this phenomenon, the consequences of which, in combination with other recent data, leads to a new and extremely simple explanation of the stereoselectivity of cyclohexanone reductions.

The half order is suggestive of pre-dissociation,

$$\text{Pr-}i\text{-OH} + \text{S (or S}^-) \overset{K}{\rightleftharpoons} \text{Pr-}i\text{-O}^- + {}^+\text{SH (or SH)} \quad (1)$$

where S could represent solvent or one of several species that could be present in the complex reaction mixture arising from reduction with, or alcoholysis of, sodium borohydride.[7] If the rate-determining reduction step is an acyclic push-pull mechanism as shown in Scheme I

Scheme I. Proposed Transition State for Borohydride Reduction of Ketones



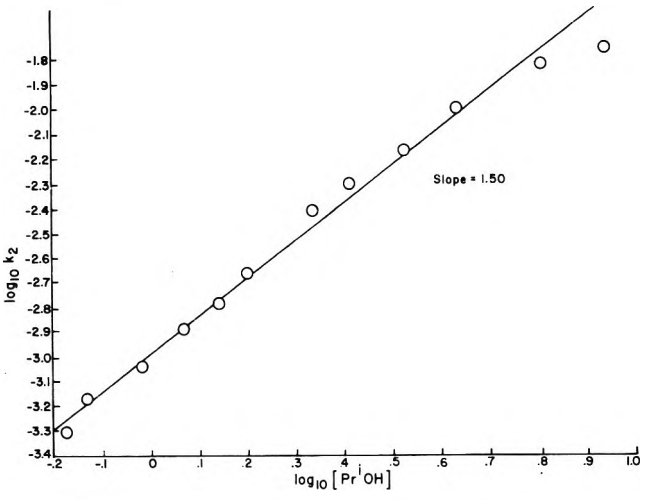


Figure 1. Reduction of cyclohexanone with sodium borohydride. Logarithm of the pseudo-second-order rate constant as a function of the logarithm of 2-propanol concentration.

involving isopropoxide and 2-propanol,[8] the rate expression must be that shown in eq 2.

$$\text{rate} = k[\text{ketone}][BH_4^-][\text{Pr-}i\text{-OH}][\text{Pr-}i\text{-O}^-] \quad (2)$$

If the isopropoxide is derived by the equilibrium of eq 1, and if [Pr-i-O$^-$] = [SH], it follows that

$$[\text{Pr-}i\text{-O}^-] = K^{1/2}[\text{Pr-}i\text{-OH}]^{1/2} \quad (3)$$

where [S] is disregarded as constant. Substituting (3) into (2) one obtains

$$\text{rate} = kK^{1/2}[\text{ketone}][BH_4^-][\text{Pr-}i\text{-OH}]^{3/2} \quad (4)$$

which is of the form experimentally observed.[13] Although a number of objections may be raised against this simple treatment, the mechanism is consistent with experimental observations, including the recent demonstration[1] that the free alcohol is the product and the alkoxy group attached to boron is derived from solvent, and, at present, there do not seem to be grounds for the proposal of a more involved kinetic scheme. It is of considerable interest that the mechanism proposed is, with the exception of the solvent participation, the linear mechanism (A) suggested by Brown and co-workers in the original mechanistic work on borohydride reductions,[15] and, in addition, this group has not only proposed a similar mechanism involving one 2-propanol molecule,[16] but has also concluded, from a solvent study, that one requirement for the reaction is the ability of the solvent to ionize.[3]

It is noteworthy that the presently proposed mechanism assigns no role to the metal cation. This is not an oversight. Although studies have indicated that, in some related reductions, the cation does play an important role,[3,17,18] there is, as far as we are aware, no evidence for a role for Na^+ in *$NaBH_4$ reductions in 2-propanol.* Indeed there is evidence to the contrary: Brown and co-workers have demonstrated a negligible rate increase in such reductions upon addition of NaI,[3] in contrast, for example, to the results of Li^+ addition, and Pierre and Handel have demonstrated the ineffectiveness of crown ethers in preventing $NaBH_4$ reductions in methanol.[17]

