VOLUME 43 SEPTEMBER 15, 1978 NUMBER 19 JOCEAH

THE JOURNAL OF Organic Chemistry

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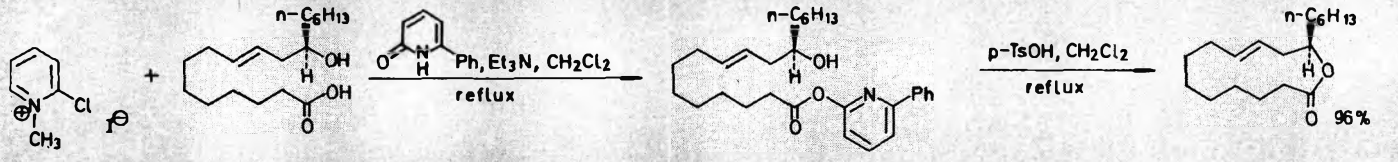

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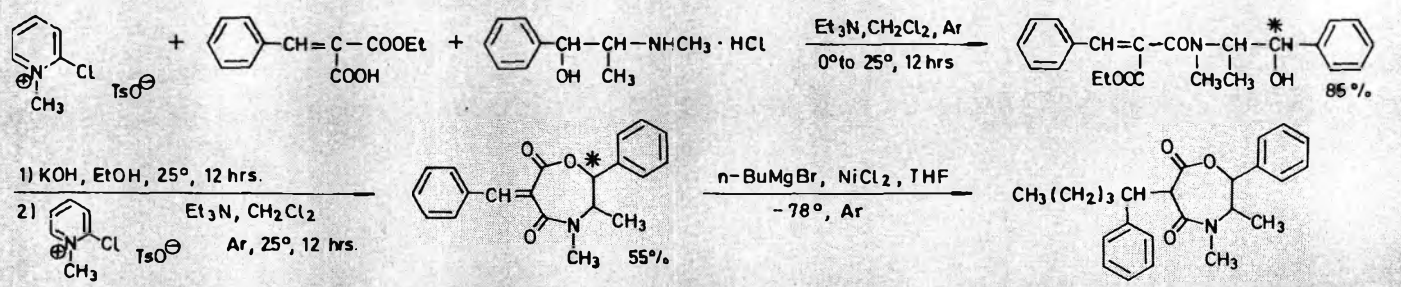

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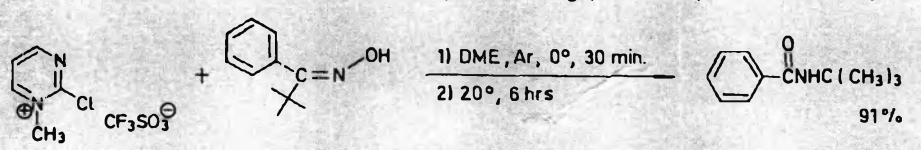

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Published biweekly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second class postage paid at Washington, D.C., and at additional mailing offices.

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Notice to Authors last printed in the issue of January 6, 1978

JOCEAH 43(19) 3635–3802 (1978)
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THE JOURNAL OF Organic Chemistry®

VOLUME 43, NUMBER 19

SEPTEMBER 15, 1978

Crystal and Molecular Structure of Phosphates. 8.[1] The Cyclic Enediol Phosphoimidazole $(C_3H_3N_2)(PO_3)(CH_3C{=}CCH_3)$

Fausto Ramirez,*[2a] John S. Ricci, Jr.,[2b] Hiroshi Okazaki,[2a] Koa Tasaka,[2a] and James F. Marecek[2a]

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Received January 30, 1978

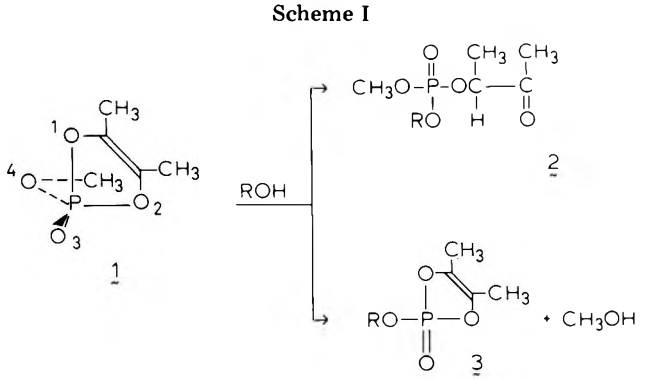
The crystal and molecular structure of *N*-(1,2-dimethylethenylenedioxyphosphoryl)imidazole, a powerful phosphorylating reagent, was solved by X-ray crystallographic methods. The compound crystallizes from benzene in space group $P\bar{1}$ of the triclinic system, with two molecules of the cyclic enediol phosphoimidazole, $C_7H_9O_3N_2P$, and one molecule of benzene in a unit cell of dimensions a = 6.766 (2), b = 7.637 (2), c = 12.125 (5) Å, α = 102.24 (3), β = 100.94 (3), γ = 98.78 (2)°; D_{calcd} = 1.34 g cm^{-3}, D_{meas} = 1.34 (1) g cm^{-3}. Data were obtained on a computer-controlled CAD-4 diffractometer. A multiple-solution direct methods technique was employed, and the structure was refined by full-matrix least-squares methods to a final R value of 4.8% on F based on 1216 independent structure amplitudes. The dioxaphospholene and imidazole rings are planar and orthogonal, with the isolated CH group of imidazole adjacent to the phosphoryl oxygen (P=O). The phospholene ring is an irregular pentagon (endocyclic O–P–O angle = 97.5°). The PO_3N group is a highly distorted tetrahedron with angles ranging from 97.5 to 118.3°. The P–N bond distance is 1.66 Å, and the phosphoryl and ester P–O distances are 1.44 and 1.59 Å, respectively. It is suggested that these departures from the respective pure single bond values reflect the existence of some p–d π bonding in the molecule. The structure and the reactivity of the phosphoimidazole are compared with those of the symmetrical pyrophosphate and the methyl phosphotriester analogues.

The molecular structure of the cyclic enediol phosphotriester **1** (Scheme I; abbreviated as CEP-OCH$_3$[3]) has been determined by X-ray crystallographic methods.[4] The dioxaphospholene ring is planar and orthogonal to another plane which includes the atoms C–O(4)–P–O(3). The methoxy group lies directly above the ring, with the carbon atom approximately centered between the two ring oxygens. CEP-OCH$_3$ reacts with alcohols to give a mixture of products resulting from a displacement at phosphorus with ring opening (acyclic triester **2**) and ring retention (cyclic triester **3**).

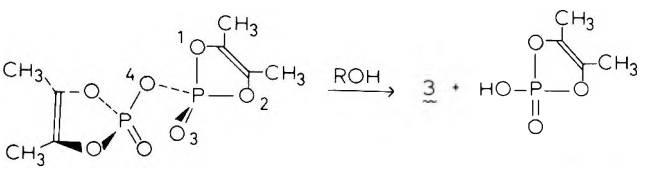
The structure of the cyclic enediol pyrophosphate **4** (Scheme II; CEP-OCEP[3]) has also been solved.[5] There are two independent molecules of the pyrophosphate in the asymmetric unit of the crystal. The two dioxaphospholene rings in both molecules are planar, but the dihedral angles formed by the two planes which contain the respective three-atom systems, O=P–O(4), of the anhydride function differ slightly (69 and 75°, respectively) in the two molecules. CEP-OCEP (**4**) is a powerful phosphorylating reagent,[6] and undergoes displacements at phosphorus with exclusive ring retention, as shown in Scheme II.

Another useful phosphorylating reagent is the cyclic enediol phosphoimidazole[7] **6** (Scheme III; CEP-IM[3]). This compound undergoes very rapid reactions with alcohols, giving exclu-

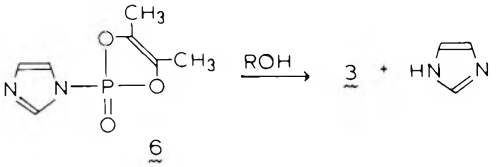
Scheme I



Scheme II



Scheme III



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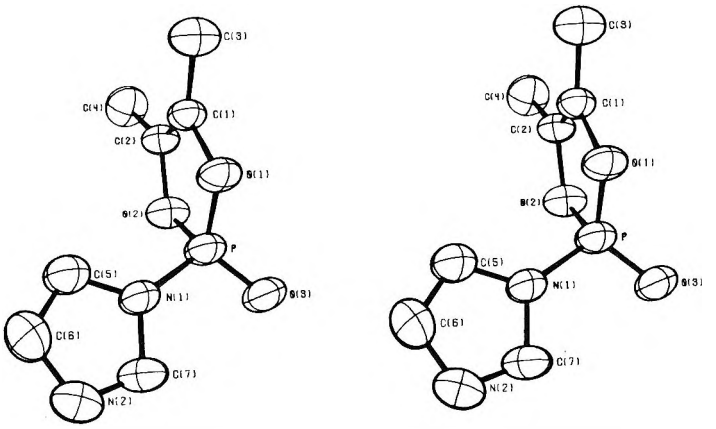


Figure 1. Stereoscopic drawing of one molecule of $C_7H_9O_3N_2P$. The 50% probability ellipsoids are shown. (Hydrogen atoms are omitted for clarity.)

sively the products of displacement with ring retention. This paper describes the crystal and molecular structure of CEP-IM (**6**), and compares the structural features of the three CEP derivatives, **1**, **4**, and **6**. In addition, possible correlations between the structures of the three compounds and their respective modes of reaction are discussed.

The significance of imidazole as a reversible carrier of phosphoryl groups in biochemistry has been recognized for a number of years.[8-10] Several structures pertinent to the present investigation have been elucidated by X-ray crystallographic methods: sodium phosphoramidate,[11] PO_3NH_3Na; phosphocreatine;[12] calcium 1,3-diphosphorylimidazole hexahydrate,[13] $Ca_{1.5}C_3H_3N_2(PO_3)_2 \cdot 6H_2O$; cyclophosphamide hydrate;[14] diphenylphosphinedimethylamide,[15] $(C_6H_5)_2P(O)N(CH_3)_2$; and trichlorobis(diethylphenylphosphine)-(diethylphenylphosphineiminato)ruthenium(IV).[16] The nature of the P–N bond in those compounds, and in other structures with higher P–N bond order, has received considerable attention.[17-21]

Experimental Section

***N*-(1,2-Dimethylethenylenedioxyphosphoryl)imidazole (6).** The compound was prepared as previously described.[7] A sample (0.5–1.0 g) was dissolved in warm benzene (~10 mL) and the solution was diluted with *n*-hexane (~10 mL). Crystals were obtained after 20 h at 5 °C.

Crystal Data. $C_7H_9O_3N_2P \cdot \frac{1}{2}C_6H_6$: triclinic; $P\bar{1}$; a = 6.766 (2), b = 7.637 (2), c = 12.125 (5) Å; α = 102.24 (3), β = 100.94 (3), γ = 98.79 (2)°; V = 588.9 (1) Å^3 ($\lambda_{Mo/Zr}$ 0.7107 at 21 °C); Z = 2 (one molecule plus one half of a solvent benzene molecule per asymmetric unit); D_{calcd} = 1.34 g cm^{-3}, D_{meas} (by flotation in cyclohexane–carbon tetrachloride) = 1.34 (1) g cm^{-3}; μ(Mo Kα) = 2.19 cm^{-1}.

Data Collection and Structure Refinement. Precession photographs and subsequent searching of reciprocal space showed the unit cell to be triclinic and of space group $P\bar{1}$. The cell dimensions were determined by a least-squares fit of the observed 2θ angles for 19 reflections centered automatically.

Three-dimensional intensity data were measured on a computer-controlled Enraf Nonius CAD-4 diffractometer using zirconium-filtered Mo Kα radiation with a colorless crystal of dimensions 0.34 × 0.49 × 0.54 mm. The data crystal was moisture sensitive, and was wedged inside a glass capillary tube along the diagonal axis [111], where it remained stable over the course of data collection. Data were collected by θ–2θ scans to 2θ (Mo Kα) = 55°. Absorption corrections were applied to 3758 observations using BNLABS, a local version of ORABS.[22]

The minimum and maximum corrections to F_o^2 were 0.914 and 0.935, respectively. The agreement between symmetry-equivalent intensities was R = 0.025. These intensities were averaged to give 1216 independent structure amplitudes with $F_o^2 > 3\sigma_{count}(F_o^2)$ with $\sigma(F_o^2)$ being based on Poisson counting statistics. The intensities of three standard reflections were measured periodically and were found to have fallen off to approximately 45% of their original values by the end of data collection. The decrease in intensity was uniform over the exposure time and the individual standards were scaled to the zero time standards. Background was measured on one-sixth of total scan width. Normal scans which did not result in sufficiently high precision on net intensity measurements were repeated at a slower speed. The takeoff angle was 5.60° and the diffracted beam was automatically corrected for coincidence losses.

Normalized structure factors (E's) were used in a multiple-solution direct methods technique as described by Germain, Main, and Woolfson[23] to determine phases from which an E map revealed the coordinates of all nonhydrogen atoms.

The structure was refined by full-matrix least squares, minimizing the function $\Sigma w\Delta^2$ with $\Delta = |F_o| - |F_c|$ with weights $w = 4F_o^2/\sigma^2(F_o^2)$ and $\sigma^2(F_o^2) = \sigma_{count}^2(I) + (0.03F^2)^2$. All 12 hydrogen atom positions were located by difference Fourier synthesis using low angle ($\sin\theta/\lambda < 0.35$) data. Atomic scattering factors for all nonhydrogen atoms were taken from a standard source,[24] while that for hydrogen was the best spherically averaged value of Stewart et al.[25]

The final least-squares cycles included anisotropic thermal parameters for the nonhydrogen atoms and individual isotropic thermal parameters on the hydrogen atoms. The final values of $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R_2 = \{[\Sigma w||F_o| - |F_c||^2]/\Sigma w|F_o^2|\}^{1/2}$ were 0.048 and 0.047, respectively, and the error in an observation of unit weight was 1.67. The maximum density in a final difference electron density synthesis was 0.23 e Å^{-3}, approximately 45% of the height of a hydrogen atom peak. The final parameters are presented in Tables VA and VB (see paragraph concerning supplementary material at the end of this paper).

Effect of Imidazole on Reactions of Alkyl 1,2-Dimethylethenylene Phosphates with Alcohols. Methyl, 2-methyl-1-propyl, 2-propyl, and cyclopentyl 1,2-dimethylethenylene phosphates (**1**, **3**) were prepared as described.[6a,7] A weighed sample of the CEP-OCH_3 (**1**) or CEP-OR (**3**) was dissolved in $CDCl_3$, and the solution was allowed to reach a constant temperature of 25 °C. An equimolar amount of the alcohol R′OH (and 1 molar equiv of imidazole when indicated) dissolved in $CDCl_3$ was added. The solutions were 0.20 M in cyclic phosphate. The ^{1}H NMR spectrum of the solution was determined immediately and then repeatedly until it became apparent that the thermodynamic mixture of products had been obtained. Analyses of these mixtures of products were performed on a Hewlett Packard 5830A gas chromatograph using $\frac{1}{8}$ in. × 2 ft, 10% Carbowax 20M column (injection temperature, 200 °C; TCD temperature, 200 °C; column temperature, 140–170 °C depending on the compound). The carrier gas was helium at 40 mL/min. The dialkyl 3-oxo-2-butyl phosphates, which are known compounds,[6a,7,26] are stable under the specified conditions. The results of the experiments are summarized in Table V. Further confirmation of the course of the reactions was obtained by ^{31}P NMR measurements (at 40.5 MHz), with the aid of the following data: ^{31}P +11.7 ± 0.7 ppm for CEP-OR, and −2.0 ± 1.0 ppm for (RO)(R′O)P(O)OAcn, in $CDCl_3$ (positive values are downfield from H_3PO_4 = 0).

Discussion of Results

Molecular Structure of the Phosphoimidazole 6. The asymmetric unit of the crystal consists of one molecule of the phosphoimidazole (depicted in Figure 1) and one-half of a molecule of benzene. The contents of the unit cell are displayed in Figure 2. Table I gives the bond distances and angles,

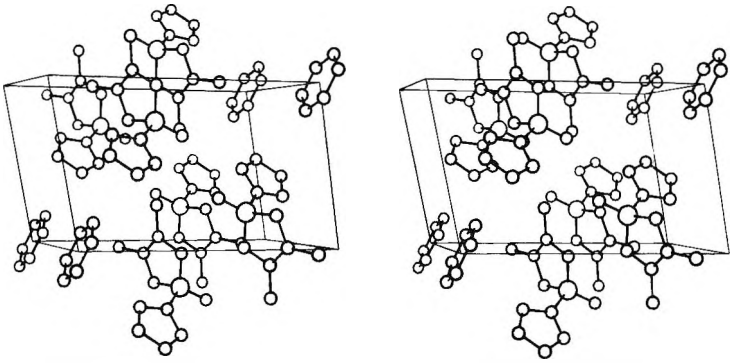


Figure 2. Stereoscopic drawing showing the unit cell contents ($Z = 2$) with all molecules completed. The view is approximately along a, and b is vertical.

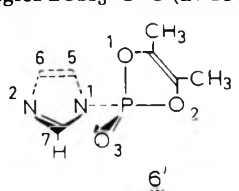
Table I. Bond Distances (Å) and Angles (deg) Involving Nonhydrogen Atoms[a,b]

Distances			
P–N(1)	1.659 (3)	C(1)–C(2)	1.285 (5)
P–O(1)	1.577 (2)	C(1)–C(3)	1.468 (5)
P–O(2)	1.586 (3)	C(2)–C(4)	1.490 (5)
P–O(3)	1.441 (3)	C(5)–C(6)	1.331 (6)
C(1)–O(1)	1.437 (4)	C(B1)–C(B2)	1.351 (7)
C(2)–O(2)	1.424 (4)	C(B2)–C(B3)	1.378 (7)
C(5)–N(1)	1.376 (5)	C(B3)–C(B1′)	1.347 (7)
C(7)–N(1)	1.390 (5)		
C(6)–N(2)	1.383 (6)		
C(7)–N(2)	1.287 (6)		
Angles			
In Cyclic Phosphate			
O(1)–P–O(2)	97.5 (1)	O(1)–C(1)–C(3)	113.7 (4)
O(1)–P–O(3)	117.8 (2)	O(2)–C(2)–C(4)	113.8 (4)
O(2)–P–O(3)	118.3 (2)	C(1)–C(2)–C(4)	133.0 (4)
O(1)–P–N(1)	106.4 (1)	C(2)–C(1)–C(3)	134.6 (4)
O(2)–P–N(1)	104.3 (2)		
O(3)–P–N(1)	110.8 (2)		
P–O(1)–C(1)	109.0 (2)		
P–O(2)–C(2)	108.5 (2)		
O(1)–C(1)–C(2)	111.7 (3)		
O(2)–C(2)–C(1)	113.2 (3)		
In Imidazole			
N(1)–C(7)–N(2)	112.3 (4)	N(2)–C(6)–C(5)	110.8 (4)
C(5)–N(1)–C(7)	104.8 (4)	P–N(1)–C(5)	128.4 (3)
C(6)–N(2)–C(7)	105.1 (4)	P–N(1)–C(7)	126.8 (3)
N(1)–C(5)–C(6)	107.0 (4)		
In Benzene			
C(B1)–C(B2)–C(B3)	119.6 (6)	C(B2)–C(B1)–C(B3′)	121.0 (6)
C(B2)–C(B3)–C(B1′)	119.4 (5)		

[a] Numbers in parentheses here and in succeeding tables are estimated standard deviations in the least significant digits. [b] Bond distances and angles involving hydrogen atoms are included in the supplementary material (Table IB).

and Table II describes several dihedral angles between planes and the best least-squares planes.

The dioxaphospholene ring is a planar and irregular pentagon. The imidazole ring is also planar, and is orthogonal to the dioxaphospholene ring, with the isolated C(7)–H group of imidazole adjacent to the phosphoryl oxygen, P=O (cf. formula 6′). The angles ∠CH_3–C–C (av 134°) and ∠CH_3–C–O



6′

Table II

A. Some Dihedral Angles between Planes Defined by Three Atoms

plane 1	plane 2	angle, deg
N(1), C(5), C(7)	P, O(1), O(2)	86.2 (3)
O(3), P, N(1)	P, N(1), C(7)	8.8 (4)
C(4), C(2), C(1)	C(2), C(1), C(3)	1.7 (9)

B. Equations of Best Least-Squares Planes and Deviations of Individual Atoms from Planarity (Å)

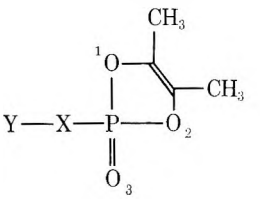
1. P, N(1), C(7), N(2), C(6), C(5)
   $4.883x - 5.592y - 3.125z = 4.672$
   P, 0.000; N(1), 0.006; C(7), 0.000; N(2), −0.002; C(6), −0.004; C(5), 0.000
2. P, O(1), C(1), C(2), O(2), C(3), C(4)
   $3.007x - 0.644y + 9.355z = -3.744$
   P, −0.005; O(1), 0.020; C(1), −0.007; C(2), −0.004; O(2), 0.026; C(3), −0.017; C(4), −0.040
3. O(3), P, N(1), C(7), N(2), C(6), C(5)
   $4.996x - 5.282y - 3.823z = 4.677$
   O(3), 0.084; P, −0.016; N(1), 0.010; C(7), −0.059; N(2), −0.026; C(6), 0.062; C(5), 0.082
4. plane through benzene molecule (three independent atoms)
   $-0.527x - 4.850y + 10.786z = -5.409$
   C(B1), 0.001; C(B2), 0.001; C(B3), 0.001

(av 114°) suggest repulsion between the two methyl groups attached to the sp^2 carbons of the dioxaphospholene ring.

The phosphate group, PO_3N, is a highly distorted tetrahedron as can be seen in Table III, which lists also the corresponding data for the pyrophosphate and phosphotriester analogues, 4 and 1. The most interesting features are the consistently small endocyclic ∠O(1)–P–O(2) angles and the relatively large ∠O(1)–P–O(3) and ∠O(2)–P–O(3) angles. The remaining endo- and exocyclic ∠O(1)–P–X and ∠O(2)–P–X angles and the exocyclic ∠O(3)–P–X angle are relatively closer to the tetrahedral 109.5° value. The net effect of these angle deformations is to displace the dioxaphospholene ring away from the phosphoryl oxygen, O(3), and toward atom X in the three CEP derivatives.

Another noteworthy feature pertains to the P–X bond distances. The P–N bond in the phosphoimidazole is significantly shorter than the P–N bond in phosphocreatine,[12] sodium phosphoramidate[11] (1.77 Å), and calcium 1,3-diphosphorylimidazole[13] (av 1.78 Å), but of about the same length as that in diphenylphosphinedimethylamide[15] (1.68 Å). The shorter bonds possibly reflect some p–d π bonding[21] involving the lone electron pairs on the nitrogen atom and the phosphorus d orbitals. However, the extent of the p–d π bonding appears to be less significant in the phosphoimidazole than in the pyrophosphate[5] and the phosphotriester[4] analogues, since the respective deviations from the P–N and P–O pure single bond distances[19,20] are 6.7, 9.0, and 13%. The anhydride

Table III. Bond Distances and Angles in the PO_3X Group of Cyclic Enediol Phosphoryl Derivatives



atoms[a]	phospho-imidazole[b]	pyrophos-phate[c]	phospho-triester[d]
P–O(1)	1.58	1.58	1.59
P–O(2)	1.59	1.58	1.57
P–O(3)	1.44	1.44	1.38
P–X	1.66[e]	1.60[f]	1.53[f]
O(1)–P–O(2)	97.5	98.4	98.5
O(1)–P–O(3)	117.8	118.7	116.8
O(2)–P–O(3)	118.3	117.4	115.6
O(1)–P–X	106.4	102.4	106.8
O(2)–P–X	104.3	105.4	108.9
O(3)–P–X	110.8	112.4	109.5
P–X–Y	127.6[g]	127.5[h]	122.0[g]

[a] Pure single bond distances: P–O = 1.76 Å, P–N = 1.78 Å, ref 19 and 20. [b] Present work. [c] Reference 5. [d] Reference 4. [e] X = N. [f] X = O. [g] Y = C. [h] Y = P.

P–O(4) bond is somewhat longer than the corresponding ester P–O(4) bond, suggesting relatively less p–d π bonding in the former, since the lone electron pairs on O(4) are sheared by two dioxaphospholene rings in the pyrophosphate.

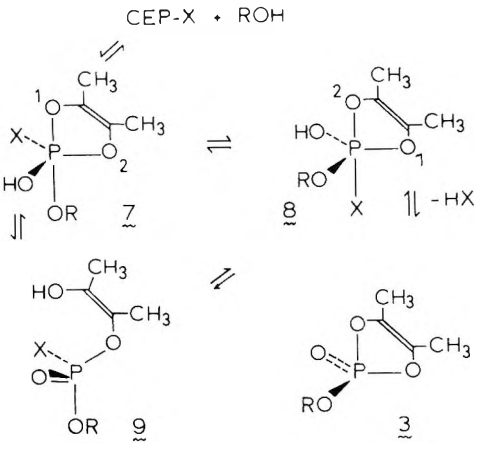
As expected, the P–O(3) bonds are the shortest of their kind in the three CEP derivatives, presumably reflecting the highest extent of p–d π bonding. The endocyclic P–O(1) and P–O(2) bonds are also relatively short, i.e., about 10% less than the pure single bond distance, and this is also consistent with the relatively large ∠O(1)–P–O(3) and ∠O(2)–P–O(3) angles.

The imidazole ring is a somewhat distorted pentagon. The C(7)–N(2) bond, which is formally double bonded in the heterocycle formula, is significantly shorter than the other three C–N bonds, as would be expected if it had a higher π-bond character. In other features, the ring is unexceptional with respect to unsubstituted[27] and *N,N*-diphosphorylated[13] imidazole.

Ring Retention and Ring Opening in Displacements at Phosphorus in Cyclic Enediol Phosphoryl Derivatives. In reactions with alcohols, the pyrophosphate **4** and the phosphoimidazole **6** give exclusively the product of ring retention at a relatively rapid rate, while the phosphotriester **1** generates mixtures of the products of ring opening and ring retention at a much slower rate. It is apparent from the data in Table III that these differences cannot be attributed to major differences in bond angles and bond distances in the three compounds. A possible mechanism for these phosphorylation reactions is shown in Scheme IV, in terms of the oxyphosphorane intermediate hypothesis[28–31] for displacements at a P(4) center.

The first step of the reaction is the addition of alcohol to P(4) to give the oxyphosphorane **7**; this step may be rate limiting in most, but not necessarily in all, cases.[30b] The formation of **7** involves relatively small additional bond angle deformations beyond those already present in the cyclic phosphate. Cyclic *phosphates*, in general, lose stability relative to the corresponding acyclic compounds mainly as a result of ring strain.[4,31] On the other hand, cyclic *oxyphosphoranes* with small and nearly planar rings gain stability relative to the corresponding acyclic oxyphosphoranes, since there is a great deal of intramolecular crowding in P(5) and the decrease in crowding resulting from the introduction of the rings outweighs any ring strain associated with bond angle deformation in P(5).[32] The extraordinary reactivity of the CEP derivatives relative to their acyclic analogues can be reasonably ascribed to these two combined effects, which increase ground state and decrease intermediate state (and presumably the corresponding transition state) energies. These effects are considerably greater in five-membered cyclic unsaturated phosphates[4] than in the corresponding saturated analogues.[31,33–35]

Scheme IV



The P(5) intermediate **7** can undergo ring opening before or after undergoing permutational isomerization,[36–38] **7** ⇌ **8**; the resulting acyclic product **9** is involved in a subsequent enol ⇌ keto equilibrium, which favors the latter. The isomerization step, **7** ⇌ **8**, opens a new reaction possibility, namely, the apical departure of ligand X to give the product of ring retention, **3**. These steps are influenced by certain properties of ligands X and OR. The position of equilibrium **7** ⇌ **8** depends on the relative apicophilicities[37] of X vs. RO. Apicophilicity[37,39] is a function of ligand electronegativity[40] and size. The equatorial and apical positions of P(5) differ in the extent to which the lone electron pairs on the atoms of the ligands which occupy those positions engage in p–d π bonding with the phosphorus d orbitals.[37] There appears to be more back-donation of electrons to the phosphorus d orbitals from an atom in the equatorial position than from the same atom in the apical position. Other things being equal, the higher the electronegativity of a ligand, the higher its apicophilicity, since a relatively electronegative group is better able to support electronic charge, and this is one of the factors required for apical occupancy. The equatorial and apical positions in P(5) differ also in the extent to which the ligands are subject to steric interactions with other ligands. An equatorial ligand encounters only two close 90° interactions, while an apical ligand encounters three such interactions. The 120° interactions among equatorial groups are of less significance. Therefore, other factors being equal, the lower the steric demand of X, the higher its apicophilicity.

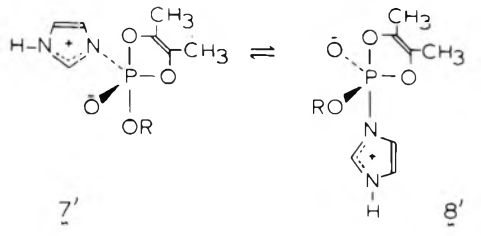
From these considerations, it is reasonable to assume that ligand X = CEPO– in the pyrophosphate **4** is more apicophilic than ligand X = RO– of the triester **1**. This is in line with the stronger acidity of the conjugate acid of the ligands themselves, XH = CEP-OH vs. ROH. Within a series of CEP-OR compounds, this trend in apicophilicity is also noted[7,26] when the alkyl group R contains electron-withdrawing substituents, e.g., $(Cl_3C)_2CH$. With respect to the imidazolyl ligand, it is conceivable that its apicophilicity is influenced by the basic properties of the group. Imidazole itself is relatively basic: $C_3H_3N_2H_2^+ \rightleftharpoons C_3H_3N_2H + H^+$, p$K$ 6.9, and the formation of the zwitterion **7′** depicted in Scheme V is possible in view of

Table IV. Effect of Imidazole on Reactions of Alkyl 1,2-Dimethylethenylene Phosphates with Alcohols, CEP-OR + R′OH → (RO)(R′O)P(O)OAcn[a] + (RO)$_2$P(O)OAcn[b] + (R′O)$_2$P(O)OAcn,[b] in 0.2 M $CDCl_3$ at 25 °C

R	registry no.	R′	registry no.	no catalyst $t_{1/2}$[c]	no catalyst unsym,[a] %	no catalyst sym,[b] %	imidazole (1 molar equiv) $t_{1/2}$	imidazole (1 molar equiv) unsym, %	imidazole (1 molar equiv) sym, %
CH_3	933-43-7	CH_3	67-56-1	25 min		100	fast[d]		100
$(CH_3)_2CHCH_2$	16764-09-3	$(CH_3)_2CHCH_2$	78-83-1	4 h		100	2 min		100
c-C_5H_9	55894-98-9	c-C_6H_9	96-41-3	28 h		100	15 min		100
CH_3		$(CH_3)_2CHCH_2$			54[e]	46		70	30
$(CH_3)_2CHCH_2$		CH_3			83	17		92	8
CH_3		$(CH_3)_2CH$	67-63-0		47	53		69	31
$(CH_3)_2CH$	55894-99-0	CH_3			92	8		98	2
CH_3		c-C_5H_9			46	54		66	34
c-C_5H_9		CH_3			91	9		98	2

[a] Unsymmetrical dialkyl 3-oxo-2-butyl phosphates. [b] Symmetrical dialkyl 3-oxo-2-butyl phosphates. [c] Time at which [CEP-OR] = [(RO)$_2$P(O)OAcn], from ^{1}H NMR spectra when the reagents are mixed in equimolar amounts; ref 26b. [d] Too fast to measure by the present technique. [e] Data from ref 26a; other data from present investigation.

Scheme V



the expected acidity of the equatorial P(5)–OH group.[30c] In this hypothesis, the protonated imidazolyl ligand becomes a relatively strong apicophile, and the isomerization to 8′ is a favorable process.

The rate of elimination of ligand X from the apical position of the oxyphosphorane 8 depends on the nucleofugicity of X. It would be expected that the CEPO ligand is more nucleofugic than the CH_3O ligand on the basis of the usual arguments derived from considerations of the corresponding acid ionization constants: CEP-OH ⇌ CEPO$^-$ + H$^+$ (pK ~ 1.5) vs. CH_3OH ⇌ CH_3O^- + H$^+$ (pK ~ 15). These eliminations of ligand X from oxyphosphorane 8 compete with the elimination of the enolate ligand, whose nucleofugicity is intermediate between the CEPO and CH_3O ligands. Since imidazole is a very weak acid,[41] $C_3H_3N_2H$ ⇌ $C_3H_3N_2^-$ + H$^+$ (pK 14.2), it might be construed that the imidazolyl ligand is weakly apicofugic; however, the group that is eliminated from the oxyphosphorane 8′ (Scheme V) is the neutral imidazole and not its conjugate base, which brings the behavior of the phosphoimidazole **6** in line with that of the pyrophosphate **4**.

From the reversibility of the steps in Scheme IV it follows that the observed product distribution in the reactions under thermodynamic control depends on the stabilities of the CEP-X compounds, **1**, **4**, and **6**, and the stabilities of the corresponding cyclic and acyclic products, **3** and **9** (and the keto tautomer), respectively. Our data[7,42,43] are consistent with the following sequences of decreasing energy contents in these compounds: CEP-OCEP > CEP-IM > CEP-OCH_3 ~ CEP-OR; and (CEPO)(OR)P(O)OAcn > (IM)(OR)P(O)OAcn > (CH_3O)(OR)P(O)OAcn. Consequently, one observes exclusively the products of ring retention from the phosphorylation of alcohols by **4** and **6**, while one observes the products of ring opening from the phosphorylation of alcohols by **1**, although in the latter case the appearance of symmetrical acyclic triesters reflects the intermediate formation of some of the product of ring retention as discussed in the following section.

Effect of Imidazole on the Reaction of Cyclic Enediol Phosphotriesters with Alcohols. Imidazole significantly increases the rate of the reaction of alcohols with cyclic phosphotriesters, CEP-OR. This effect is shown in the first three entries of Table IV, which refer to reactions in which the alcohol and the triester contain the same alkyl group.

Table IV includes a series of reactions in which the alkyl groups in the alcohol and the triesters are different. In those cases symmetrical as well as unsymmetrical dialkyl 3-oxo-2-butyl phosphates are produced according to the following equations:

$$\text{CEP-OR} + \text{R′OH} \rightarrow (\text{RO})(\text{R′O})\text{P(O)OAcn} \quad (1)$$

$$\text{CEP-OR} + \text{R′OH} \rightarrow \text{CEP-OR′} + \text{ROH} \quad (2)$$

$$\text{CEP-OR} + \text{ROH} \rightarrow (\text{RO})_2\text{P(O)OAcn} \quad (3)$$

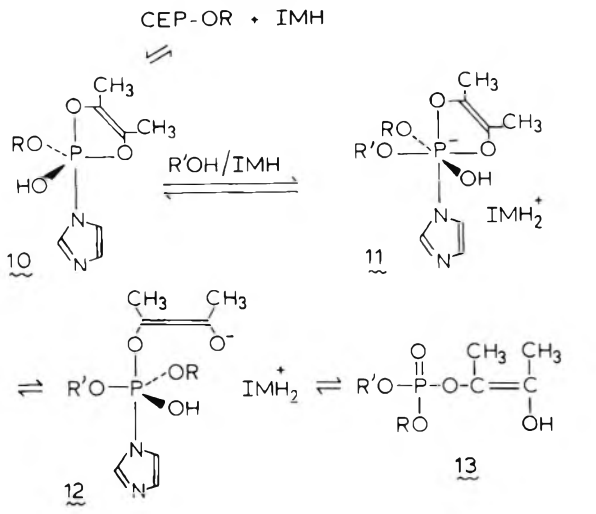
$$\text{CEP-OR′} + \text{R′OH} \rightarrow (\text{R′O})_2\text{P(O)OAcn} \quad (4)$$

Equation 2 corresponds to substitution at phosphorus with ring retention, and the proportion of unsymmetrical to symmetrical triesters reflects the ratio of ring opening to ring retention in these reactions. Several conclusions can be drawn from Table IV.

(a) In the absence of imidazole, the reactions must be under kinetic control, since the proportion of unsymmetrical to symmetrical triesters varies significantly in the pair of reactions CEP-OCH_3 + $(CH_3)_2CHCH_2OH$ and CEP-$OCH_2CH(CH_3)_2$ + CH_3OH. According to Scheme IV, the product composition in both reactions should approach the same value after several cycles of permutational isomerization. Other examples listed in Table IV confirm the generality of this phenomenon. The size of the alkyl group, R, present in the triester, CEP-OR, seems to have the greatest effect on the product composition. When R is relatively small (i.e., CH_3), the amount of symmetrical triester is higher; in fact, the product composition does not vary much in the three reactions of CEP-OCH_3 listed, although the size of the alcohols, R′OH, varies significantly.

(b) Imidazole significantly alters the ratio of the product of ring opening and ring retention in these reactions.[7,26] Further investigation of this phenomenon in the present work confirms its generality. Moreover, in spite of the effects of imidazole on rate and product composition, the heterocycle is not incorporated into the products. A $CDCl_3$ solution containing equimolar amounts of CEP-OR and imidazole is stable for several days[42] (except for a relatively slow demethylation in the case of CEP-OCH_3). Scheme VI provides a reasonable explanation for these observations. In this hypothesis, imidazole adds to the cyclic triester to form the oxyphosphorane **10**; this intermediate is an isomer of 8′ (Scheme V) with a proton in the equatorial oxygen rather than on the apical imidazolyl ligand. For thermodynamic reasons,[42] **10** does not

Scheme VI



undergo further reaction in the absence of alcohols. However, in the presence of alcohols, a P(6) intermediate **11** is generated. This step, P(5) + R'OH ⇌ P(6), could be rate limiting, since the structure of the alcohol has a marked effect on the rate of disappearance of CEP-OR in the reaction CEP-OR + R'OH + [IMH] ⇌ (R'O)(RO)P(O)OAcn. A collapse of the P(6) intermediate (**11**) with ring opening yields a new P(5)' intermediate (**12**) and then the observed acyclic triester (upon enol–keto tautomerization of **13**). The ring-opening step **11** ⇌ **12** accounts for the effect of imidazole on the unsymmetrical/symmetrical triesters shown in Table IV. Other experimental observations in support of the P(6) intermediate hypothesis have been previously offered.[7,26,44,46]

The demonstrated imidazole catalysis of the reaction CEP-OR + R^{1}OH suggests the possibility that imidazole may also catalyze the reaction CEP-IM (**6**) + ROH ⇌ CEP-OR + IMH; i.e., the latter reaction could be autocatalytic. This deduction is, in fact, supported by observations made on the reaction CEP-IM + $(CH_3)_3COH$ ⇌ CEP-OC$(CH_3)_3$ + IMH.

Conclusions

The X-ray analysis of three CEP-X derivatives discloses similar molecular structures in the crystals, in spite of different behavior in reactions with alcohols. These differences can be rationalized in terms of the oxyphosphorane intermediate hypothesis for displacement at P(4) centers. The new structure of the cyclic enediol phosphoimidazole reveals a relatively small shortening of the P–N bond due, possibly, to a modest participation of p–d π bonding. The orientation of the imidazolyl ring in the conformation of the molecule can be accounted for simply on steric grounds, although more subtle stereoelectronic interactions of the type recently discussed in acyl phosphonates[45] are not ruled out.

Registry No.—**6**, 57648-76-7; imidazole, 288-32-4; $C_7H_9O_3N_2P \cdot \frac{1}{2}C_6H_6$, 67145-87-3.

Supplementary Material Available: Table IB, carbon–hydrogen bond distances (Å) and angles (deg); Table VA, positional and thermal parameters for nonhydrogen atoms; Table VB, calculated hydrogen atom positions (3 pages). Ordering information is given on any current masthead page.

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(3) CEP = cyclic enediol phosphoryl or 1,2-dimethylethenylenedioxyphosphoryl. Acn = 3-oxo-2-butyl. IMH = imidazole. P(4), P(5), P(6) = four-, five-, six-coordinate phosphorus.

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(36) The permutational isomerization can occur by the *turnstile rotation* mechanism (ref 37), with the ring as the ligand pair, or by the *pseudorotation* mechanism (ref 38), with ligand HO as the pivot.

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(38) R. S. Berry, *J. Chem. Phys.*, **32**, 933 (1960).

(39) See also: (a) S. Trippett, *Phosphorus Sulfur*, **1**, 89 (1976); (b) K. E. DeBruin and D. M. Johnson, *J. Chem. Soc., Chem. Commun.*, 753 (1975); (c) J. A. Boudreau, C. Brown, and R. F. Hudson, *ibid.*, 679 (1975).

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(41) G. Yagil, *Tetrahedron*, **23**, 2855 (1967).