Finally, we note that the idea of the long acyclic transition state apparently generates a new rationalization of stereo-

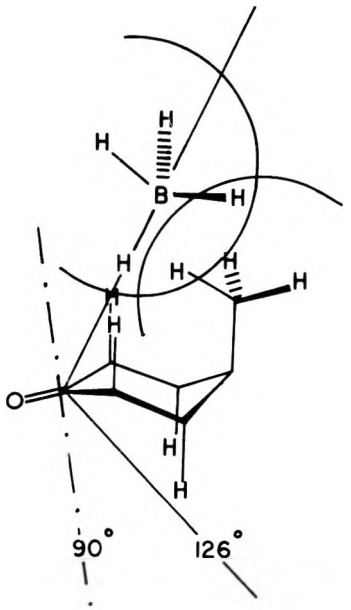


Figure 2. Attack on cyclohexanone at 126°, illustrating the effect of an axial group at C-4.

selectivity in these cyclohexanone reductions. If this attack occurs at 126° to the carbonyl group,[19] rather than at 90°, it is evident from molecular models that steric interactions with the axial hydrogen or other group at C-4 may become severe. We attempt to illustrate this point in Figure 2; what is not evident from this diagram is that the groups attached to C-4 are the only ones in the same plane as the carbonyl group. Molecular models indicate that in fact an attacking group at 126° approaches as closely to the axial group at C-4 as it does to the other axial groups, all of which are already known to markedly affect stereoselectivity. We propose that the intrinsic preference for "axial" attack may simply be the balance between the interference of two (axial 3, 5) vs. three (axial 2, 6, *and 4*) hydrogens, and that this stereoselection is modified in a predictable manner[20] by larger groups at these crucial positions. An axial methyl group at C-4 does in fact have a pronounced effect,[20] which is not accounted for by other rationalizations.

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

References and Notes

(1) D. C. Wigfield and F. W. Gowland, *Tetrahedron Lett.*, 3373 (1976).
(2) For more detailed discussion of these mechanisms, see ref 1.
(3) H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **83**, 4372 (1961).
(4) F. W. Gowland, B.S. report, Carleton University, 1974.
(5) The details of the kinetic procedure have previously been published: D. C. Wigfield and D. J. Phelps, *J. Chem. Soc., Perkin Trans. 2*, 680 (1972); D. C. Wigfield and D. J. Phelps, *Can. J. Chem.*, **50**, 388 (1972).
(6) The original range considered was 0.2 M to 2.0 M, above which concentration, flattening of the plot may be expected. As it turns out such flattening in this reaction is not apparent until the solvent concentration reaches ~6.5 M. We wish to acknowledge some most helpful and informative discussions with Professor C. H. Langford on the question of appropriate solvent concentrations.
(7) N. P. Nies and G. W. Campbell in "Boron, Metallo-Boron Compounds and Boranes", R. M. Adams, Ed., Interscience Publishers, New York, N.Y., 1964, pp 53–109.
(8) It is interesting that a somewhat similar step involving hydroxide ion and water has been proposed in the mechanism of homogeneous hydrogenation of ketones by rhodium catalysts.[9] We are grateful to Professor B. R. James for bringing this to our attention. It is also noteworthy that the four- and six-center mechanisms for reaction of ketones with aluminum alkyls have recently been discarded.[10] The unusual feature of nucleophilic attack on an apparently negatively charged site is not without precedent;[11] LCAO–SCF calculations, however, indicate the boron of BH_4^- to be nearly neutral, with all of the negative charge spread on the hydrogens.[12]
(9) R. R. Schrock and J. A. Osborne, *Chem. Commun.*, 567 (1970).
(10) J. J. Eisch and K. C. Fichter, *J. Am. Chem. Soc.*, **97**, 4772 (1975).
(11) B. M. Trost, "Sulfur Ylides," Academic Press, New York, N.Y., 1975, pp 112, 121.
(12) R. A. Hegstrom, W. E. Palke, and W. N. Lipscomb, *J. Chem. Phys.*, **46**, 920 (1967).
(13) The possibility exists that the apparent order of 1.5 could arise from the fortuitous mixing of true first- and second-order processes. The benzidene rearrangement, for example, shows an apparent order of 1.6 for this reason.[14] In the present reaction, however, a plot of $k/$[Pr-*i*-OH] vs. [Pr-*i*-OH] showed marked curvature, inconsistent with the mixture of processes.
(14) P. Sykes, "The Search for Organic Reaction Pathways", Longman, London, 1972, p 19.
(15) H. C. Brown, O. H. Wheeler, and K. Ichikawa, *Tetrahedron*, **1**, 214 (1957).
(16) H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955).
(17) J.-L. Pierre and H. Handel, *Tetrahedron Lett.*, 2317 (1974).
(18) E. C. Ashby and J. R. Boone, *J. Am. Chem. Soc.*, **98**, 5524 (1976).
(19) H. B. Burgi, J. M. Lehn, and G. Wipff, *J. Am. Chem. Soc.*, **96**, 1956 (1974).
(20) D. C. Wigfield, *Can. J. Chem.*, in press.
(21) NRCC Scholar.