(42) The pyrophosphate reacts with imidazole rapidly and quantitatively to yield the products of ring retention: CEP-OCEP (**4**) + 2IMH → CEP-IM (**6**) + $CEPO^-$ IMH_2^+. There is no observable ring opening of either the pyrophosphate nor the phosphoimidazole by imidazole, which may reflect a relatively higher energy content of the respective acyclic derivatives, (CEPO)(IM)P(O)OAcn and $(IM)_2P(O)OAcn$. The 3-oxo-2-butyl phosphate

moiety, >P(O)(OAcn), already represents a relatively energy-rich phosphate bond, i.e., an α-ketol or sugarlike phosphate, as shown by the following hydrolysis (see ref 30a): $(CH_3O)_2P(O)(OAcn) + HO^- \rightarrow (CH_3O)_2P(O)O^- + HO\text{-}Acn$; $k_2 = 360$ L mol^{-1} s^{-1} (25 °C, pH 7.7–8.3). Only 5% of the alternate hydrolysis products are observed: $(CH_3O)P(O)(OAcn)O^- + CH_3OH$ (see ref 43).

(43) D. S. Frank and D. Usher, *J. Am. Chem. Soc.*, **89**, 6360 (1967).
(44) F. Ramirez, J. F. Marecek, H. Tsuboi, and H. Okazaki, *J. Org. Chem.*, **42**, 771 (1977).
(45) P. E. Clark, K. D. Berlin, J. Mosbo, and J. G. Verkade, *Phosphorus*, **2**, 265 (1973).
(46) **Note Added in Proof:** It should be emphasized that the P(5) ⇌ P(6) intermediate hypothesis is advanced in connection with reactions of *phosphotriesters* exclusively, and may not be operative in reactions of phosphomonoesters and diesters where other mechanistic alternatives may be favored.

Absolute Configuration of Glycerol Derivatives. 5.[1] Oxprenolol Enantiomers

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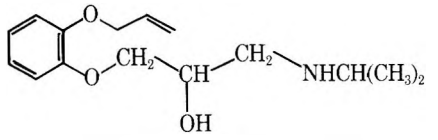
Received April 7, 1978

Synthesis of the optical isomers of oxprenolol [(2*R*)- and (2*S*)-1-(isopropylamino)-3-(*o*-allyloxyphenoxy)-2-propanol ((2*R*)- and (2*S*)-**1**)] was accomplished starting from (2*R*)- and (2*S*)-1-tosyloxypropane-2,3-diol acetonide. Cupra A CD spectra are reported for the intermediate diols [(2*R*)- and (2*S*)-1-(o-allyloxyphenoxy)-2,3-propanediol ((2*R*)- and (2*S*)-**3**)] and the oxprenolol isomers. These spectra were consistent with the previous results, allowing assignment of the absolute configuration based on transitions in the 285 nm region. The NMR spectra of the oxprenolol enantiomers (2*R*)- and (2*S*)-**1** in the presence of a chiral shift reagent, Eu(hfbc)$_3$, and of the amides formed from optically active α-methoxy-α-trifluoromethylphenacetyl chloride (Mosher reagent) were examined. The spectra of the diastereoisomeric amides showed upfield shifts of partial resonances for the isopropyl methyl groups, which result from shielding effects of the aromatic ring of the acyl fragment. The assignments were confirmed by use of specifically deuterated oxprenolol amides.

Oxprenolol [3-(*o*-allyloxyphenoxy)-1-(isopropylamino)-2-propanol (**1**)] is an important β-adrenergic blocking agent of the 3-aryloxy-1-(alkylamino)-2-propanol type. Many of the drugs in this class have significant therapeutic utility in a wide variety of cardiovascular disorders.[2] Oxprenolol and others are used extensively in Europe in the treatment of cardiac arrhythmias, angina pectoris, and hypertension.[3] Some of the related compounds have useful effects in other unrelated disease states.[4]



The absolute configuration of β-adrenergic blocking agents of the 3-aryloxy-1-(alkylamino)propanol type is extremely important in the determination of pharmacological properties and metabolic disposition of these agents. Differences in pharmacological activity of the optical isomers in in vitro assays show differences of up to 50–500-fold between individual enantiomers.[5a–c] Differences in rates of uptake into tissues[5d] and in rates of metabolism[5e] of the individual enantiomers are also observed. Previous work has noted a significant difference in the in vitro pharmacological activity (blockade of isoproterenol induced contraction of bronchial muscle) of the resolved enantiomers of oxprenolol of 10–35-fold,[5c] with the (−)-enantiomer being more active. Although the (−)-enantiomer was likely to have the 2*S* absolute configuration, based on the analogy of the sign of optical rotation, compared to other aryloxypropanolamines, the assignment was not unequivocal. Absolute configuration of enantiomers of many of these agents have been assigned on the basis of experience with the Horeau method.[6] Few instances of establishment of absolute configuration by unequivocal means are reported.[7]

We had previously noted that individual enantiomers of the 3-aryloxy-1-amino-2-propanol nucleus of known chirality can readily be prepared from optically active glycerol derivatives of known absolute configuration, which are obtained from naturally occurring mannitol.[7d] This paper reports extension of the use of this method to the oxprenolol isomers. The results of NMR experiments on these enantiomers in the presence of a chiral shift reagent, Eu(hfbc)$_3$, and on the diastereomeric amides prepared using Mosher reagent and the Cupra A CD spectra of the individual enantiomers of oxprenolol and the intermediate diols are reported.

Synthesis

Preparation of (2*R*)- and (2*S*)-oxprenolol [(2*R*)- and (2*S*)-**1**] was accomplished utilizing (2*R*)-3-tosyloxy-1,2-propanediol acetonide [(2*R*)-**2**] and the corresponding (2*S*)-acetonide [(2*S*)-**2**], respectively. Both are derived from (2*S*)-glyceraldehyde 2,3-acetonide,[7d,8] which is readily available from (2*R*,3*S*,4*S*,5*R*)-mannitol 1,2,5,6-diacetonide.[9] The synthesis (Figure 1) of the (2*R*)-oxprenolol [(2*R*)-**1**] was accomplished by allowing catechol monoallyl ether to react with an equimolar quantity of (2*R*)-3-tosyloxy-1,2-propanediol acetonide [(2*R*)-**2**] and a 1 molar excess of NaOMe (EtOH–H_2O). The resulting intermediate (2*R*)-3-(*o*-allyloxyphenoxy)-1,2-propanediol acetonide was hydrolyzed to afford the corresponding (2*R*)-diol [(2*R*)-**3**]. Diol (2*R*)-**3** was converted to its monotosylate [(2*S*)-**4**][10] using an equimolar quantity of tosyl chloride in pyridine–benzene. Epoxide formation from tosylate (2*S*)-**4** was effected using an equimolar quantity of NaOMe in aqueous MeOH, affording (2*R*)-3-(*o*-allyloxyphenoxy)-1,2-epoxypropane [(2*R*)-**5**].[10] Ring opening with isopropylamine at 110 °C gave the desired (2*R*)-oxprenolol [(2*R*)-**1**]. The synthesis of the (2*S*)-oxprenolol [(2*S*)-**1**] was achieved in an analogous fashion starting with (2*S*)-1-tosyloxy-2,3-propandediol acetonide [(2*S*)-**2**].

The magnitude of the optical rotations of the synthesized enantiomers were very similar to that reported for one of the enantiomers prepared by resolution,[5c] $[\alpha]_D$ +5.4 and −5.7° compared to $[\alpha]_D$ +5.5 ± 0.5°, suggesting that the synthetic processes occur without major racemization. Since none of the reaction steps involve a chiral center, major epimerization would not be expected.

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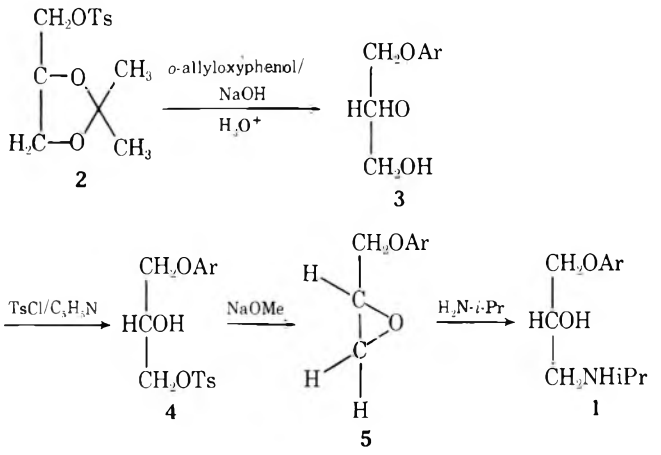


Figure 1.

NMR Experiments

A detailed analysis of the proton NMR spectrum of oxprenolol was made because substantial use of NMR methods was planned for possible determination of enantiomeric purity. Although multiplets were observed in the 60-MHz spectrum of oxprenolol (1), a spectrum with better signal separation of the allyl side chain was obtained at 80 MHz (Figure 2). The propanolamine side chain, however, remained poorly resolved, because of very similar chemical shifts of protons at differently substituted carbons.

In oxprenolol, $H_{2'}$ appears as a ten-peak signal resulting because $J_{2'3'cis} = 2J_{2'1'}$ ($J_{2'3'cis} = 10.2$ and $J_{2'1'} = 5.1$ Hz) and protons at C-1′ behave as a set. Coupling constant $J_{2'3'trans} = 17.2$ Hz. The signals for protons $H_{3'cis}$ and $H_{3'trans}$ are located at δ 5.35 and 5.24, respectively, $J_{gem} = 3.2$ Hz and allylic $J_{3'1'} = 1.4$ Hz. Protons H_1 appear at δ 4.54 as two triplets with couplings $J_{1'3'}$ and $J_{1'2'}$.

The determination of enantiomeric purity using a chiral lanthanide shift reagent has been successfully applied to many compounds especially using tris[3-(heptafluorobutyryl)-*d*-camphorato]europium, Eu(hfbc)$_3$. We had previously used this reagent in LIS spectra for related benzodioxanes[1] and in some other aryloxypropanolamines (unpublished results). At high molar ratios (shift reagent to compound), e.g., 0.60, the aromatic singlet of (2*R*)-oxprenolol [(2*R*)-1] remained as a singlet, whereas using the 2*S* enantiomer the aromatic protons became an unsymmetrical doublet, with one of the signals being identical in chemical shift with that of the aromatic residue of the 2*R* enantiomer. By spiking the 2*S* enantiomer with known amounts of the 2*R* enantiomer (MR = 0.80), addition of 10% 2*R* enantiomer could be readily detected. Conversely, the method is slightly less sensitive, e.g., at about 12–14%, using the *S* enantiomer to spike synthetic 2*R* material (MR = 0.80). Within the limits of this detection method, none of the wrong isomer was found, suggesting that the compounds prepared by chiral synthesis are at least 82% ee (91:9) and probably greater.

An alternative NMR method for determination of enantiomeric purity involved derivatization of amines with optically active α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (Mosher reagent).[12a] Many diastereomeric amides from a wide variety of amine derivatives have been successfully differentiated by NMR[12] and/or GC.[13]

Using 1 equiv of the (−)-Mosher acyl halide, we prepared the diastereomeric amides (as evidenced by a single carbonyl band in the IR at 1634 cm^{-1}) using 2*R* and 2*S* enantiomers of oxprenolol [(2*R*)- and (2*S*)-1] as well as with racemic oxprenolol (1). In the NMR spectra of the amides, the methoxy groups appeared as a series of closely grouped signals rather than as one or two peaks. More notable, however, was the

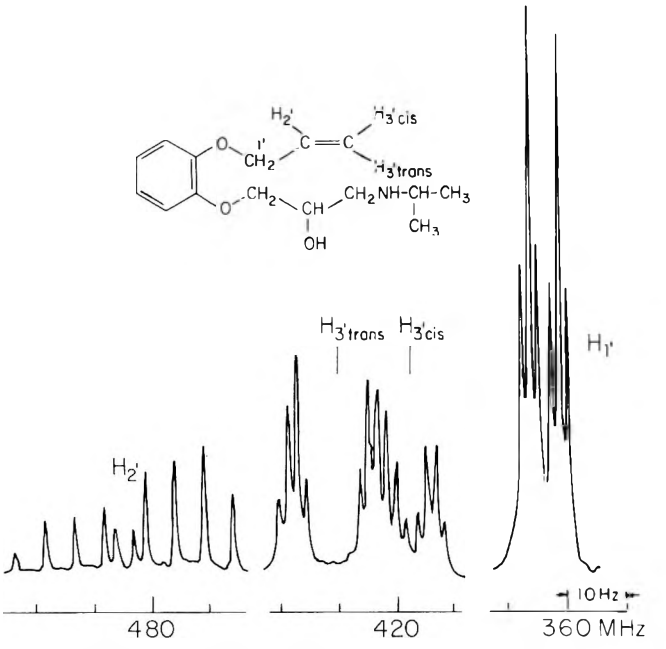


Figure 2. Partial 80-MHz NMR spectrum ($CDCl_3$) of racemic oxprenolol (1).

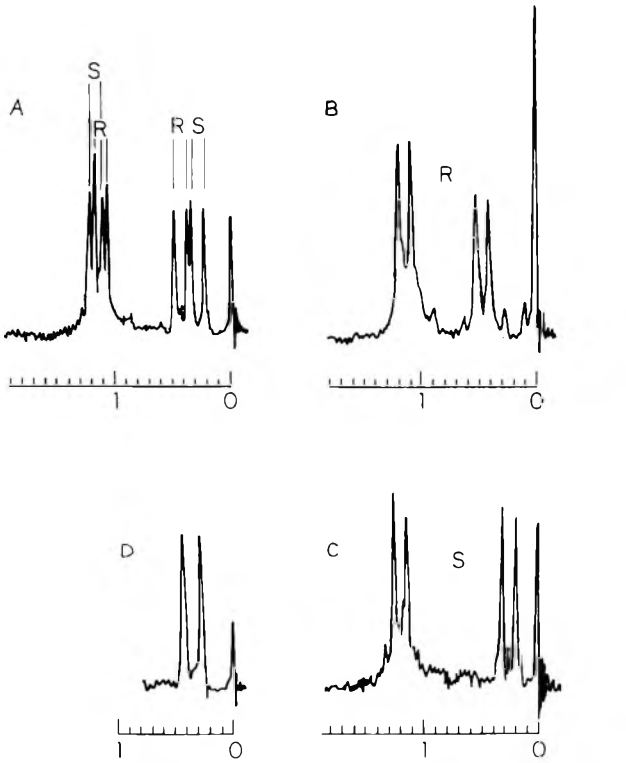
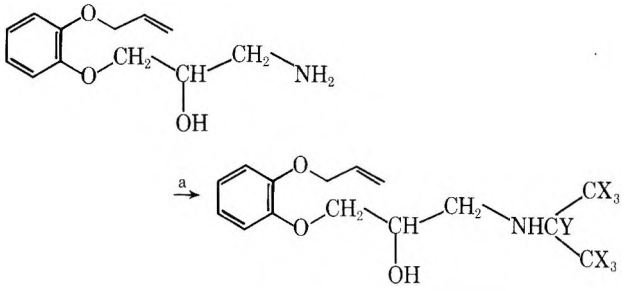


Figure 3. (A) 60-MHz NMR spectra ($CDCl_3$) of (−)-α-methoxy-α-(trifluoromethyl)phenylacetylamide (Mosher reagent) of racemic **1**; (B) (−)-α-methoxy-α-(trifluoromethyl)phenylacetylamide of (2*R*)-**1**; (C) (−)-α-methoxy-α-(trifluoromethyl)phenylacetylamide of (2*S*)-**1**; (D) (−)-α-methoxy-α-(trifluoromethyl)phenylacetylamide of 8 (oxprenolol-*isopropyl*-d_1).

appearance of two very high field doublets in the spectrum of the mixture of diastereomeric amides from *rac*-oxprenolol (1) (Figure 3). The spectra of the amides from the *R*- and *S*-enantiomers each showed one doublet. Signals were noted at δ 0.46 (J = 6.5 Hz) for the *R*-enantiomer and δ 0.32 (J = 6.5 Hz) in the *S*-enantiomer. These signals integrated for approximately two protons each. Additionally, in these spectra the isopropyl methyl groups appeared as doublets at δ 1.14, J = 6.5 Hz, for the *R*-enantiomer and δ 1.19, J = 6.5 Hz, for

the *S*-enantiomer, integrating for less than the expected number of protons. One likely explanation seemed to be that the slow rotation about the amide carbon–nitrogen bond was probably responsible for the observation of two different isopropyl methyl signals with different chemical shifts. However, since the signals were considerably upfield from the normal methyl groups (~0.7 ppm), further characterization and some explanation was required.

Oxprenolol (1) with deuterium substituted in the isopropyl group was prepared to corroborate the assignment of the signals to the methyl peaks. Oxprenolol-*isopropyl*-d_6 (7) and -*isopropyl*-d_1 (8) were prepared by reductive alkylation of deisopropyloxprenolol (6) with acetone-d_6 (or acetone) with sodium borohydride (or borodeuteride).



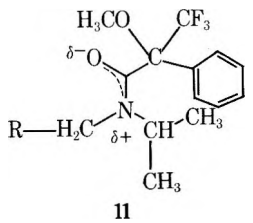
7, X = D; Y = H (a = $CD_3C(=O)CD_3/NaBH$)

8, X = H; Y = D (a = $CH_3C(=O)CH_3/NaBD_4$)

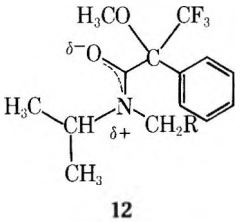
In the NMR spectrum of the mixture of diastereomeric Mosher reagent amides from the oxprenolol-d_6 (7), no methyl group signals were observed. No signals were observed at field strength above 1.5 ppm. In diastereomeric amides from oxprenolol-d_1 (8), upfield doublets became singlets, at δ 0.46 and 0.31. These results confirmed the assignment of these signals to protons from the methyl groups.

The upfield shift must result because these protons lie in a shielding zone of one of the two aromatic rings in the molecule, the catechol ring or the aromatic ring from the Mosher reagent. In order to determine which was responsible, amides were prepared from several acid chlorides including the cyclohexane derivative of Mosher reagent, α-methoxy-α-(trifluoromethyl)-α-cyclohexylacetyl chloride (9). The NMR spectra of benzamide and phenylacetic acid amides of oxprenolol showed no large upfield shifts. The NMR spectrum of the reduced Mosher reagent amide derivative also showed no large upfield signals. These data suggest that the aromatic ring of the Mosher reagent contributes significantly to the observed shielding.

The results are explicable in terms of a shielding effect of the aromatic ring of the phenylacetyl fragment Mosher reagent on the isopropyl methyl groups, principally in one of the conformers of the amide, probably 11. There are two major conformations resulting from isomerism about the carbon–nitrogen bond of the amide (11 and 12).[14] Since the major shielding effect was only noted in α,α-disubstituted phenylacetylamide derivative (Mosher reagent amide), and not in the simpler phenylacetylamide, it seems likely that the substituents at the α carbon aid in shifting the conformational equilibrium toward a conformation like 11, in which the shielding effect is noted. Since no corresponding shift of the



11



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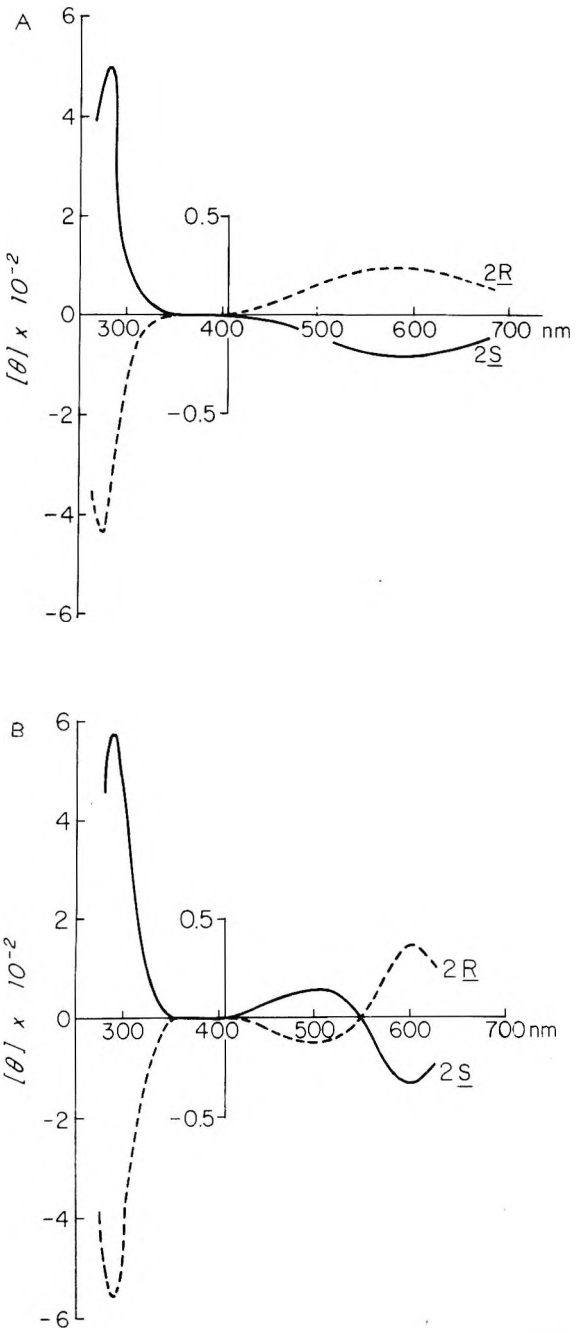

Figure 4. (A) Cupra A CD spectra of diols (2*R*)-3 and (2*S*)-3; (B) Cupra A CD spectra of amino alcohols (2*R*)-1 and (2*S*)-1.

methyl groups of the Mosher reagent diastereomeric amides of propranolol are noted (unpublished observation), it may be that other factors in the molecule also contribute to the population of conformations in the oxprenolol Mosher reagent amide.