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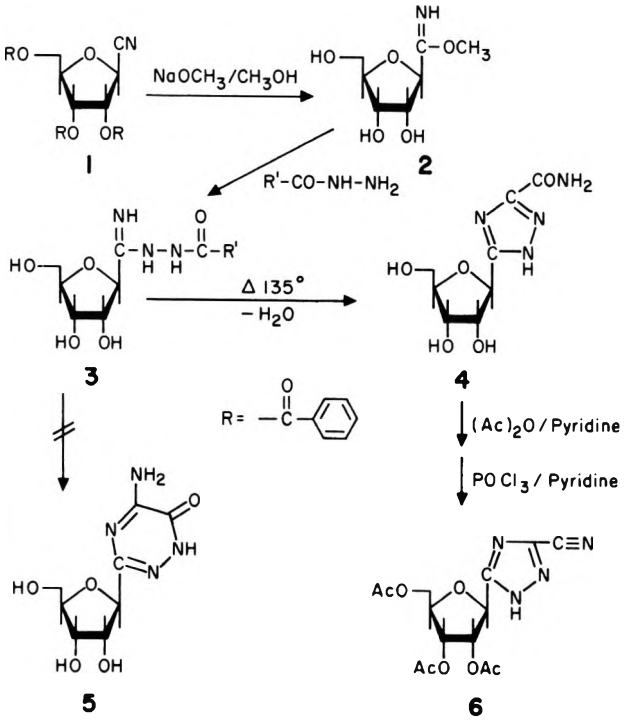
Received October 20, 1976

A Total Synthesis of *C*-Nucleoside Analogue of Virazole

Summary: A synthesis of 5-carboxamido-3-(β-D-ribofuranosyl)-1,2,4-triazole has been developed by treating β-D-ribofuranosyl-1-carboximidic acid methyl ester with oxamido hydrazide followed by dehydrative ring closure of the open chain product by heating at 135 °C.

Sir: Several approaches[1–10] have recently been developed for synthesis of nucleosides possessing the unusual *C*-ribosyl linkage (*C*-nucleosides). In the area of *C*-triazole nucleosides, the recently reported method[9] lends itself only to the synthesis of 1,2,3-triazole *C*-nucleosides. A synthesis of DL-5-(1-β-ribofuranosyl)-3-amino-1,2,4-triazole has also been achieved[3] by a reaction of DL-2,5-anhydro-3,4-*O*-isopropylidene allonic acid lactone with aminoguanidine and subsequent removal of the isopropylidene blocking, but the approach seems to have limited application as far as the variation of C-5 substituents on the triazole nucleus is concerned. We describe here a high yield procedure for the synthesis of *C*-nucleosides of 1,2,4-triazole derivatives which has potential for wider application in the synthesis of such nucleosides. The utility of our method has been demonstrated by a total synthesis of 5-carboxamido-3-(β-D-ribofuranosyl)-1,2,4-triazole (**4**) which is a *C*-nucleoside analogue of 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide.[11]