Although the upfield signals seem to be the major difference in the diastereomeric amides, their use in determination of optical purity is somewhat limited because these signals result from only one conformation of the amide and do not represent the entire molecule or concentration. However, no extraneous signals were noted to suggest that other diastereoisomers were present, although limits the detection of signals >3% since the Mosher reagent is only 97% pure.

Cupra A Circular Dichroism

Correlation of the Cotton effects observed with chiral 1,2-amino alcohols and 1,2-diols in Cupra A solution has allowed facile determination of absolute configuration in closely

related series of compounds.[7d,15] A weak, long wavelength transition is observed for diols and amino alcohols in Cupra A showing a λ_{max} near 560–580 nm and a stronger, shorter wavelength transition, λ_{max} 280 nm. This latter transition is used more often for the assignment of absolute configuration. *R* enantiomers in these series of aryloxypropanediol derivatives give negative Cotton effects in Cupra A solution at the shorter wavelength and positive Cotton effects at the longer one. *S* enantiomers give mirror image spectra. It has also been shown that amino alcohols in which the amine is secondary give a second weak long wavelength Cotton effect near 500 nm, which is of the same sign as the short wavelength transition at 280 nm.[16] Diols and primary amino alcohols do not exhibit this second long wavelength transition.

Cupra A CD spectra were determined for the synthesized (*R*)- and (*S*)-oxprenolol [(2*R*)- and (2*S*)-**1**] and the corresponding diols [(2*R*)- and (2*S*)-**3**] (Figure 4). The spectra were consistent with previous results. The *R* enantiomers (diol and amine) show Cotton effects [$\epsilon_{277} = -380$ for (2*R*)-**3**, $\epsilon_{288} = 560$ for (2*R*)-**1**] as expected and the *S* enantiomer diol gave transitions of $\epsilon_{277} = +460$ and $\epsilon_{288} = +580$ for (2*S*)-**1**. The other expected bands are also observed (see Figure 4 and Experimental Section). These compounds add to the growing number of examples of aryloxypropanediols and -propanolamines where the Cupra A CD method is useful to assign the absolute configuration.[17]

Further work on other glycerol-related systems related to aryloxypropanol derivatives is in progress.

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 Varian EM-360, T-60, and CFT-20 spectrometers using Me_4Si as internal standard. Notations used in the descriptions are s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Circular dichroism spectra were recorded on a Jobin Yvon Dichrographe R. J. Mark III instrument. Microanalyses were performed by Dr. F. B. Strauss, Oxford, England.

(2*R*)-3-(*o*-Allyloxyphenoxy)-1,2-propanediol [(2*R*)-3]. A solution of 8.75 g (0.162 mol) of NaOMe and 24.30 g (0.162 mol) of catechol monoallyl ether in 40 mL of ethanol and 10 mL of H_2O was added to 24.24 g (0.081 mol) of (2*R*)-3-tosyloxy-1,2-propanediol acetonide [(2*R*)-**2**][7d] and the mixture was refluxed for 24 h. The solution was cooled and solvent was removed by rotary evaporation to yield a dark brown sludge. The residue was dissolved in 200 mL of ether, washed with 5% aqueous NaOH (5 × 100 mL) and water (4 × 100 mL), dried (Na_2SO_4), and evaporated affording 27.88 g of an orange oil, which was determined by NMR to be 72% product. Integration of the area of protons of the tosyl group was used as a measure of remaining starting material. The crude acetonide, 27.88 g (representing 20.00 g, 0.071 mol), in a mixture of 50 mL of acetone and 10 mL of aqueous 2 N HCl, was refluxed for 5 h. Evaporation of the solvent afforded an oil which was crystallized repeatedly from ether (charcoal), affording diol (2*R*)-**3**: 6.83 g (35% overall yield); mp 82–83 °C; $[\alpha]^{20}_D$ −7.4° (c 0.10, absolute EtOH); CD (c 0.10 Cupra A) $[\theta]_{522}$ +17, $[\theta]_{412}$ 0, $[\theta]_{357}$ 0, $[\theta]_{277}$ −380; IR (KBr) 3.03, 3.41, 6.30, 6.66, 6.90, 7.98, 8.20, 8.91, 9.48, 9.66, 10.66, 10.92, 13.69 μm; NMR ($CDCl_3$) δ 6.97 (s, 4, ArH), 5.76–6.63 (m, 1, $H_{2'}$), 5.06–5.73 (m, 2, $2H_{3'}$), 4.57 (d, 2, $2H_{1'}$), 4.08 (s, 3, H_2, $2H_3$), 3.79 (s, 2, $2H_1$), 3.21 (s, 2, OH, exchangeable). Anal. Calcd: C, 64.27; H, 7.19. Found: C, 64.26, H, 7.18.

(2*S*)-3-(*o*-Allyloxyphenoxy)-1,2-propanediol [(2*S*)-3]. Diol (2*S*)-**3** was prepared from (2*S*)-3-tosyloxy-1,2-propanediol acetonide [(2*S*)-**2**][7d] and catechol monoallyl ether by a procedure analagous to that for the preparation of (2*R*)-**3**. Hydrolysis of the intermediate acetonide afforded (2*S*)-**3** in 28% overall yield: mp 82–83 °C; $[\alpha]^{20}_D$ = +7.7° (c 0.094, absolute EtOH); CD (c 0.010, Cupra A), $[\theta]_{522}$ −16, $[\theta]_{412}$ 0, $[\theta]_{357}$ 0, $[\theta]_{277}$ +460. Anal. Calcd: C, 64.27; H, 7.19. Found: C, 64.11, H, 7.24.

(2*S*)-3-(*o*-Allyloxyphenoxy)-1-(*p*-toluenesulfonoxy)-2-propanol [(2*S*)-4].[10] *p*-Toluenesulfonyl chloride, 4.64 g (0.024 mol), in 75 mL of anhydrous benzene was added slowly (9 h) to a cold (0 °C) solution of 5.44 g (0.024 mol) of diol (2*R*)-**3** in 20 mL of anhydrous pyridine and the mixture stirred for 5 days at room temperature. The mixture was diluted with 200 mL of Et_2O, filtered, washed with 1 N HCl (5 × 100 mL) and H_2O (5 × 100 mL), and dried (Na_2SO_4) and solvent was evaported to afford 8.07 g (88% yield) of an orange oil which was used without further purification: IR 2.82, 3.25, 3.39, 6.27, 6.68, 6.90, 7.34, 7.96, 8.52, 8.90, 9.12, 10.03, 10.07, 12.03 μm; NMR ($CDCl_3$) δ 7.79 and 7.22 (two d, *J* = 5 Hz, tosyl ArH), 6.91 (s, 4, ArH), 6.53–6.59 (m, 1, $H_{2'}$), 5.64–5.03 (m, 2, $2H_{3'}$), 4.52 (d, 2, $2H_{1'}$), 3.63–4.39 (m, 5, $2H_1$, H_2, $2H_3$), 3.23 (s, 1, OH), 2.41 (s, 3, $ArCH_3$).

(2*R*)-3-(*o*-Allyloxyphenoxy)-1-(*p*-toluenesulfoxy)-2-propanol [(2*R*)-4].[10] Tosylate (2*S*)-**4** was prepared from (2*S*)-**3** and *p*-toluenesulfonyl chloride by a procedure analagous to that for preparation of (2*S*)-**4**, affording (2*R*)-**4** in 87% crude yield, which was used without further purification.

(2*R*)-1-(Isopropylamino)-3-(*o*-allyloxyphenoxy)-2-propanol [(2*R*)-1]. A solution of 539 mg (10.0 mmol) of NaOMe in 12 mL of 80% MeOH was added to 3.77 g (10.0 mmol) of tosylate (2*S*)-**4** and the solution was refluxed for 2 h. The MeOH was evaporated, 50 mL of ether was added, and the precipitated NaOTs was removed by filtration. The ether was evaporated affording 2.50 g of a yellow oil, which was 42% of the desired epoxide (2*R*)-**5** as determined by NMR. The NMR determination was done by comparison integration of the signal of tosyl aromatic protons with other aromatic protons. Crude epoxide (2*R*)-**5** was used without further purification.

A solution of 2.58 g of crude epoxide [representing 733 mg (3.4 mmol) of pure epoxide] in 15 mL of isopropylamine was sealed in a Parr bomb and heated at 110 °C for 16 h. After cooling, the resulting liquid was evaporated and dissolved in 50 mL of 2 N HCl. The aqueous acidic solution was washed with ether (3 × 50 mL), made alkaline with solid NaOH, and extracted with ether (3 × 50 mL). The combined ether extracts were dried (Na_2SO_4) and evaporated, affording a brown oil which solidified. Repeated crystallization afforded 800 mg (84% yield) of (2*R*)-**1**: IR (KBr) 2.92, 3.42, 6.30, 6.67, 6.92, 7.99, 8.24, 8.93, 9.81, 13.62 μm; NMR ($CDCl_3$, Me_4SI) δ 6.97 (s, 4, ArH), 6.53–5.73 (m, 1, $H_{2'}$), 5.66–5.06 (m, 2, $2H_{3'}$), 4.58 (d, 2, $2H_{1'}$), 4.05 (s, 3, H_2, $2H_3$), 3.13–1.19 (m, 5, $2H_1$, H_α, NH, OH), 1.09 (d, *J* = 6 Hz, $2CH_3$); $[\alpha]^{20}_D$ +5.8° (lit. $[\theta]_D$ +5.5 ± 0.5°); CD (c 0.10, Cupra A) $[\theta]_{700}$ +14, $[\theta]_{600}$ +36, $[\theta]_{540}$ 0, $[\theta]_{500}$ −10, $[\theta]_{430}$ 0, $[\theta]_{360}$ 0, $[\theta]_{330}$ −90, $[\theta]_{288}$ −560, $[\theta]_{280}$ 0.

At 80 MHz the NMR spectrum ($CDCl_3$) was done on racemic **1**; a complete analysis of the allyl side chain revealed: δ 6.05 (2q, $H_{2'}$, $J_{2'1'}$ = 5.1, $J_{2'3'cis}$ = 10.2, $J_{2'3'trans}$ = 17.2 Hz), 5.35 and 5.24 (m, $H_{3'trans}$ and $H_{3'cis}$, $J_{3'trans2'}$ = 17.2, J_{gem} = 3.2, $J_{3'1'}$ = 1.4, $J_{3'cis2'}$ = 10.2 Hz), 4.54 (2t, $2H_{1'}$, $J_{1'2'}$ = 5.1, $J_{1'3'}$ = 1.4 Hz). Anal. Calcd: 67.89; H, 8.74; N, 5.28. Found: C, 67.83; H, 8.71; N, 5.30.

(2*S*)-1-(Isopropylamino)-3-(*o*-allyloxyphenoxy)-2-propanol [(2*S*)-1]. The 2*S* enantiomer (2*S*)-**1** was prepared from tosylate (2*R*)-**4** in a manner analagous to the preparation of (2*R*)-**1**, in 24% overall yield: $[\theta]_{700}$ −13, $[\theta]_{600}$ −34, $[\theta]_{540}$ 0, $[\theta]_{500}$ +13, $[\theta]_{430}$ 0, $[\theta]_{360}$ 0, $[\theta]_{320}$ +85, $[\theta]_{288}$ +580, $[\theta]_{280}$ 0. Anal. Calcd: C, 67.98; H, 8.74; N, 5.28. Found: C, 68.01, H, 8.75; N, 5.26.

3-(*o*-Allyloxyphenoxy)-1,2-epoxypropane (5). Epoxide **5**, prepared according to a literature method,[18] was obtained in 41% yield: bp 117–119 °C (0.4 mm) [lit. bp 145–157 °C (11 mm)]; NMR (80 MHz, $CDCl_3$) δ 6.98 (s, 4, ArH), 4.23 and 3.99 (2 q, H_{3a} and H_{3b}, J_{gem} = 11.3, $J_{3a,2}$ = 3.7, $J_{3b,2}$ = 5.1 Hz), 3.34 (11-peak multiplet, H_2, $J_{2,3a}$ = 3.7, $J_{2,3b}$ = 5.1, $J_{2,1cis}$ = 4.2, $J_{2,1trans}$ = 2.7 Hz), 2.86 and 2.72 (2q, H_{1cis} and H_{1trans}, J_{gem} = 5.0, $J_{1cis,2}$ = 4.2, $J_{1trans,2}$ = 2.7 Hz). Cis and trans refer to the relationship between H_2 and protons at C_1 of the epoxide. The allyl side chain appeared very similar to the one in oxprenolol, discussed for compound (2*R*)-**1**: δ 6.05 (2q, $H_{2'}$, $J_{2'1'}$ = 5.1, $J_{2'3'cis}$ = 10.1, $J_{2'3'trans}$ = 17.2 Hz), 5.35 and 5.24 (m, $H_{3'trans}$ and $H_{3'cis}$, $J_{3'trans2'}$ = 17.2, J_{gem} = 3.2, $J_{3'1'}$ = 1.4, $J_{3'cis2'}$ = 10.2 Hz), 4.56 (2t, $2H_{1'}$, $J_{1'2'}$ = 5.1, $J_{1'3'}$ = 1.4 Hz).

1-Amino-3-(o-Allyloxyphenoxy)-2-propanol (6). Into a 200-mL solution of 2-propanol previously saturated with NH_3 at −70 °C was added 1.0 g (4.8 mmol) of 3-(o-allyloxyphenoxy)-1,2-epoxypropane (**5**). The mixture was stirred at room temperature, lightly stoppered, for 24 h. Warming (hood) removed excess NH_3, and the remaining solvent was rotary evaporated. The residue was crystallized (hexane–2-propanol), affording 0.81 g (62%) of **6**: mp 80–82 °C; NMR ($CDCl_3$) δ 6.87 (s, 4, ArH), 6.30–5.67 (m, 1, $H_{2'}$), 5.53–5.07 (m, 2, $2H_{3'}$), 4.63–4.43 (m, 2, $2H_{1'}$), 3.97 (s, 3, $2H_3$, H_2), 3.0–2.73 (s, 3, OH, NH_2), 2.98–2.75 (m, 2, $2H_1$).

1-(β,β,β,β′,β′,β′-Hexadeuterioisopropylamino)-3-(o-allyloxyphenoxy)-2-propanol (Oxyprenolol-*isopropyl*-d_6) (7).[19] Amino alcohol **6**, 500 mg (2.2 mmol), in 10 mL of absolute EtOH was warmed to effect solution. Acetone-d_6, 1.20 mL (4.4 mmol, Stohler > 99%), was added in two portions. After the first 600 mg of acetone, $NaBH_4$ (210 mg, 5.5 mmol) was added slowly in three portions. Five minutes after the third portion, the entire set of borohydride additions were repeated after adding the second portion of acetone-d_6. After 20 min,

20 mL of H_2O was added and the mixture was extracted with ether (1 × 75 mL, 3 × 50 mL). The combined ether extracts were washed with 3 × 50 mL of 5% aqueous NaOH and H_2O and dried ($NaSO_4$), and the solvent was evaporated, affording a yellow oil. Crystallization from 2-propanol–hexane afforded 120 mg of **7**. Evaporation of the filtrate and crystallization from hexane afforded an additional 200 mg of **7**: mp 72–74.5 °C; total yield 54%; MS (EI, 70 eV) *m/e* 271 (35, M^+), 253 (30, M − CD_3), 227 (100, M − CH_2O), 150 (85, $C_9H_{10}O_2$).

1-(α-Deuterioisopropylamino)-3-(*o*-allyloxyphenoxy)-2-propanol) (Oxyprenolol-*isopropyl*-d_1) (8). Amino alcohol **6**, 200 mg (0.90 mmol), was dissolved in 5.0 mL of absolute EtOH and 260 mg (4.5 mmol) of acetone was added. Over a 3-min period, 190 mg (4.5 mmol) of $NaBD_4$ (Stohler, >99%) was added with stirring. After 5 min, an additional 260 mg (4.5 mmol) of acetone was added and the mixture was stirred for 45 min.

The pH was lowered to 5 with aqueous HCl, and the alcohol was evaporated. The residue was partitioned between aqueous 5% KOH and ether. The ether layer was washed with 5% aqueous KOH (3 × 5 mL), dried (Na_2SO_4), and evaporated, affording 163 mg of **8** (67% yield) as a yellow oil which solidified.

α-Methoxy-α-(trifluoromethyl)-α-cyclohexylacetyl Chloride (10). To a solution of 1.0 g (4.3 mmol) of (−)-α-methoxy-α-(trifluoromethyl)-α-phenylacetic acid (Aldrich) in 40 mL of 95% EtOH with 0.5 mL of HOAc was added 500 mg of 5% $RhAl_2O_3$. The mixture was hydrogenated at 45 psig for 22 h, after which time the required 3 equiv of hydrogen had been taken up. Filtration (Celite) and evaporation afforded 1.07 g of acid **9** (100% yield) as a white solid, mp 103–105 °C, which could be distilled: bp 130 °C (3 mm); *m/e* 241 (MH^+); IR (KBr) 2.89, 3.41, 5.83, 7.82, 8.63, 8.83, 9.94, 10.23 μm; NMR ($CDCl_3$) δ 10.60 (s, br, 1, COOH), 3.53 (m, 3, OCH_3), 2.77–0.90 (m, 11, cyclohexane ring).

The acid chloride was prepared similar to the method of Mosher[12] by refluxing 250 mg (1.04 mmol) of acid **9** for 23 h in 4 mL of $SOCl_2$. Evaporation of the excess $SOCl_2$ under nitrogen afforded an oil (**10**), which was dissolved in methylene chloride and used for amide preparation.

Amides for NMR Experiments. The following procedure is illustrative of the method used for amines (2*R*)-**1**, (2*S*)-**1**, and racemic **1**. To a solution of **1**, 100 mg (0.38 mmol), in 2 mL of 1,2-dichloroethane and 0.5 mL of NEt_3 was added to 0.8 mL of a 4.9 M solution of (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.39 mmol) in 1,2-dichloroethane. The mixture was refluxed for 3 h. Thin-layer chromatography (silica gel G, 250 μm, developed in $CHCl_3$/EtOAc/MeOH/NH_4OH, 40:12:20:0.5) was run and no starting oxprenolol (R_f 0.56) was present. The solvent was evaporated, affording a yellow oil with some crystalline NEt_3·HCl present. The mixture was transferred to a 10-mL centrifuge tube with 3 mL of ether and 2 mL of 1 N HCl. The HCl layer was removed with a pipette, and the ether layer was washed with 2 mL of 5% NaOH and dried ($MgSO_4$). Removal of ether gave an oil, 141 mg (77%) (carbonyl 1634 cm^{-1}), which was used for NMR analysis. The individual enantiomers (2*R*)-**1** and (2*S*)-**1** were subjected to similar procedures using the same acid chloride. In subsequent runs, benzoyl chloride, phenylacetyl chloride, or acid chloride **10** was used to prepare amides of **1** for NMR analysis.

Acknowledgment. This work was supported in part by Research Grant GM 20357 from the National Institute of General Medical Sciences, by the Edwin Leigh Newcombe Memorial Fellowship from the American Foundation for Pharmaceutical Education to T.R.B. and by a Career Development Award (5-K04-GM 70,023) to W.L.N. from NIGMS, 1971–1976.

Registry No.—(±)-**1**, 22972-98-1; (2*R*)-**1**, 31576-00-8; (2*S*)-**1**, 22972-96-9; **1** α-methoxy-α-(trifluoromethyl)phenylacetylamide derivative, 66901-81-3; (2*R*)-**1** (−)-α-methoxy-α-(trifluoromethyl)-phenylacetylamide derivative, 66966-17-4; (2*S*)-**1** (−)-α-methoxy-α-(trifluoromethyl)phenylacetylamide derivative, 66966-18-5; (2*R*)-**2**, 23788-74-1; (2*S*)-**2**, 23735-43-5; (2*R*)-**3**, 66901-82-4; (2*S*)-**3**, 66901-83-5; (2*R*)-**4**, 66901-84-6; (2*S*)-**4**, 66901-85-7; (2*R*)-**5**, 66966-19-6; (2*S*)-**5**, 66966-20-9; (±)-**5**, 34183-66-9; (±)-**6**, 51469-71-7; (±)-**7**, 66901-86-8; (±)-**8**, 66901-87-9; **8** α-methoxy-α-(trifluoromethyl)-phenylacetylamide derivative, 66901-88-0; **9**, 66901-89-1; **10**, 66901-90-4; catechol monoallyl ether, 1126-20-1; *p*-toluenesulfonyl chloride, 98-59-9; 2-propanol, 67-63-0; (−)-α-methoxy-α-trifluoromethyl)-α-phenylacetic acid, 17257-71-5; (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 39637-99-5.

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New Nitrogen Bases with Severe Steric Hindrance Due to Flanking *tert*-Butyl Groups. *cis*-2,6-Di-*tert*-butylpiperidine. Possible Steric Blocking of Olfaction

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Received March 20, 1978

New severely hindered nitrogen bases, 2,6-di-*tert*-butyl-1,4-dihydropyridine (**2**), 2,6-di-*tert*-butyl-3,4-dihydropyridine (**3**), 2,6-di-*tert*-butyl-3,4,5,6-tetrahydropyridine (**5**), *cis*-2,6-di-*tert*-butylpiperidine (**6**), and a novel endoperoxide, 1,5-di-*tert*-butyl-8-aza-6,7-dioxabicyclo[3.2.1]octane (**7**), were obtained by lithium metal reduction of 2,6-di-*tert*-butylpyridine (**1**). Dihydropyridine **2** tautomerizes to **3** in deuteriochloroform at 38 °C. Pyridine **1** loses its characteristic "2,6-dimethylpyridine-like" odor upon silica gel column chromatography. The significance of this observation is discussed.

The great value in organic synthesis of sterically hindered bases[1] has recently become more and more apparent. Their unique ability to abstract protons in reaction media containing sites intrinsically more reactive toward nucleophilic attack has allowed the direct generation of a wide variety of carbanionic species. Alkylations, acylations, and carboxylations employing such carbanions are too numerous to cite.[2]

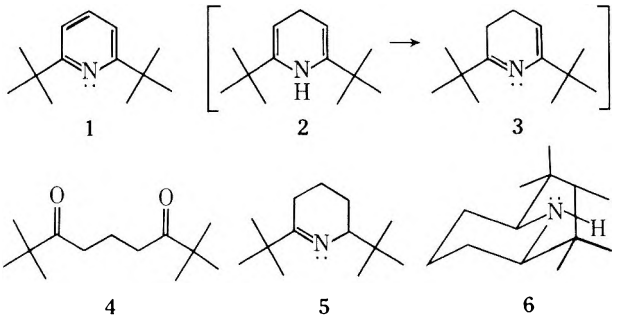
Steric inhibition of competing reaction routes has permitted the strong but severely hindered base lithium 2,2,6,6-tetramethylpiperidide to be used as proton abstracter in the generation of various benzyne and carbene (or carbenoid) species.[3] The Hünig base ethyldiisopropylamine[4] has been used as proton-specific base in a direct synthesis of di-*tert*-butyl ether by O-alkylation of *tert*-butyl alcohol with *tert*-butyl cation.[5]

Sterically hindered amines are routinely used as precursors of stable nitroxyl radicals employed as ESR probes in biologically oriented studies[6] and are also of interest as ganglionic blocking agents in the treatment of hypertension.[7] It has been suggested that "the degree of shielding of the basic nitrogen atom by substituents on the adjacent carbon atoms is the primary factor controlling ganglionic blocking activity".[7c] Sterically hindered amines have also been used to protect polypropylene from photodegradation.[8]

However, the use of sterically hindered bases to favor deprotonation at sterically more accessable sites relative to less accessable sites has met with very limited success. Bartsch and co-workers have clearly delineated the effects of steric hindrance and base strength on orientation in base-promoted eliminations of 2-substituted butanes.[9] Even the most severely hindered bases studied (including the potassium salts of tricyclohexylcarbinol, tri-2-norbornylcarbinol, and 1,1-di-*tert*-butylnonadecanol) yielded less than 30% 1-butene in the butene mixture produced upon reaction with 2-iodobutane in Me_2SO at 50 °C.[9b,c] The use of Corey–Pauling–Koltun space-filling models indicates that *existing bases are just not sterically hindered enough to effectively distinguish between protons at C-1 and C-3 in the 2-halobutanes.*

Results and Discussion

With the aim of extending the already successful applications of severely hindered bases and the future goal of simple, direct "Hoffmann orientation" control in base-promoted elimination reactions, we have synthesized bases **2, 3, 5,** and **6** in a preparative approach to these problems. They and their common precursor, 2,6-di-*tert*-butylpyridine[10] (**1**), share the feature of having two *tert*-butyl groups flanking the basic nitrogen. All of these bases are water-insoluble oils which readily dissolve in aqueous acid. The bulky *tert*-butyl groups effectively limit access to the basic lone-pair electrons since they are held in the proper orientation by a six-membered ring



1 **2** **3**

4 **5** **6**

incorporating the nitrogen and both α carbons. The use of space-filling models clearly shows that in these species the basic site is located at the bottom of a deeper "well" than in such bases as 2,2,6,6-tetramethylpiperidine, and indeed in all the great variety of sterically hindered bases previously studied,[2-9,11] including the ganglionic blocker 1,2,2,6,6-pentamethylpiperidine.[7b,c] The great magnitude of the steric attenuation of nucleophilicity of **1** was demonstrated by the observation that it could be N-methylated only at very high pressures (5000–6000 atm).[12]

Reaction of **1** with 2 to 7 molar equiv of Li in NH_3 with excess *t*-BuOH as the proton source[13] yielded mixtures of **2** and **3** (various ratios, up to 60% **2**). These tautomeric dihydropyridines were identified by 60 MHz ^1H NMR spectroscopy and also by hydrolysis of such mixtures to the novel diketone 2,2,8,8-tetramethyl-3,7-nonanedione (**4**). Mixtures of **2** and **3** underwent tautomerization over a period of several hours to greater than 98% **3** when present at about 40% total concentration of **2** and **3** in $CDCl_3$ at 38 °C (as observed by ^1H NMR). The greater stability of the 3,4-dihydropyridine is possibly due to relief of steric compression strain present in the 1,4-dihydropyridine. This is not an argument that the N lone pair in **3** occupies less space than the N–H group in **2** since **3** must have a quite twisted conformation. The bis(vinyl)-amine structure has been shown for the parent 1,4-dihydropyridine,[14] but only postulated (30 years ago) for its 2,6-dimethyl derivative on the basis of the isolated hydrolysis product, heptane-2,6-dione.[15] In any case **3** appears to be the only observed 3,4-dihydropyridine[16] apart from earlier examples having additional oxygen or nitrogen substitution at the 2 position[17] (resonance stabilization of the carbon–nitrogen double bond). The rearrangement of **2** to **3** clearly illustrates the tautomerization process that probably accounts for the often observed Birch reduction of aromatic species past the 1,4-dihydro stage.[13]

Silica gel column chromatography (distilled pentane–diethyl ether gradient elution) of 2.00 g of a product thought by 60 MHz ^1H NMR analysis to consist of a 1 to 3 mixture of **2** to **3** together with about 6 to 8% of the starting pyridine **1**

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yielded 1.64 g of pure diketone **4** by adventitious hydrolysis and 0.137 g of a rapidly eluted compound having a 60 MHz ^{1}H NMR spectrum identical to that of precursor **1**. This liquid possessed only a faint "hydrocarbon-like" odor and no trace of the "lutidine-like" odor of all samples of **1** not subjected to silica gel column chromatography. Its thin layer chromatographic behavior and solubility in aqueous acid were indistinguishable from the corresponding properties of other samples of **1**. The absence in **1** of a lutidine-like odor[18] and the observation that 4,5-dimethylacridine lacks the severe lachrymatory and skin irritating properties of acridine itself[11] may both be due to steric blocking of coordination to relatively large electron-pair acceptors in the tissues affected. Possibly a transition metal serves in the olfaction of certain functional groups. Aliphatic amines seem highly resistant to the "steric masking" observed for **1** but these stronger bases are very likely detected as their conjugate acids at physiological pH.

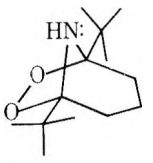
Reaction of **1** in ammonia with 5 molar equiv of Li and only 1 molar equiv of *t*-BuOH (insufficient to protonate all the strongly basic species generated) yielded a mixture from which successive vacuum distillation and silica gel column chromatography provided a 46% yield of pure 2,6-di-*tert*-butyl-3,4,5,6-tetrahydropyridine (**5**). This imine has its sp^2 hybridized nitrogen lone pair electrons enormously hindered by the flanking *tert*-butyl groups and can therefore be expected to show exceptional resistance to any potential coordinating metal or Lewis acid other than a proton.

Reaction of **1** in 1,2-ethanediamine[19] at 90 °C (oil bath temperature) with 18 molar equiv of concurrently added Li and *t*-BuOH gave a product whose ^{1}H NMR spectrum showed no peaks below δ 2.25 except for those due to the presence of 5 to 7% of imine **5**, the separation of which proved difficult. In the hope of carboxylating the conjugate base of the latter (and removing the expected zwitterionic imino acid side product by subsequent aqueous extraction), the procedure was modified to include the addition of 50 to 100 molar equiv of solid CO_2 to the cooled reaction mixture.[20] The resulting products, after aqueous extraction, drying, and evaporation of the volatile components, exhibited an ^{1}H NMR spectrum virtually identical to that of a subsequently prepared analytical sample of **6**. Vacuum distillation provided an 86% yield of the pure liquid *cis*-2,6-di-*tert*-butylpiperidine.

All spectral data are consistent with the assignment of the cis configuration to **6**. In view of proposed mechanisms[13] for Lithium amine reductions, in particular the configuration determining protonation step, the highly strained trans configuration would not be expected. Reduction of 2,6-dimethylpyridine with sodium in refluxing ethanol was reported to yield *cis*- and *trans*-2,6-dimethylpiperidine in a 74/26 ratio.[21] If one assumes staggered *tert*-butyl rotamers as shown for **6**, equatorial NH would have two additional peri CH_3/H interactions and axial NH would have two additional syn-axial interactions relative to piperidine itself, the conformational preference of which is clearly quite small, although controversial.[22] Thus the additional conformational interactions in **6** relative to piperidine appear to be equal with respect to the CH_3/NH and CH_3/N lone pair interactions, and the NH axial–equatorial equilibrium may be similar to that in the parent amine.

Uniquely hindered secondary amine **6** exhibits a tiny, barely detectable absorption at about 3375 cm^{-1} in its infrared spectrum (neat). However, the Raman spectrum (Ar laser, 514.5 nm) of neat **6** shows two separate peaks at 3376 and 3308 cm^{-1} with relative band area ratio intensities of about 3.0 to 1.0 at 20 °C. The more intense, high frequency Raman band at 3376 cm^{-1} may be due to equatorial NH stretching.[22] Prominent low-frequency CH stretching bands (expected for the axial lone pair conformation) are observed at 2774 and 2715 cm^{-1} in the Raman spectrum of **6**, and corresponding Bohlmann bands[23] are seen in its infrared spectrum. The smaller of the two Raman NH stretching bands (at 3308 cm^{-1}) may then be due to axial NH stretching, but confirmation of these tentative assignments must await further study.

Analysis of small crystals that appeared in the neck of a rotary evaporator during work-up of one of the NH_3/Li reaction products indicated the absence of vinyl protons and an apparent mass spectral parent peak of *m/e* 195, corresponding to an isomer of imine **5**. An initially considered bicyclic *cis*-di-*tert*-butylaziridine was ruled out when trial reactions led to the production of this compound in improved yield: Its microanalysis corresponded to $C_{13}H_{25}NO_2$ and its mass spectrum revealed a tiny parent peak at *m/e* 227. The downfield ^{13}C NMR peak at 102.7 ppm (bridgehead carbons) and all the other data now seem consistent only with the "ozonide-like" endoperoxide 1,5-di-*tert*-butyl-8-aza-6,7-dioxabicyclo[3.2.1]octane (**7**). Apparently a precursor adds dioxygen



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and readily eliminates it upon mass spectral fragmentation. Work is in progress to see if the precursor is the aziridine with compressed *cis*-di-*tert*-butyl groups considered initially.

Experimental Section

General. All chemicals were anhydrous reagent grade and used as supplied unless otherwise stated. Precursor **1** was used as received from Willow Brook Labs., Inc., Waukesha, Wis. Lithium (Alfa, 1/8 in. wire) contained 0.01% sodium. Ammonia vapor was passed through a 2 × 40 cm column of sodium hydroxide pellets prior to condensation. Baker silica gel (60–200 mesh) was used for column chromatography. Pentane was distilled and oxacyclopentane was distilled from lithium aluminum hydride and stored under nitrogen. Fisher 1,2-ethanediamine was heated with sodium at 85–90 °C for 48 h, distilled, and stored under nitrogen.

All reaction vessels used in the lithium reductions were flushed with nitrogen, but the nitrogen source was disconnected prior to addition of the lithium. Appropriate reflux condensers equipped with calcium chloride drying tubes were employed. Teflon-coated magnetic stirring bars were used except in the preparation of **6** which required an all-glass mechanical stirrer. Syringe techniques were used whenever possible.

Proton magnetic resonance spectra were recorded on a Varian A-60A spectrometer using deuteriochloroform with internal tetramethylsilane. Carbon and nitrogen NMR spectra were obtained in the Fourier transform mode on a JEOL PS/PFT-100 spectrometer in hexadeuteriobenzene taken as 128.5 ppm. Raman spectra were obtained on a Spex Industries Model 1401 spectrometer using an argon laser at 514.5 nm. Infrared spectra were recorded on a Perkin-Elmer infracord. Mass spectra were recorded on an AEI Model MS-9 spectrometer. Melting points were measured on a Mel-Temp apparatus and are uncorrected. Analyses were performed by Schwartzkopf Microanalytical Laboratories, Woodside, N.Y.

2,6-Di-*tert*-butyl-1,4-dihydropyridine (2) and 2,6-Di-*tert*-butyl-3,4-dihydropyridine (3). A solution of 9.56 g (50 mmol) of **1** in 50 mL (530 mmol) of dry *t*-BuOH was added to 100 mL of freshly condensed ammonia. Lithium (0.763 g, 110 mmol) was added in 16 approximately equal-sized pieces over a 10-min period, and after allowing the resulting mixture to gently reflux for another 60 min, 8.02 g (150 mmol) of ammonium chloride was added in portions. A water bath (40 °C) was used to evaporate the ammonia and 300 mL of diethyl ether was then added to the residue. The resulting ether solution was filtered, shaken with anhydrous sodium sulfate, filtered again, and evaporated under vacuum to yield 9.25 g of **2** and **3** (96%, crude). Analysis by 60 MHz ^{1}H NMR indicated the presence of a 3 to 2 ratio of **2** to **3** with about 15% of **1** remaining. **2**: δ 1.09 (s, 6 CH_3), 2.91 (t, J = 3.4 Hz, CH_2), 4.22 (m, 2 CH=), 4.33 (br s, NH). **3**: δ 1.10 (s, 3 CH_3), 1.15 (s, 3 CH_3), 1.97 (m, CH_2CH_2), 5.16 (m, CH=).

A 0.238-g portion of this product mixture was dissolved in 5.0 mL of 10% HCl and the resulting solution was allowed to stand at 25 °C

for 24 h. The resulting products were shaken with 20 mL of diethyl ether and 15 mL of water and the ether extract was washed, dried ($MgSO_4$), and evaporated under vacuum to yield 0.219 g of an oil consisting of **4** together with about 10% of **1** (60 MHz ^1H NMR analysis).

2,2,8,8-Tetramethyl-3,7-nonanedione (4). A 2.00-g portion of a product mixture thought by ^1H NMR spectroscopic analysis to consist of a 1 to 3 ratio of **2** to **3** together with 6 to 8% of **1** was subjected to silica gel column chromatography using a 0 to 10% diethyl ether gradient in distilled pentane to yield, in order of elution: (a) 0.137 g of pure **1** having only a faint "hydrocarbon-like" odor; (b) 0.022 g of impure **7**; (c) 1.64 g of pure **4**, mp 29.0–31.0 °C [60 MHz ^1H NMR δ 1.13 (s, 6 CH_3), 1.81 (p, CH_2), 2.53 (t, 2 CH_2); IR ($CDCl_3$) 1705 cm^{-1}; mass spectrum (*m/e*, 50 eV) 212 (M^+), 155, 127, 110, 109, 85, 71, 69, 57, 55. Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.68; H, 11.55.].

2,6-Di-*tert*-butyl-3,4,5,6-tetrahydropyridine (5). A solution of 1.913 g (10 mmol) of **1** and 0.741 g (10 mmol) of *t*-BuOH in 5.0 mL of oxacyclopentane was added to 35 mL of freshly condensed ammonia. Lithium (0.555 g, 80 mmol) was added in ten approximately equal-sized pieces over a 15-min period. The resulting mixture was allowed to gently reflux for another 2 h and then 4.28 g (80 mmol) of ammonium chloride was added in portions along with 20 mL of oxacyclopentane to facilitate stirring. A water bath (40 °C) was used to evaporate the ammonia and the residue was shaken with 50 mL of pentane and 35 mL of water. The separated pentane layer was washed with water, dried ($MgSO_4$), and evaporated under vacuum to yield 1.64 g of an oil which was subjected to silica gel column chromatography using a 0 to 6% diethyl ether gradient in distilled pentane to yield 1.37 g of crude **5**. Vacuum distillation of this product removed a substantial amount of high boiling impurity and yielded 0.895 g (46%) of pure **5**: bp 99–100 °C (16.5 mm); 60 MHz ^1H NMR δ 0.92 (s, 3 CH_3), 1.08 (s, 3 CH_3), ca. 1.00–2.25 (m, $CH_2CH_2CH_2$), 2.90 (m, CH); ^{13}C NMR 21.2 (CH_2), 23.0 (CH_2), 24.3 (CH_2), 27.4 (3 CH_3), 28.9 (3 CH_3), 35.6 (C), 40.5 (C), 66.9 (CH), 174.0 (=C); IR ($CDCl_3$) 1650 cm^{-1}; mass spectrum (*m/e*, 70 eV) 195 (M^+, 3), 180 (5), 155 (20), 138 (16), 109 (56), 84 (25), 69 (25), 57 (100, base), 55 (23), 43 (40), 41 (93). Anal. Calcd for $C_{13}H_{25}N$: C, 79.93; H, 12.90; N, 7.17. Found: C, 79.68; H, 12.78; N, 7.28.

Imine **5** is stored under nitrogen at room temperature to prevent discoloration and slow decomposition.

***cis*-2,6-Di-*tert*-butylpiperidine (6).** A solution of 4.78 g (25 mmol) of **1** in 5 mL of dry *t*-BuOH was added to 175 mL of anhydrous 1,2-ethanediamine. With vigorous stirring and heating of this mixture (90 °C oil bath) 3.12 g (450 mmol) of lithium was added over a 30-min period in 12 approximately equal-sized pieces alternating with approximately equal portions of dry *t*-BuOH, such that the total amount of *t*-BuOH used, including the initial 5 mL, was 33.4 g (450 mmol). After all the lithium metal had been consumed (2–3 min additional), the mixture was rapidly cooled to about 25 °C (water bath) and 60–90 g of dry ice was added to it in small portions (*exothermic* reaction). After another 15 min 700 mL of diethyl ether was added to the reaction products, followed by 32.1 g (600 mmol) of ammonium chloride (in portions and with ice-bath cooling). After an additional 10 min the resulting mixture was shaken with 350 mL of water, dried ($MgSO_4$), and evaporated under vacuum to yield 4.69 g (95%, crude) of **6**. Vacuum distillation of the product yielded 4.21 g (86%) of pure **6**: bp 95.0–97.0 °C (10 mm); 60 MHz ^1H NMR δ 0.88 (s, 6 CH_3), ca. 0.8–2.1 (m, $CH_2CH_2CH_2$), 1.13 (br s, NH, assignment by D_2O exchange), 2.14 (br d, J = 10.0 Hz, 2 CH); ^{13}C NMR 26.6 (C_4), 27.4 (6 CH_3), 27.6 (C_3, C_5), 34.5 (2 quaternary C), 67.4 (C_2, C_6), assignments confirmed by off-resonance proton decoupling; ^{15}N NMR (C_6D_6, downfield from external aqueous $^{15}NH_4Cl$) δ 30.0; mass spectrum (*m/e*, 70 eV) 197 (M^+, 0.3), 196 (1.3), 182 (9.4), 141 (18), 140 (100, base), 97 (15), 56 (33), 55 (28), 41 (29). Anal. Calcd for $C_{13}H_{27}N$: C, 79.11; H, 13.79; N, 7.10. Found: C, 79.36; H, 13.82; N, 7.07.