Reaction of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide[12] (**1**) with catalytic amounts of $NaOCH_3$ in CH_3OH at room temperature for 1 h led to the formation of the deblocked imidic ester **2** (mp 142–143 °C) in 60–85% yield: NMR (Me_2SO-d_6) δ 3.59 (s, 3, OCH_3), 3.50–3.90 (m, 5, 2′-, 3′-, 4′-C—H and 5′-CH_2), 4.06 (d, 1, 1′-C—H, $J_{1'-2'}$ = 2 Hz), 4.93 (br s, 3, 2′-, 3′-, 5′-OH), 8.25 (s, 1, C=NH). The imidic ester **2** is susceptible to a facile nucleophilic displacement reaction with a variety of nucleophiles. For instance with ammonia or hydrazine, it formed the corresponding amidine and amidrazone ribosyl derivatives respectively. For the synthesis of open-chain precursors **3** of 1,2,4-triazole nucleosides, the imidic ester **2** was treated with the appropriate carboxylic acid hydrazides. Compound **3** (R′ = $CONH_2$) was thus synthesized in almost quantitative yield by reacting stoichiometric amounts of **2** and oxamido hydrazide in dimethyl sulfoxide at room temperature for 18 h. The structure of **3** (R′ = $CONH_2$) was established by ^1H NMR (Me_2SO-d_6): δ 3.6 (m, 2, 2′- and 3′-C—H), 3.8 (m, 1, 4′-C—H), 3.95 (m, 2, 5′-C—H_2),



4.15 (d, 1, 1′-C—H, $J_{1'-2'} \sim 1$ Hz), 5.2 (br m, 3, 2′-, 3′-, 5′-OH), 6.62 (br s, 2, $CONH_2$), 7.68, 8.0 (br s, 2, CONHNHC), 10.05 (br s, 1, C=NH). When precursor **3** (R′ = $CONH_2$) was heated at 135 °C under vacuum (0.1 mmHg), dehydrative ring closure occurred within ~15 min to give an 80% yield of *C*-Virazole **4** (mp 193–195 °C). Compound **3** (R′ = $CONH_2$) appears to have thermodynamic propensity to form compound **4** as shown by a slow conversion in aqueous solution at ambient temperature. The cyclized product gave the following proton NMR pattern (Me_2SO-d_6): δ 3.53 (m, 2, 5′-C—H_2), 3.82 (m, 1, 4′-C—H), 3.45, 4.17 (m, 1 each, 2′-, 3′-C—H), 4.73 (d, 1, 1′-C—H, $J_{1'-2'}$ = 5 Hz), 7.64, 7.84 (br s, 1 each, $CONH_2$), extremely broad hydroxyl and NH protons between 5–7. Since the NMR data of the cyclized product do not allow a clear-cut distinction between structures **4** and **5**, further proof in favor of structure **4** was obtained by converting the product to its cyano derivative **6**. This was done by subjecting the tri-*O*-acetyl derivative of the product to conditions of dehydration in $POCl_3$ and pyridine. The resulting compound was shown to be 5-cyano derivative **6**: IR ($CHCl_3$) 2260 cm^{-1}; NMR (Me_2SO-d_6) δ 1.94 (s, 3, $COCH_3$), 2.07 (s, 6, 2-$COCH_3$), 3.9–4.4 (m, 3, 4′-C—H and 5′-CH_2), 5.24 (d, 1, 1′-C—H, $J_{1'-2'}$ = 5 Hz), 5.31 and 5.56 (two t, 1 each, 2′- and 3′-C—H). To establish the anomeric configuration of the triazole moiety in **4**, it was converted into its 2′,3′-*O*-isopropylidene derivative which gave the following NMR pattern (Me_2SO-d_6): δ 1.32 and 1.50 [two s, 3 each, *C*-$(CH_3)_2$], 3.40 (d, 2, 5′-CH_2), 3.45 (br, 1, 5′-OH), 4.05 (m, 1, 4′-C—H), 4.73 (m, 1, 3′-C—H), 4.94 (d, 1, 1′-C—H, $J_{1'-2'}$ = 4 Hz), 5.05 (m, 1, 2′-C—H), 7.69 and 7.91 (two br s, 1 each, $CONH_2$), 1 NH proton burried under $CONH_2$ signals. The NMR chemical shifts of the methyl protons in the isopropylidene derivative (δ 1.32 and 1.50, δΔ = 0.18) supported the β stereochemistry[13] of compound **4**.