1,5-Di-*tert*-butyl-8-aza-6,7-dioxabicyclo[3.2.1]octane (7). A solution of 1.913 g (10 mmol) of **1** and 3.71 g (50 mmol) of *t*-BuOH in 27 mL of diethyl ether was added to 25 mL of freshly condensed ammonia. With rapid stirring of the resulting heterogeneous mixture, lithium (0.347 g, 50 mmol) was added in eight approximately equal-sized pieces over a 10-min period. After another 30 min 15 mL of additional ammonia was condensed into the mixture, and after an additional 60 min ammonium chloride (2.94 g, 55 mmol) was added in portions. A water bath (40 °C) was used to evaporate the ammonia and the residue was shaken with 30 mL of pentane and 30 mL of water. The separated pentane layer was washed with water, dried ($MgSO_4$), and evaporated under vacuum to yield 1.851 g of an oil which was estimated by 60 MHz ^1H NMR analysis to consist of approximately equal parts of **1**, **3**, and **7**. Silica gel column chromatography of this mixture using a 0 to 8% diethyl ether gradient in pentane yielded in order of elution: (a) 0.509 g of pure **1** (^1H NMR analysis); (b) 0.552 g of **7** (24%), mp 90.0–92.5 °C; (c) 0.435 g of **4**. Vacuum sublimation yielded an analytical sample of **7**: mp 92.0–93.0 °C; 60 MHz ^1H NMR δ 1.04 (s, 6 CH_3), ca. 1.5–2.2 (m, $CH_2CH_2CH_2$), 3.45 (br s, NH); ^{13}C NMR 19.1 (CH_2), 25.5 (6 CH_3), 29.1 (2 CH_2), 35.8 (2 C), 102.7 (2 C, bridgehead); IR (CCl_4) 3365 cm^{-1} (w); mass spectrum (*m/e*, 70 eV) 227 (M^+), 195 ($M^+ - O_2$), 181, 180, 178, 57, 55, 41, 39, 29, 28. Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.59; H, 11.03; N, 6.03.

Acknowledgments. We thank Professor R. Lichter for obtaining the ^{13}C and ^{15}N NMR spectra and Dr. K. Krishnan for obtaining the Raman spectrum. Funds for a JEOL PS/PFT-100 NMR spectrometer were provided in part from NSF Instrumentation Grant No. GP-37025.

Registry No.—**1**, 585-48-8; **2**, 66922-14-3; **3**, 66922-15-4; **4**, 66922-16-5; **5**, 66922-17-6; **6**, 66922-18-7; **7**, 66966-53-8.

References and Notes

(1) Steric hindrance here refers to spatial limitations upon access to the lone pair electrons of a base by an approaching Lewis acid. The descriptive term "sterically crowded" implies internal congestion.
(2) The increasing popularity of the more severely hindered lithium dialkylamides (including lithium 2,2,6,6-tetramethylpiperidide) and of the lithium, sodium, and potassium salts of bis(trimethylsilyl)amine is seen by scanning the more recent volumes of M. Fieser and L. Fieser, "Reagents for Organic Synthesis", Wiley-Interscience, New York, N.Y., 1967–1977.
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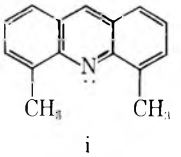

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of **1**. For example, 2,4-di-*tert*-butylpyridine, an isomer of **1** coproduced in the synthesis of **1** by direct alkylation[10] using *t*-BuLi, may not have been entirely removed.

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Sterically Hindered Silyl Perchlorates as Blocking Reagents

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Received November 8, 1977

Tri-*tert*-butylsilane, di-*tert*-butylmethylsilane, and *tert*-butyldimethylsilane were converted into the corresponding silyl perchlorates through a rapid and quantitative exchange with trityl perchlorate. Tri-*tert*-butylsilyl perchlorate proved somewhat difficult to prepare and was quite unreactive. *tert*-Butyldimethylsilyl perchlorate reacted with alcohols much more rapidly than did the usual reagent, *tert*-butyldimethylsilyl chloride. The ethers formed from di-*tert*-butylmethylsilyl perchlorate proved far more stable to acidic conditions than THP or *tert*-butyldimethylsilyl ethers.

In synthetic organic chemistry silylating agents are often used to protect hydroxyl functions. However, unhindered silyl groups such as trimethylsilyl are of limited value because of their extreme reactivity toward acid- and base-catalyzed solvolysis. Since 1972, one of the most popular protecting reagents has been *tert*-butyldimethylsilyl chloride.[1] Ethers formed from this hindered silyl chloride are many times more stable toward solvolysis than are trimethylsilyl ethers. The use of increasing steric bulk on silicon to provide increased solvolytic stability has recently been extended to *tert*-butyldiphenylchlorosilane by Hanessian and Lavallee.[2] Of course, the same steric bulk which affords the additional protection also resists the formation of the silyl ether in the first place. However, Corey[1] found *tert*-butyldimethylsilyl chloride to be satisfactory for primary and secondary alcohols when imidazole is utilized as a catalyst, though extended reaction times are sometimes required.

We wished to continue the replacement of methyl groups on silicon by *tert*-butyl groups to its logical conclusion. However, we anticipated that even two *tert*-butyl groups on silicon would render the silyl chloride ineffective in reactions with alcohols. Thus the need for a better leaving group than chloride was considered of prime necessity. We recently discovered that perchlorate is an extremely labile leaving group on silicon.[3] Thus, when triethylsilyl perchlorate is treated with sodium borohydride at room temperature, there is immediate and quantitative formation of triethylsilane. This reduction is particularly dramatic in view of the usual requirement of the more reactive $LiAlH_4$ for reduction of alkoxysilanes.

$$Et_2SiOClO_3 \xrightarrow{NaBH_4} Et_3SiH$$

In view of the striking reactivity of silyl perchlorates as demonstrated in the above example, we felt that the perchorate group might overcome any reactivity obstacles inherent for silyl chlorides. This paper will report the syntheses of *tert*-butyldimethylsilyl, di-*tert*-butylmethylsilyl, and tri-*tert*-butylsilyl perchlorates, and their reactions with alcohols.

Results and Discussion

Synthesis. Silyl perchlorates were first prepared some 20 years ago by Wannagat and Liehr[4] through the reactions of silyl chlorides with silver perchlorate.

$$R_3SiCl + AgClO_4 \rightarrow R_3SiClO_4 + AgCl$$
$$(R = Me, Et, n\text{-}Pr, Ph, p\text{-}MeC_6H_4)$$

Their studies revealed no evidence for ionic character, and it was concluded that these compounds were simply covalent esters of perchloric acid.

While the above method of synthesis is quantitative, we were loath to become involved with a process requiring considerable amounts of an expensive silver salt. Thus, a less costly route was sought. We have found[3] that the long-established trityl salt–silyl hydride exchange reaction[5] works quite well when the organic salt is trityl perchlorate. Indeed, we have found that all silyl hydrides attempted to date, save the most highly hindered for which the reaction is slower, react with trityl perchlorate in methylene chloride to instantaneously decolorize the solution and afford triphenylmethane and silyl perchlorate.[6] For example, triethylsilane reacts with trityl perchlorate to produce triphenylmethane and triethylsilyl perchlorate, both in essentially quantitative yield. The silyl perchlorate can be distilled out as a colorless liquid.

$$Et_3SiH + Ph_3ClO_4^- \xrightarrow{CH_2Cl_2} Et_3SiOClO_3 + Ph_3CH$$

tert-Butyldimethylsilane (**1**) was prepared in 90% yield from chlorodimethylsilane and *tert*-butyllithium. Addition of **1** to a methylene chloride solution of trityl perchlorate yielded upon workup 91% of clear, odorless *tert*-butyldimethylsilyl perchlorate (**2**) [bp 35 °C (0.06 Torr)].

Di-*tert*-butylmethylsilane (**3**) was synthesized from methyldichlorosilane and *tert*-butyllithium in 82% yield. This material had a bp of 152–4 °C and had identical spectral properties with the impure **3** (bp 148–155 °C) prepared by the more tedious, multistep method of Doyle and West.[7] Conversion of **3** to di-*tert*-butylmethylsilyl perchlorate (**4**) was accomplished in 87% yield [bp 65 °C (0.1 Torr)] through exchange with trityl perchlorate.

The method of Dexheimer and Spialter[8] was used to prepare tri-*tert*-butylsilane (**5**). While tri-*tert*-butylsilyl perchlorate (**6**) could be prepared from reaction of **5** with trityl perchlorate, the reaction was quite sluggish and separation from triphenylmethane proved difficult. Thus **5** was converted

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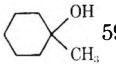
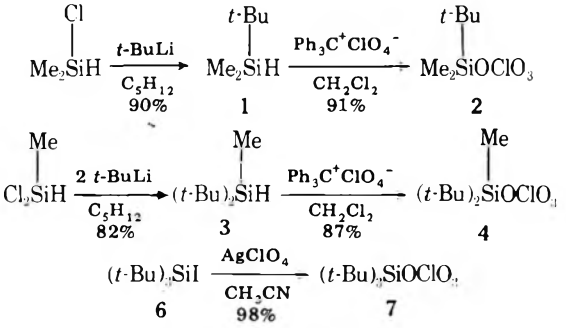
Table I. Reactivity Comparison of *tert*-Butyldimethylsilyl Perchlorate and *tert*-Butyldimethylsilyl Chloride with Tertiary Alcohols

	registry no.	*t*-BuMe$_2$SiOClO$_3$ (**2**)[a] Py/CH$_3$CN	*t*-BuMe$_2$SiCl[b] imidazole/DMF
t-BuOH	76-65-0	$t_{1/2} \sim 30$ s 100% in 5 min	30% in 3 days
	590-67-0	$t_{1/2} \sim 3$ min 100% in 20 min	10% in 3 days

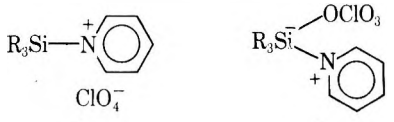
[a] Registry no.: 67124-66-7. [b] Registry no.: 18162-48-6.

to the silyl iodide **7** by the method of Weiderbruch and Peter,[9] and then transformed with silver perchlorate in acetonitrile to **6** in 98% yield. Sublimation produced white, crystalline **6** in 91% yield (dec >150 °C).

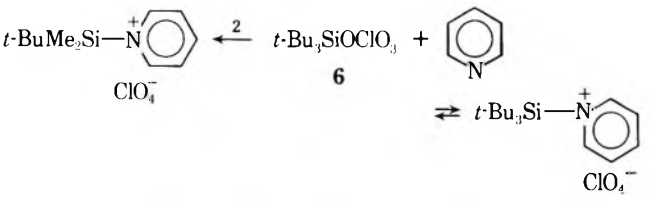


All the silyl perchlorates (**2**, **4**, and **6**) were found to react quite rapidly with water, so normal precautions for their handling must be taken.

Reactions with Alcohols. All reactions of silyl perchlorates were conducted in acetonitrile solution with 1 equiv of a pyridine present. It is unlikely that the silyl perchlorate is actually the ultimate reactant, as the NMR spectrum of this solution reveals the pyridine ring protons to be considerably shifted downfield. This could be accounted for by either **8** or **9**. However, the pyridinium salt **8** most easily accounts for the

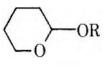


downfield shifts of ~0.25 ppm observed for methyl on silicon for **2** and **4**. While **2** and **4** exhibited similar behavior with regard to the formation of a pyridinium complex, the NMR spectrum of tri-*tert*-butylsilyl perchlorate (**6**) and pyridine was quite different with regard to the chemical shift and sharpness of the pyridine region. This part of the spectrum was reminiscent of the addition of 0.5 equiv of perchloric acid to pyridine, namely, the peaks were broad and their chemical shifts were between those of pyridine and pyridinium ion. If this was the result of an equilibrium situation it should be disturbed by the presence of **2**. Indeed, when a slight excess of **2** was added to the system, the aromatic signals became identical with those observed for **2** alone with pyridine.



Attempts were made to eliminate this complexation by using 2,6-di-*tert*-butyl-4-methylpyridine in place of pyridine.

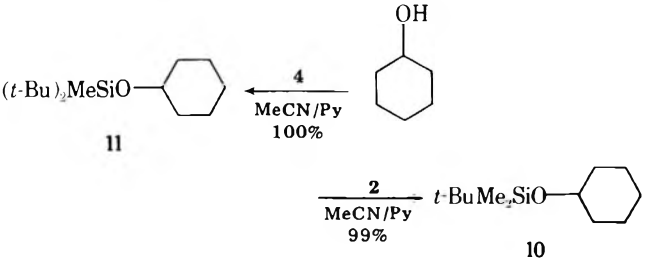
Table II. Relative Solvolytic Stabilities of Blocked Alcohols

ether[a]	registry no.	1% HCl in 95% EtOH	5% NaOH in EtOH
t-BuMe$_2$SiOR	67124-67-8	100% removal in 15 min at room temp	~15% removal after 9 h at 80 °C
	709-83-1	100% removal in 15 min at room temp	stable
t-Bu$_2$MeSiOR	67124-68-9	no dec after 3 days at room temp 50% dec 24 h at 90 °C	no dec after 3 days at 80 °C

[a] R = cyclohexyl.

Quite surprisingly NMR studies showed that all three silyl perchlorates reacted with this extremely hindered base.

To determine whether or not silyl perchlorates reacted in the desired fashion, to afford silyl ethers, **2** and **4** were reacted with cyclohexanol. Cyclohexanol was added to a stirred solution of **2** and pyridine in acetonitrile, and after 1.5 h, aqueous workup afforded a 99% yield (>95% pure by GC) of *tert*-butyldimethylsilyl cyclohexyl ether (**10**). A similar reaction using **4** produced a 100% yield (>95% pure by GC) of di-*tert*-butylmethylsilyl cyclohexyl ether (**11**).



In order to compare the relative reactivities of silyl chlorides and silyl perchlorates, the reactions of **2** and *tert*-butyldimethylsilyl chloride with two tertiary alcohols were examined and the results are shown in Table I. For the protection of these tertiary alcohols it is apparent that the silyl perchlorate/pyridine system is by far the more useful silylating agent, rapidly providing quantitative yields of the desired silyl ether at room temperature. No olefin formation was detected in these reactions of **2**.

To compare the relative reactivities of the hindered silyl perchlorates, **2**, **4**, and **6** were each added to acetonitrile solution containing *tert*-butyl alcohol and 1 equiv of 2,6-di-*tert*-butyl-4-methylpyridine. The reactivity order of the series was observed to be **2** ($t_{1/2} < 30$ s) > **4** ($t_{1/2} < 60$ s) > **6** (no reaction). Thus it was decided that in view of both the considerable difficulty in preparation of **6** (drybox or Schlenk tube techniques and sublimation) and its extreme lack of reactivity that this hindered perchlorate was never likely to play a role in organic synthesis. Another disturbing feature of this comparison was the discovery that for the reaction of **4** a significant amount of isobutene was formed. This elimination was also observed in the reaction of **4** and *tert*-butyl alcohol in the presence of a 20% excess of pyridine, thus removing the possibility of **4** as a protecting reagent for tertiary alcohols and presumably others which can readily form a stabilized carbocation.

Solvolytic Stability of Di-*tert*-butylmethylsilyl Ethers. Di-*tert*-butylmethylsilyl ethers have been reported by Doyle and West[10] when they reduced cyclohexanones with di-*tert*-

butylmethylsilane; however, the stabilities of these ethers were not investigated. Thus we set out to compare the stability of di-*tert*-butylmethyl cyclohexyl ether (**11**) relative to the *tert*-butyldimethylsilyl cyclohexyl ether (**10**) under both acidic and basic conditions. These results are summarized in Table II.

In 5% ethanolic sodium hydroxide solution **10** is relatively stable, though it does decompose slowly, while **11** is totally inert under these conditions. However, this represents no improvement over the traditional THP blocked alcohol as it is also completely stable. More importantly, it was found that the di-*tert*-butylmethylsilyl system answered the frequent complaint on the acid lability of the *tert*-butyldimethylsilyl block. Indeed **11** was totally inert to acidic conditions which quickly and quantitatively solvolyzed both **10** and the THP derivative of cyclohexanol.

Since Doyle[10] had reported that tri-*tert*-butylsilyl ethers resisted cleavage, we were concerned that the di-*tert*-butylmethylsiloxy system would also have a cleavage problem. This fear was realized when cesium fluoride in Me_2SO failed to react with **11** even at elevated temperatures. However, boron trifluoride in methylene chloride quickly and cleanly cleaved this ether even at 0 °C. Under these conditions the alcohol is never subjected to boron trifluoride as the hydroxylic functionality is protected as a borate ester until liberation by aqueous bicarbonate.

$$\mathbf{11} \xrightarrow[CH_2Cl_2]{BF_3} t\text{-}Bu_2MeSiF + F_2BOC_6H_{11} \xrightarrow[H_2O,\ 0\ °C,\ 30\ min]{NaHCO_3} C_6H_{11}OH \quad 94\%$$

Of course it is expected that BF_3 would cause unwanted side reactions for some molecules of synthetic interest. On the other hand, one would probably not be interested in the di-*tert*-butylmethylsilyl blocking group unless protection against rather rigorous acidic conditions were required to effect the desired transformation(s).

Conclusions

Silyl perchlorates are easily prepared by the trityl exchange reaction and, if normal precautions are taken, are stable reagents. However, since the compounds are perchlorates, it is highly recommended that safety shields be employed when using significant quantities. *tert*-Butyldimethylsilyl perchlorate represents a significant improvement over *tert*-butyldimethylsilyl chloride with respect to reactivity. For protection of primary and secondary alcohols di-*tert*-butylmethylsilyl perchlorate provides a block that is far more stable to acidic conditions.

Experimental Section

General. Infrared spectra (IR) were recorded on a Beckman spectrophotometer. Routine NMR spectra were determined on a Varian HA-100 instrument and chemical shifts are reported as parts per million (δ scale) from tetramethylsilane, though it was not always used as the internal standard (benzene and methylene chloride were often used). ^{13}C and ^{29}Si NMR were recorded on a Bruker 90-MHz FT spectrophotometer as were the kinetic experiments of the silyl perchlorates with 2,6-di-*tert*-butyl-4-methylpyridine.

Routine and high-resolution mass spectra (MS) were recorded on an AEI MS-902. Gas chromatographic/mass spectral (GC/MS) analysis was accomplished on a Perkin-Elmer 270 mass spectrometer. Routine analytical gas chromatography (GC) was accomplished on a Varian aerograph 600-C flame ionization instrument using a 1/8 in. diameter, 6-ft long column packed with 10% Dexel 300 on Chromosorb P. GC yields were accomplished by adding known amounts of an inert standard.

Solvents were dried by distillation from P_2O_5 under nitrogen, and were stored over molecular sieves.

Although the silyl perchlorates are covalent liquids, they should be treated as potential explosives with all proper safety equipment. Our only explosion occurred when a syringe, used for injecting a sample of triethylsilyl perchlorate into a reaction flask, exploded long *after* the addition was complete. The reaction itself was unharmed.

Tri-*tert*-butylsilane (5) and Tri-*tert*-butylsilyl Iodide (7). The method of Dexheimer and Spialter[8] was used to prepare **5**, and **7** was prepared from **5** by the method of Weiderbruch and Peter[9] and recrystallized from acetonitrile. All spectral and physical properties of the materials so prepared matched those previously reported for the two compounds. Some additional spectral data was obtained for **7**: ^{13}C NMR showed singlets at δ ($CDCl_3$,^1H-decoupled) 30.7 and 24.5 in the ratio of 4.1:1 and its ^{29}Si NMR ($CHCl_3$) showed a singlet at δ 47.9.