References and Notes

(1) E. M. Acton, A. N. Fujiwara, L. Goodman, and D. W. Henry, *Carbohydr. Res.*, **33**, 135 (1974).
(2) M. Fuertes, M. T. Garcia-Lopez, G. Garcia-Muñoz, and R. Madroñero, *J. Carbohydr.—Nucleosides Nucleotides*, **2**, 277 (1975).
(3) G. Just and M. Ramjeesingh, *Tetrahedron Lett.*, **No. 12**, 985 (1975).
(4) G. Trummlitz, D. W. Repke, and J. G. Moffatt, *J. Org. Chem.*, **40**, 3352 (1975), and references therein.
(5) T. Huynh-Dinh, J. Igolen, J. P. Marquet, E. Bisagni, and J. Lhoste, *J. Org. Chem.*, **41**, 3124 (1976).
(6) S. De Bernardo and M. Weigele, *J. Org. Chem.*, **41**, 287 (1976).
(7) L. Kalvoda, *J. Caroohydr.—Nucleosides Nucleotides*, **3**, 47 (1976).
(8) G. Just and S. Kim, *Tetrahedron Lett.*, **No. 14**, 1063 (1976).
(9) F. G. De Las Heras, S. Y-K. Tam, R. S. Klein, and J. J. Fox, *J. Org. Chem.*, **41**, 84 (1976).
(10) F. G. De Las Heras, C. K. Chu, S. Y-K. Tam, R. S. Klein, K. A. Watanabe, and J. J. Fox, *J. Heterocycl. Chem.*, **13**, 175 (1976).
(11) J. T. Witkowski, R. K. Robins, R. W. Sidwell, and L. N. Simon, *J. Med. Chem.*, **15**, 1150 (1972).
(12) M. Bobek and J. Farkaš, *Collect. Czech. Chem. Commun.* **34**, 247 (1968).
(13) B. Rayner, C. Tapiero, and J. Imbach, *Carbohydr. Res.*, **47**, 195 (1976); *J. Carbohydr.—Nucleosides Nucleotides*, **3**, 1 (1976).

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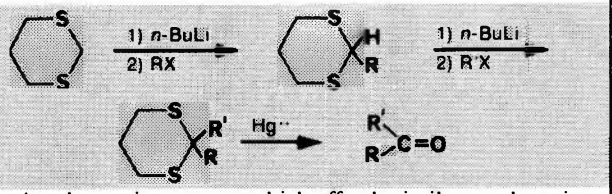
Umpolung of Functional Group Reactivity

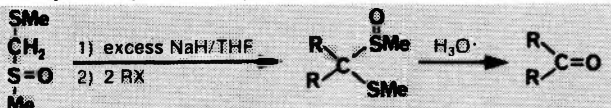
Umpolung, the term first proposed by Seebach,[1] refers to the reversal of the normal polarity of a functional group. In carbonyl chemistry, reversal of polarity creates an acyl anion. Nucleophilic acylation can then be achieved by either the acyl anion or an equivalent, "masked" intermediate.