Tri-*tert*-butylsilyl Perchlorate (6). A sample of $AgClO_4$ was placed in a flask and dried by heating at 150 °C under vacuum overnight. This sample of $AgClO_4$ and a sample of **7** were placed in a "drybox" in which all subsequent manipulations were carried out. A quantity of **7** (2.25 g, 6.91 mmol) and $AgClO_4$ (1.30 g, 6.31 mmol) were placed in 40 mL of acetonitrile and heated to 75 °C with the immediate formation of a yellow precipitate presumed to be AgI. Heating was continued for 5 h. After the mixture had cooled it was filtered and the yellow precipitate (AgI) was washed with acetonitrile and allowed to dry (1.44 g, 98%). The filtrate was extracted several times with 15-mL portions of hexane and then evaporated to yield 1.83 g of a slightly yellow solid which was sublimed at 95 °C and 0.02-mm pressure to furnish white crystalline **6** (1.71 g, 5.74 mmoles, 91% based on $AgClO_4$). The material could also be prepared outside of the "drybox" using Schlenk tube, syringe, and rubber septum techniques.

The white cyrstalline **6** was found to soften and begin to decompose at 150 °C. It became completely black at 185 °C: ^1H NMR (CD_3CN) δ 1.27 (s); ^{13}C NMR (CD_3CN, ^1H decoupled) δ 29.18, 23.18; ^{29}Si NMR (CD_3CN) δ 29.27; IR (cm^{-1}, film was prepared by placing a small amount of a very concentrated CH_2Cl_2 solution between two salt plates, pressing the plates together, and evacuating them in a vacuum desiccator) 2960 m, 2910 m, 2880 m, 1486 m, 1476 m, 1399 m, 1374 m, 1270 m, 1231 s, 1034 s, 1021 w, 1014 w, 935 s, 820 s, 808 s, 743 s, 708 w, 690 w.

Reaction of 7 with Alkali. A quantity of **7** (40 mg, 0.12 mmol) was placed in an NMR tube with 0.5 mL of CD_3CN and 5 μL (0.28 mmol) of water. After heating overnight at 75 °C there was no change in the NMR spectrum relative to the starting solution. To the reaction mixture was added 25 μL of a 50% aqueous KOH solution. After again heating overnight at 75 °C it appeared that the ^1H NMR absorption of **7** at δ 1.24 was being slowly replaced by a singlet at δ 1.15 and one at δ 1.06.

Reaction of 6 with Water. The NMR tube used to obtain the proton spectrum of **6** contained ~40 mg (0.13 mmol) in ~0.4 mL of CD_3CN. To this solution was added 3 μL (0.17 mmol) of water and the NMR spectrum was changed immediately from a singlet at δ 1.27 to a singlet at δ 1.08.

Triethylsilyl Perchlorate. Trityl perchlorate (10.39 g, 30 mmol) was placed in a flask equipped with a rubber septum and a magnetic stirrer. The The flask was cooled in an ice bath and 40 mL of methylene chloride was added (yellow-orange slurry). Triethylsilane (3,5 g, 30 mmol) was added dropwise via syringe. As the addition was completed the mixture became homogeneous and colorless. After warming to room temperature the rubber septum was removed and quickly replaced by a short-path distilling head (some fuming was observed). The system was heated to 50 °C at atmospheric pressure for 30 min to drive off the methylene chloride. The residue was then carefully evacuated (tends to bump and foam) and distilled at 10 mm to furnish 5.91 g (92% yield) of a clear, colorless liquid: bp 43–45 °C (0.5 mm) [lit. (4) bp 45–46 °C at (1 mm)]; 60-MHz ^1H NMR δ 0.95 (m); ^{29}Si NMR (neat with 10% C_6D_6) δ 45.6.

***tert*-Butyldimethylsilane (1).** Freshly distilled chlorodimethylsilane (9.46 g, 0.1 mol) was added to 20 mL of pentane cooled in an ice bath. Dropwise addition of *tert*-butyllithium in pentane (50 mL of 2.0 M solution, 0.1 mol) was accomplished using a syringe and after the addition was complete the reaction mixture was allowed to warm to room temperature overnight. The product mixture was poured into a mixture of ice and bicarbonate solution. After extraction with water the pentane solution was distilled to afford 10.4 g (90% yield) of *tert*-butyldimethylsilane: bp 81–83 °C; ^1H NMR (CCl_4) δ 3.61 (septet, 1 H, J = 3.5 Hz), 0.89 (s, 9 H), 0.01 (d, 6 H, J = 3.5 Hz); IR (film) 2950 s, 2925 s, 2895 m, 2880 m, 2855 s, 2099 s, 1460 m, 1420 w, 1382 w, 1358 m, 1252 s, 1060 m, 1004 m, 982 s, 872 s, 830 s, 791 w, 771 w, 751 m, 713 m; MS *m/e* (rel intensity) 116 (14), 101 (2), 75 (20), 73 (30), 59 (100), 58 (34), 57 (43), 56 (49); MS Calcd for $C_6H_{16}S$, *m/e* 116.1021; found *m/e* 116.1022.

***tert*-Butyldimethylsilyl Perchlorate (2).** This compound was prepared from *tert*-butyldimethylsilane (1.16 g, 10 mmol) and trityl

perchlorate (3.65 g, 10.5 mmol) in the same manner as triethylsilyl perchlorate to afford 1.95 g (91% yield) of clear, odorless **2**: bp 35 °C (0.06 mm); ^{1}H NMR (CD_3CN) δ 0.99 (s, 9 H), 0.51 (s, 6 H); IR (film) 2955 m, 2935 m, 2885 w, 2865 m, 1471 m, 1465 m, 1394 s, 1367 w, 1226 s, 1101 m, 1032 s, 1011 s, 1001 s, 938 w, 850 m, 780 s, 708 m, 662 m.

Di-*tert*-butylmethylsilane (3). This compound was prepared from *tert*-butyllithium (110 mL, 2.1 M in pentane, 0.23 mol) and methyldichlorosilane (12.6 g, 0.11 mol) in the manner used to prepare *tert*-butyldimethylsilane except that aqueous NH_4Cl was used to neutralize the product mixture. Fractional distillation produced 14.39 g (82% yield) of di-*tert*-butylmethylsilane (bp 152–154 °C) which was found to have identical spectral properties with the impure material (bp 148–155 °C) prepared by the more tedious multistep method of Doyle and West.[7]

Preparation of Di-*tert*-butylmethylsilyl Perchlorate (4). This compound was prepared from 3 (7.21 g, 45.6 mmol) and trityl perchlorate (15.7 g, 45.6 mmol) in 30 mL of methylene chloride by the same method used for triethylsilyl perchlorate (except the reaction mixture was stirred 1 h at room temperature). Distillation furnished 10.2 g (39.8 mmol, 87% yield) of clear, colorless **4**: bp 65 °C (0.1 mm); ^{1}H NMR (CD_3CN) δ 1.11 (s, 18 H), 0.57 (s, 3 H); IR (film) 2975 s, 2945 s, 2900 m, 2870 s, 1472 s, 1395 w, 1371 m, 1230 s, 1114 s, 1034 s, 1010 s, 938 w, 826 m, 790 s, 739 m, 680 m.

NMR Tube Reactions of Silyl Perchlorates 2, 4, and 6. A number of the reactions of **2, 4,** and **6** were conducted in essentially the same fashion. A small septum was placed on an NMR tube and the tube was purged with dry nitrogen via a long, syringe needle. Deuterioacetonitrile (CD_3CN, 0.5 mL) was injected into the tube along with 30 μL of methylene chloride as an internal lock. A quantity of silyl perchlorate (0.126 mmol) was injected into the tube and its spectrum then obtained. For the two liquid perchlorates **2** and **4** volumetric measurements of the pure materials were used based on the approximate densities of 1.15 g/mL for **2** and 1.08 g/mL for **4**. For the solid **6** a stock solution was prepared by diluting 0.74 g (2.5 mmol) of **6** to 5 mL with CD_3CN to provide a 0.5 M solution. The requisite volume (250 μL, 0.125 mmol) of this solution was injected into an NMR tube containing 0.280 mL of CD_3CN and 30 μL of CH_2Cl_2 to approximate the final concentrations used for **2** and **4**.

Reactions of 2 and the 2–Pyridinium Complex with Water. To each of the NMR tube reaction mixtures with and without pyridine was added 0.4 mL each of water and pentane. After vigorous shaking the pentane layer was removed and GC/MS of each product mixture was obtained and a single product was found from both reactions. The remaining pentane solutions were allowed to evaporate in open vials. A small amount of CCl_4 was added to the residue and solution IR and NMR spectra were obtained which showed the products of the two reactions to be identical and the structure was assigned as *tert*-butyl dimethylsil and: ^{1}H NMR (CCl_4) δ 0.86 (s, 9 H), 0.01 (s, 6 H); IR (CCl_4) 3090 w, 3070 w, 3035 w, 2950 s, 2925 s, 2860 s, 1740 m, 1390 w, 1362 w, 1255 s, 1170 s, 1105 m, 940 w, 840 s, 675 s; GC/MS *m/e* (rel intensity) 246 (0.4, 231 (1), 189 (24), 147 (100), 133 (4), 132 (4), 117 (5), 73 (15), 66 (2), 59 (2), 57 (1), 45 (1), 41 (2).

Reactions of 4 and the 4–Pyridinium Complex with Water. Spectral data on the pentane extracts was obtained in identical fashion as for **2**. Again only one product was found for both reactions and its structure was assigned as di-*tert*-butylmethylsilanol: ^{1}H NMR (CCl_4) δ 1.10 (s, 1 H) (for the reaction of the perchlorate itself this peak was seen at 0.91), 0.96 (s, 18 H), 0.01 (s, 3 H); IR (CCl_4) 3700 m, 3090 w, 3075 w, 3035 w, 2960 s, 2930 s, 2885 m, 2855 s, 2470 m, 1385 w, 1361 w, 1250 m, 1005 w, 981 w, 969 w, 670 s; GC/MS *m/e* (rel intensity) 174 (2), 117 (12), 75 (100), 61 (4), 60 (4), 57 (3), 56 (2).

Reaction of 6 and the 6–Pyridinium Complex with Water. Spectral data on the pentane extracts was obtained in identical fashion as for **2** and **4**; however, for **6** there was a significant difference between the reactions. The reaction of **6** with water produced a single product whose structure was assigned to be tri-*tert*-butylsilanol: ^{1}H NMR (CCl_4) δ 1.09 (s); IR (CCl_4) 3700 m, 2980 m, 2955 s, 2905 m, 2875 s, 1480 m, 1385 m, 1368 w, 1010 s, 965 w, 620 m; GC/MS *m/e* (rel intensity) 159 (16), 117 (35), 87 (2), 75 (100), 61 (3), 57 (3), 41 (5). Silanol prepared by Dexheimer and Spialter[21] from the ozonolysis of tri-*tert*-butylsilane was reported to have the following spectral properties: ^{1}H NMR (CCl_4) δ 3.12 (s, 1 H), and 1.10 (s, 27 H); IR 3448 w, 2950 s, 2874 s, 1481 m, 1393 w, 1368 w, 1075 w, 821 s; MS parent ion peak *m/e* 216.

The product mixture from the reaction of the **6**–pyridinium complex with water was found to be primarily tri-*tert*-butyl silanol and the GC/MS showed nothing more; however, the NMR showed some new absorptions at δ 1.22 and 1.19 and the IR showed new absorptions at 3410 w, 2210 m, 1620 m, 1593 w, 1455 m, 1445 m, 885 w, 693 w. The source of these new absorptions remains unidentified.

Comparison of the Reactivities of the *tert*-Butyldimethylsilyl Perchlorate–Pyridine System to the Silyl Chloride–Imidazole System. These reactions were conducted in NMR tubes in a fashion similar to previous descriptions. For the reactions of 2 with *tert*-butyl alcohol and 1-methylcyclohexanol a quantity of **2** (46 mg, 0.215 mmol) was injected into an NMR tube containing 0.75 mL of CD_3CN and 5 μL of benzene as an internal lock. Pyridine (20 mg, 0.25 mmol) was then added. To this solution was added 14.5 mg (0.196 mmol) of *tert*-butyl alcohol and the change in the O-*t*-Bu absorption was monitored by NMR. The *tert*-butyl alcohol peak at δ 1.22 was gradually replaced by the SiO-*t*-Bu peak at δ 1.26. The conversion was over 50% at 30 s and was complete at 5 min: ^{1}H NMR (CD_3CN reaction solution) δ 1.26 (s, 9 H), 0.89 (s, 9 H), 0.12 (s, 6 H).

The reaction was repeated with 1-methylcyclohexanol (22 mg, 0.193 mmol) replacing *tert*-butyl alcohol. The methyl peak of the alcohol at δ 1.18 was gradually replaced by a peak at δ 1.26. The conversion was ~50% at 3 min and complete at 20 min: ^{1}H NMR (CD_3CN reaction solution) δ 1.49 (m, 10 H), 1.19 (s, 3 H), 0.87 (s, 9 H), 0.07 (s, 6 H).

Attempts to derivatize these tertiary alcohols using *tert*-butyldimethylsilyl chloride were then made to provide a strict comparison. The chloride (32 mg, 0.213 mmol) and imidazole (30 mg, 0.44 mmoles) in the proportions suggested by Corey and Venkateswarlu[1] were added to 0.75 mL of DMF. The same amounts of each of the two alcohols were added as before and the changes in NMR spectrum of the solution were monitored. After 3 days the conversion of *tert*-butyl alcohol to the ether was ~30%; for 1-methylcyclohexanol it was ~10%.

Preparative Scale Reaction of 2 with 1-Methylcyclohexanol. To a flask equipped with a magnetic stirrer and a rubber septum was added 0.862 g (4.03 mmol) of **2** and 5 mL of acetonitrile. Pyridine (0.332 g, 4.2 mmol) was added slowly and finally 0.45 g (3.95 mmol) of 1-methylcyclohexanol was injected to the stirred solution. Just after the mixture became homogeneous a phase separation occurred. Stirring was continued for 1.5 h. The reaction mixture was then poured into a small separatory funnel containing 15 mL of pentane and 15 mL of saturated $NaHCO_3$ solution. The pentane layer was then extracted several times until the smell of pyridine could no longer be detected in the aqueous phase. Evaporation of the pentane solution then afforded 0.891 g (99% yield) of the desired silyl ether (>95% pure by GC): ^{1}H NMR (CCl_4) δ 1.48 (m, 10 H), 1.18 (s, 3 H), 0.86 (s, 9 H), 0.05 (s, 6 H); IR (film) 2930 s, 2855 s, 1460 m, 1445 w, 1372 w, 1358 w, 1275 w, 1253 s, 1168 m, 1135 m, 1061 s, 1024 s, 1000 m, 831 s, 768 s; MS *m/e* (rel intensity) 228 (2), 213 (6), 185 (6), 177 (26), 95 (11), 75 (100), 59 (11), 57 (4); MS calcd for $C_{13}H_{28}OSi$ *m/e* 228.1909, found *m/e* 228.1905.

Preparative Scale Reaction of 2 with Cyclohexanol. Silyl perchlorate **2** (0.854 g, 4.0 mmol) was reacted with pyridine (0.38 g, 4.8 mmol) and finally with 0.401 g (4.0 mmol) of cyclohexanol in the fashion described above. Workup as above furnished 0.848 g (99% yield) of the desired silyl ether (>95% pure by GC): ^{1}H NMR (CCl_4) δ 3.58 (br s, 1 H), 1.47 (m, 10 H), 0.88 (s, 9 H), 0.02 (s, 6 H); IR (film) 2930 s, 2860 s, 1465 m, 1445 w, 1371 w, 1360 w, 1255 m, 1132 w, 1096 s, 1050 m, 1018 w, 1002 w, 992 w, 935 w, 883 w, 868 m, 834 s, 790 w, 771 m; MS *m/e* (rel intensity) 214 (1), 199 (1), 157 (63), 75 (100), 73 (11); MS calcd for $C_{12}H_{26}SiO$ *m/e* 214.1753, found *m/e* 214.1759.

Preparative Scale of 4 with Cyclohexanol. A quantity of **4** (5.60 g, 21.9 mmol) in 20 mL of CH_3CN was reacted with pyridine (1.9 g, 24 mmol) and finally with 2.19 g (21.9 mmol) of cyclohexanol. Again a phase separation occurred immediately after the dissolution of the cyclohexanol. After stirring the mixture for 1 h, 20 mL of pentane was added and the mixture extracted once with dilute HCl and twice with water. Evaporation of the pentane solution provided 5.62 g (100%) of the desired silyl ether (>95% pure by GC): ^{1}H NMR (CCl_4) δ 3.62 (br s, 1 H), 1.50 (m, 10 H), 0.95 (s, 18 H), 0.04 (s, 3 H); IR (film) 2930 s, 2860 s, 1465 m, 1445 w, 1381 w, 1368 m, 1250 m, 1128 w, 1092 s, 1048 m, 1016 m, 1006 m, 992 w, 931 w, 883 w, 871 w, 856 m, 820 s, 776 m, 750 m, 692 m; MS *m/e* (rel intensity) 256 (6), 241 (3), 199 (36), 157 (48), 75 (100), 73 (18), 61 (12), 41 (15); MS calcd for $C_{15}H_{32}OSi$ *m/e* 256.2222, found *m/e* 256.2210.

Solvolytic Stability Comparison of *tert*-Butyldimethylsilyl (10), Di-*tert*-butylmethylsilyl (11), and Tetrahydropyranyl (THP) Ethers of Cyclohexanol. For the acid stability test a stock solution of 1% HCl in aqueous ethanol was prepared by adding 2.9 g of concentrated (35%) aqueous HCl to 97.1 g of 95% ethanol. A sample of each ether (50 μL) was placed in a test tube containing 0.5 mL of the 1% HCl in aqueous ethanol solution and a septum placed over the mouth of the tube. The decomposition of the ethers was followed by GC. Both **10** and the THP ether were completely reacted in 15 min at room temperature; however, the DTBMS ether showed no de-

composition after 3 days at room temperature. Upon heating some decomposition was observed, but after 24 h at 80 °C <50% decomposition had occurred.

For the alkaline stability test a stock solution of 5% NaOH in aqueous ethanol was prepared by dissolving 5 g of NaOH in 95 g of 95% ethanol. The THP ether was assumed to be stable under basic conditions, but samples of both silyl ethers (50 μL) were placed in NMR tubes containing 0.9 mL of the 5% NaOH in aqueous ethanol solution. The spectrum of **11** showed no change after heating at 80 °C for 3 days; however, **10** was found to decompose slowly under these conditions as ~15% of the silyl ether methyl absorption at δ 0.03 had been converted to a new peak at δ −0.07 after 9 h at 80 °C.

Cleavage of the Di-*tert*-butylmethylsilyl Ether of Cyclohexanol (11) with BF_3. A sample of **11** (0.278 g) was placed in a flask with 10 mL of methylene chloride. Decane (0.081 g) was added as an internal GC standard. The flask was cooled in an ice bath and BF_3 was slowly passed over the stirred solution for 30 min. Saturated aqueous $NaHCO_3$ (15 mL) was added to the mixture and it was allowed to stir at room temperature for 5 h. The mixture was placed in a separatory funnel and the methylene chloride layer drained off. The aqueous layer was then extracted once with 10 mL of diethyl ether and the ether extract combined with the methylene chloride layer. After stirring the solution was found (by GC) to contain di-*tert*-butylmethylfluorosilane and cyclohexanol (94% yield; cyclohexanol was further identified by comparison of GC/MS with authentic material).

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Institutes of Health (Grant GM 16689) for their support of this work.

Registry No.—**1**, 29681-57-0; **3**, 56310-20-4; **4**, 67124-69-0; **5**, 18159-55-2; **6**, 61150-01-4; **7**, 56348-26-6; triethylsilyl perchlorate, 18244-91-2; **2**–pyridinium complex, 67124-71-4; **4**–pyridinium complex, 67124-73-6; **6**–pyridinium complex, 67124-75-8; *tert*-butyl dimethylsilanol, 18173-64-3; di-*tert*-butylmethylsilanol, 56889-84-0; tri-*tert*-butylsilanol, 56889-90-8; cyclohexanol, 108-93-0; boron trifluoride, 7637-07-2; silver perchlorate, 7783-93-9; potassium hydroxide, 1310-58-3; water, 7732-18-5; trityl perchlorate, 3058-33-1; triethylsilane, 617-86-7; chlorodimethylsilane, 1066-35-9; *tert*-butyllithium, 594-19-4; methyldichlorosilane, 75-54-7.

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Enones with Strained Double Bonds: The Bicyclo[3.3.1] System[1]

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Received January 18, 1978

Since examination of models suggests that bridgehead enones of the types **17** and **18** may have unusual chemical and physical properties, a variety of methods (Schemes III–VI) have been explored to form the enone **18**. Although various base-catalyzed elimination reactions (Scheme III) and pyrolytic elimination reactions (Schemes IV–VI) appear to generate the desired enone **18**, the tendency of this strained enone to undergo conjugated addition of nucleophiles or thermal rearrangement has thus far prevented us from isolating it.