Aldrich offers a growing line of reagents to utilize new techniques based on the *Umpolung* concept. Research employing the concept of *Umpolung* has been summarized in recent reviews.[1,2] Several interesting applications are described below.

Lithiated 1,3-dithianes have been shown to be useful masked acyl anions.[3]

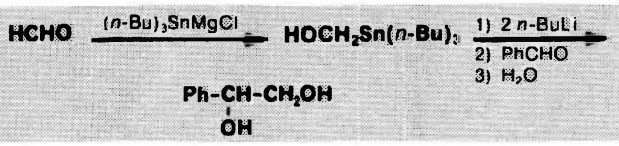


An alternative reagent which affords similar products is methyl methylthiomethyl sulfoxide (MMTS).[4]

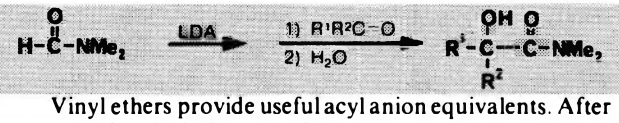


MMTS

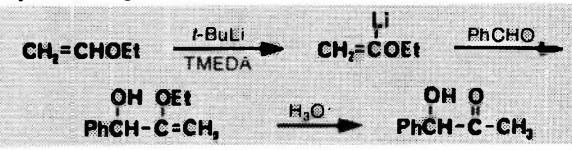
Seebach and Meyer,[5] utilizing an *Umpolung* of the normal reactivity of formaldehyde, have recently developed the first direct hydroxymethylation of carbonyl compounds, using a doubly lithiated derivative of methanol.



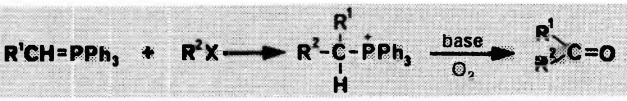
Electrophiles undergo reaction with the carbonyl anion derived from dimethylformamide [using lithium diisopropylamide (LDA)] at -100°.[6] Similarly, dimethylthioformamide has been used for nucleophilic *thio*acylation.[7]



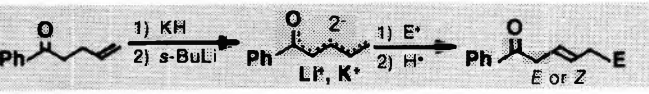
Vinyl ethers provide useful acyl anion equivalents. After reaction of their lithio salts with carbonyl compounds in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA), the ethers obtained may be left intact or solvolyzed (using methanolic HCl) to the corresponding ketones.[8]



The *Umpolung* concept has also been extended to phosphorus ylids.[9]



Recently, Seebach furnished an illustration of the *Umpolung* of carbon-*carbon* double bonds.[10]



References:

1) D. Seebach and M. Kolb, *Chem. Ind. (London)*, 687 (1974).
2) O.W. Lever, Jr., *Tetrahedron*, **32**, 1943 (1976).
3) D. Seebach and E.J. Corey, *J. Org. Chem.*, **40**, 231 (1975).
4) G. Schill and P.R. Jones, *Synthesis*, 117 (1974).
5) D. Seebach and N. Meyer, *Angew. Chem., Int. Ed. Engl.*, **15**, 438 (1976).
6) B. Banhidai and U. Schöllkopf, *ibid.*, **12**, 836 (1973).
7) D. Seebach, W. Lubosch, and D. Enders, *Chem. Ber.*, **109**, 1309 (1976).
8) J.E. Baldwin, G.A. Höfle, and O.W. Lever, Jr., *J. Amer. Chem. Soc.*, **96**, 7125 (1974); U. Schöllkopf and P. Hänssle, *Justus Liebigs Ann. Chem.*, **763**, 208 (1972).
9) H.J. Bestmann and R. Zimmermann, *Chem.-Ztg.*, **96**, 649 (1972); H.J. Bestmann, *Angew. Chem., Int. Ed. Engl.*, **4**, 830 (1965).
10) V.M. Pohmakotr and D. Seebach, submitted for publication in *Angew. Chem.*