An earlier investigation[2] of the structure of the $C_{27}H_{38}O$ compound formed from isophorone and hot aqueous alkali had suggested the intermediacy of the dienone **1** (Scheme I) with a bridgehead C=C. A stepwise synthesis of this C_{27} compound was effected utilizing as one step the base-catalyzed dehydrohalogenation of the chloro enone **2** to generate the dienone **1** that underwent a rapid Michael reaction. To learn whether this ready dehydrohalogenation **1** → **2** was dependent on the presence of an allylic chloride (albeit a twisted allylic system) in the chloro ketone **2**, we have now examined an analogous reaction with the saturated chloro ketone **3**. This ketone **3** was prepared from dimer **4**[3] of 3,5-dimethylcyclohexenone (**5**) by reduction to the ketol **6** and subsequent reaction with $SOCl_2$. Reaction of this chloro ketone **3** with $NaNH_2$ in a liquid NH_3–THF mixture formed the amino ketone **8**. As in our earlier study,[2] it seems most improbable that the conversion **3** → **8** occurs by either an S_N1 or an S_N2 process. Instead, we presume that a base-promoted dehydrohalogenation formed the enone intermediate **7** that was rapidly trapped by the conjugate addition of either ammonia or amide anion.

The ability to form, and in many cases isolate, bridgehead olefins of the type **10** (Scheme II) is now well established through the efforts of many investigators.[4] Several systems containing a bridgehead C=C that is part of a conjugated enone are also known.[4a,b] These include enones **11**,[5a–c] **12**,[5d–f] **13**,[5d,g] and **14**.[5h] The enone systems **11** appear to be relatively unstrained, while the systems **12** in part minimize strain by some distortion of the C=C accompanied by twisting about the C–C bond of the enone system so that the C=C and C=O functions are not coplanar.[5d] The failure of the enones **12** to undergo Michael additions is attributable both to this nonplanarity (and resultant poor conjugation) in the enone system and to the fact that the enolate anion **15** formed by Michael addition to the enones **12** would be more strained than the starting enone.[5d,f] Other examples of enone systems with considerable internal strain energy are the trans cyclic enones **16**[6] formed by photochemical isomerization.

In examining molecular models of these various bridgehead enone systems, we were impressed by the observation that while enones such as **12**–**14** seemed unlikely to have their C=C and C=O functions coplanar, such coplanarity appeared to add little strain to enones such as **17** (the parent system of intermediates **1** and **7**) and **18**. The main relief of strain in these latter two enones appeared to result from allowing the molecules to twist at the center of the C=C functions (indicated with arrows in structures **17** and **18**). A twist at this location would correspond to the geometry that might be expected for the photochemically excited states[7] or the radical anions derived from these enone systems. Consequently, it was of interest to seek preparative routes to enones such as **17** or **18** to learn whether these systems would exhibit unusual

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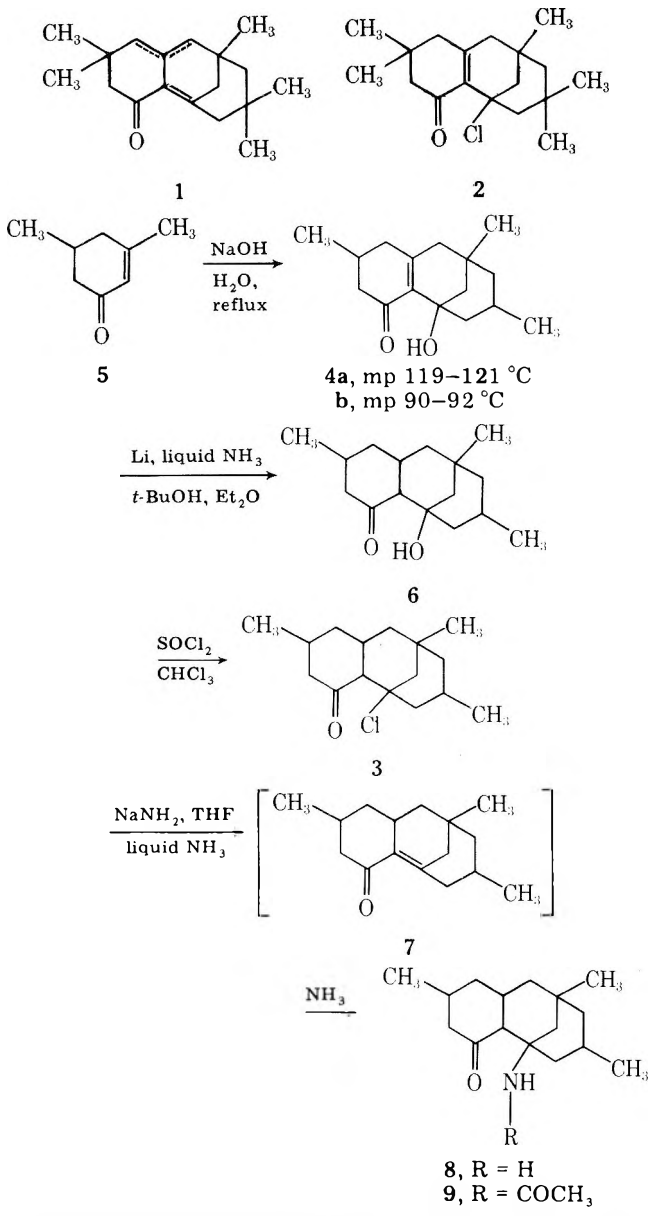
Scheme I



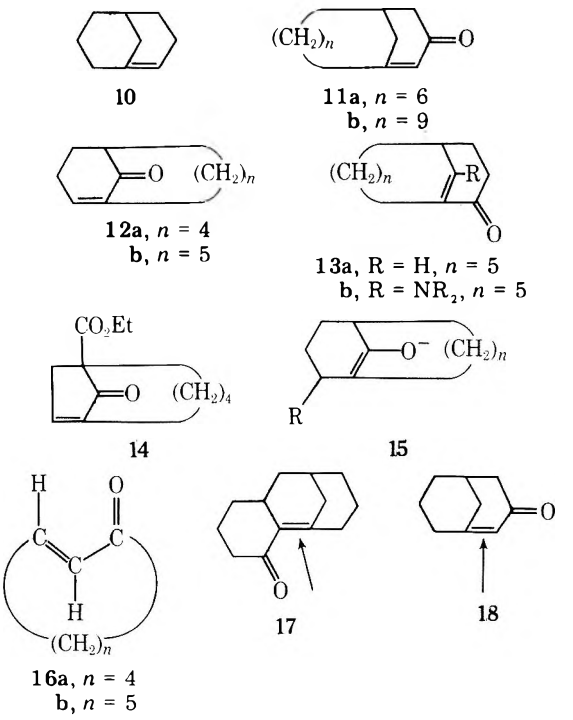
chemical, electrochemical, or photochemical behavior. This paper describes our efforts to prepare the bridgehead enone system **18**.

A suitable synthetic precursor for the enone **18** appeared to be the known ketol **19**[8] (Scheme III) obtained by the Michael addition of ethyl acetoacetate to cyclohexenone followed by decarboethoxylation and an intramolecular aldol reaction. Similar synthetic routes have been employed to obtain the relatively unstrained enones **11**.[5a–c] When we employed mild reaction conditions in the reaction of ethyl acetoacetate with cycloheptenone, the diketone **20** was isolated. However, our preliminary attempts to convert this diketone **20** to a ketol analogous to **19** have produced complex mixtures of aldol products.

Reaction of the ketol **19** with $SOCl_2$ formed the chloro ketone **21**. We presume that this conversion **19** → **21**, like the comparable preparations of chloro ketones **2** and **3**, proceeds by the formation and subsequent ionic decomposition of a chlorosulfite intermediate. An attempt to prepare the chloro ketone **21** by reaction of the ketol **19** with $(COCl)_2$ resulted in the formation of the diketo lactone **22** isolated as one of its enol forms (e.g., **23**).

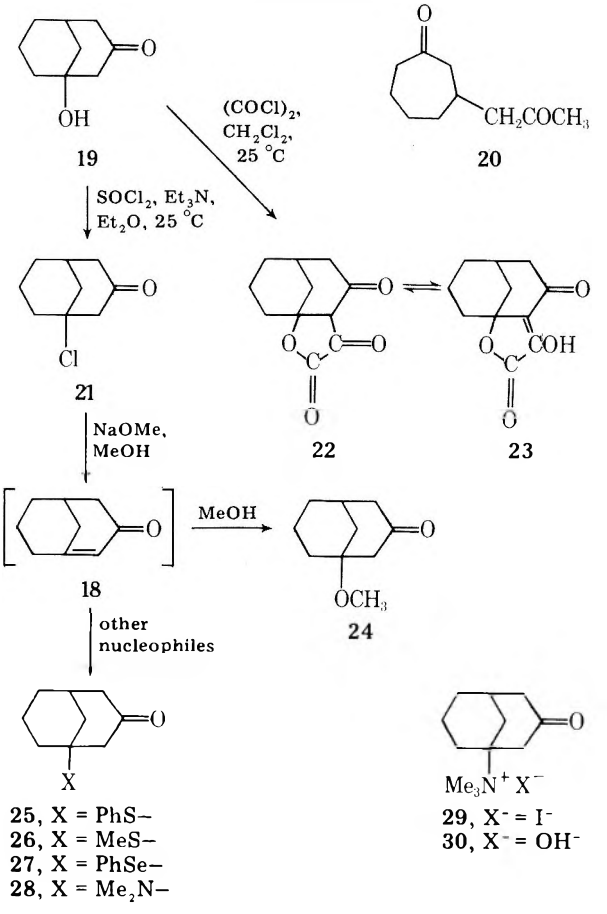
Although the chloro ketone **21** failed to react (or formed an intermediate that was reconverted to **21**) when heated with amine bases (Et_3N, γ-collidine), it reacted rapidly (<15 min

Scheme II

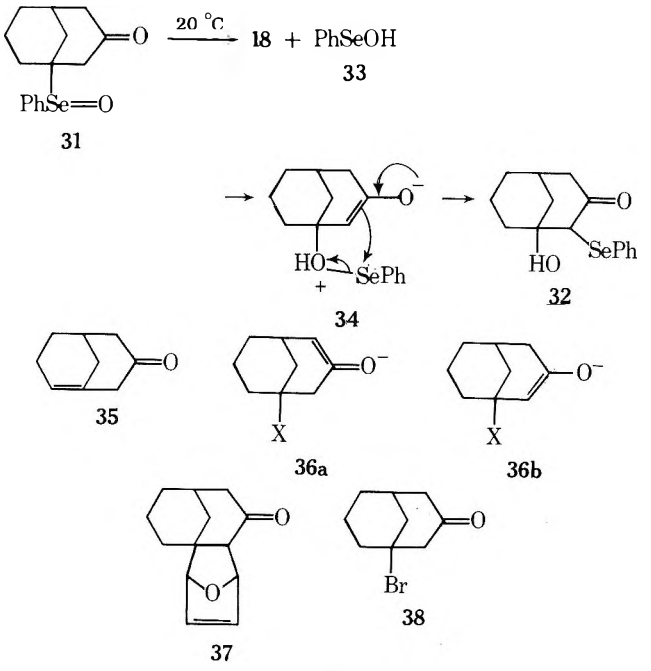


at 25 °C) with methanolic NaOMe to form the ketone **24**. This rapid conversion, **21** → **24**, clearly required the presence of base and was not a solvolytic transformation. Thus, it seems very probable that the enone **18** was generated and then rapidly trapped by the conjugate addition of MeOH. Support for this viewpoint was obtained by performing the chloro ketone–NaOMe reaction in the presence of other good nucleophiles (PhSH, MeSH, PhSeH, Me_2NH) to produce the substituted bicyclic ketones **25**–**28**.

Scheme III



Scheme IV



Several other observations also suggest that the enone **18** is an exceptionally reactive Michael acceptor for nucleophiles. Hofmann degradation of the solvent-free quaternary ammonium hydroxide **30** at 150 °C resulted in sublimation of the ketol **19** (presumably form **18** + H_2O) as the only volatile product. Also, the selenoxide **31** (Scheme IV), formed by oxidation of the selenide **27** with *m*-$ClC_6H_4CO_3H$[9] in furan at 4–5 °C, underwent thermal decomposition at about 20 °C to form the hydroxy selenide **32.** Although the electrophilic addition of benzeneselenenic acid (**33,** present in equilibrium with Ph_2Se_2 and $PhSeO_2H$)[10a] to reactive olefins is now known to be a common side reaction in selenoxide decomposition,[10] the analogous electrophilic addition to the electron-poor C=C of enones is normally not observed.[9] In the present case, we believe we are observing such a nucleophilic addition of the selenenic acid **33** (or its anion) to the strained enone **18,** followed by an intramolecular transfer of a phenylselenide unit (see structure **34**), a process analogous to the addition of benzeneselenenamides to enones.[11] In any case, the conversion **31** → **32** suggests that we have generated the conjugated enone **18** and not its unconjugated isomer **35.** An additional example of the tendency of the enone **18** to undergo conjugate addition reactions was found in the reaction of the chloro ketone with the sterically hindered alkoxide, KOBu-*t*, in various reaction solvents. We did not find any *tert*-butyl ether as had been observed earlier[2] in reaction of the sterically hindered chloro ketone **2** with KOBu-*t*. Instead, reaction of the chloro ketone **21** with KOBu-*t* formed a mixture of polymeric materials with properties suggesting that one of the enolate anions, **36** (X = Cl or *t*-BuO), had undergone Michael addition to the enone **18,** forming a new enolate anion, **36b,** capable of further anionic polymerization with more enone **18.**

The above observations suggested that, although the enone **18** could readily be generated by either base-promoted dehydrochlorination of the chloro ketone **21** or by thermal decomposition of the selenoxide **31** at about 20 °C, the avidity with which the enone **18** added nucleophiles would make its isolation from such reaction mixtures difficult. A number of experiments were performed in which we attempted to trap the enone **18** (generated from **21** and a base) as its cycloadduct with excess furan, CH_2=CHCH=CH_2, CH_2=CHOEt, or PhN_3. In all cases where the enone **18** was generated with NaOMe, the sole product isolated was the methoxy ketone **24** in spite of the fact that only 1 mol equiv of NaOMe and a large excess of the trapping agent were employed. When the enone **18** was generated with 1 mol equiv of KOBu-*t* and excess trapping agent, the major product in all cases was the polymeric material described previously. In one case (**21** + KOBu-*t* in furan) a small amount of a monomeric material was isolated with IR and mass spectral properties suggesting that it may be the cycloadduct **37.** Thus far, we have been unsuccessful in finding reaction conditions that will produce a sufficient amount of this product to permit its adequate characterization. We also sought to trap the enone **18,** generated by thermal decomposition of the selenoxide **31** in CH_2Cl_2, by reaction with Br_2 to form a vicinal dibromide. Unfortunately, this experiment was apparently complicated by reaction of Br_2 with the various selenium-containing byproducts to form HBr; the major reaction product was the bromo ketone **38.** Although the attempted trapping experiments described are hardly definitive, they do suggest that the enone **18** is not an exceptionally reactive component in various cycloaddition reactions.

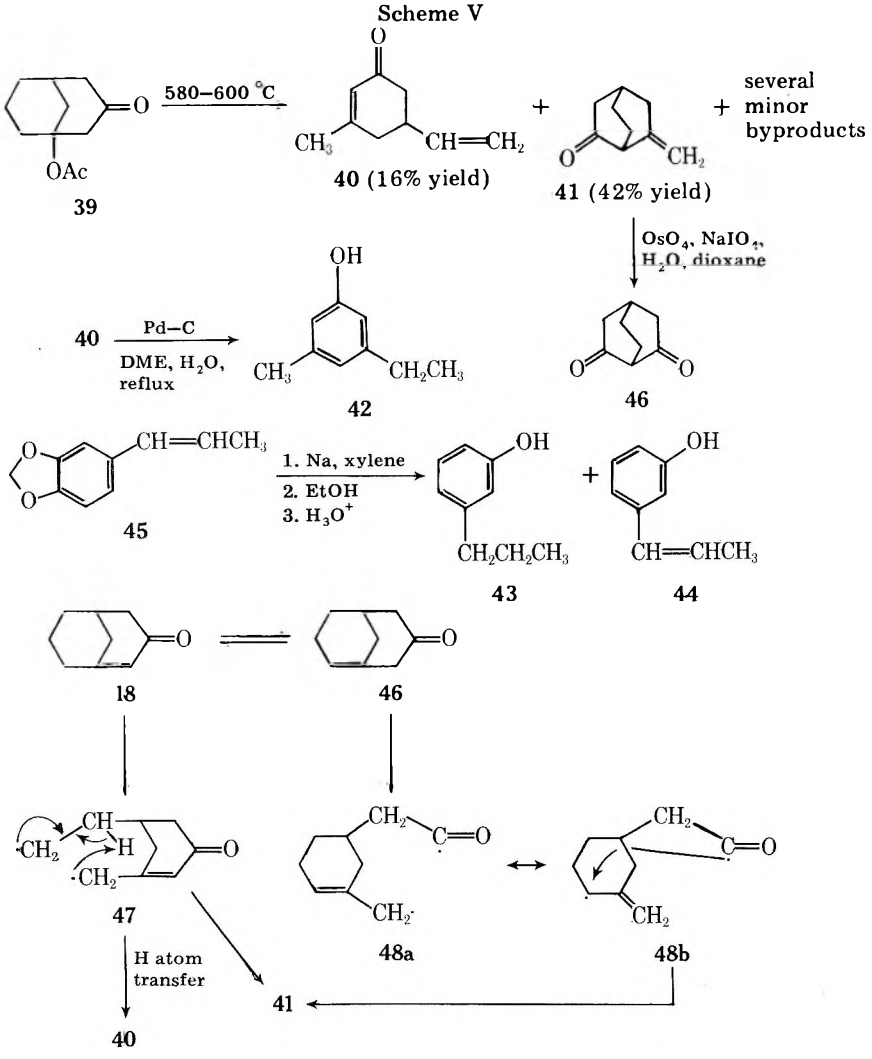
The foregoing experiments suggested the desirability of exploring methods that might generate the enone **18** under circumstances where its subsequent reaction with nucleophilic reagents could be minimized. Accordingly, we turned our attention to gas-phase pyrolysis of the keto acetate **39** (Scheme V). The slow addition of a solution of this acetate **39** in CH_2Cl_2–pentane to a tube packed with glass helices and heated with an oven at 580–600 °C resulted in the complete consumption of the acetate **39** with the formation of two major volatile products, each a $C_9H_{12}O$ ketone. Unfortunately, both of these products were structural isomers of the desired enone **18.** The minor product was demonstrated to have structure **40** both by its spectrometric properties and by isomerization over a Pd–C catalyst to the phenol **42.** This phenol **42** was identified with an authentic sample and shown to be different from the isomeric phenol **43,** prepared along with an unsaturated phenol believed to be **44** by reduction[12] of isosafrole (**45**). The major pyrolysis product was shown to be the bicyclic ketone **41** both by its spectrometric properties and by oxidative degradation to the known crystalline diketone **46.**

The precursor of these two pyrolysis products, **40** and **41,** would appear to be the dienone **18** or its double bond isomer **46,** formed by isomerization in the pyrolysis column. Either concerted rearrangements or the homolytic cleavage of a C–C bond in each intermediate, **18** and **46,** to yield the diradial intermediates **47** and **48** would constitute reasonable pathways for the formation of the final products **40** and **41.**

Although the photolytic decomposition of the keto lactone **22** (Scheme VI) produced a very complex mixture, pyrolysis in a hot tube (a known procedure for olefin formation)[13] produced a mixture of the two previously described olefins **40** and **41** along with a third $C_9H_{12}O$ ketone, the previously described[14a] C=C isomer (**49**) of ketone **41.** We presume that the enone **49** is formed by an acid-catalyzed isomerization of the enone **41** as it passes through the pyrolysis tube. An authentic sample of the enone **49** was obtained by isomerization of the enone **41** over a supported palladium catalyst. The hot-tube pyrolysis of the sulfoxide **50,**[14b,c] prepared by oxidation of the sulfide **25** with *m*-$ClC_6H_4CO_3H$, produced a mixture of volatile products containing PhSH and the enones **41** and **49.** Presumably the acidic byproducts[14c] formed in this pyrolysis account for the increased amount of the enone **49.**

Thus, our presently completed studies suggest that the bridgehead enone **18** can be generated by several olefin-forming reactions. However, the isolation of pure samples of this enone, **18,** for further study has proved to be a remarkably elusive goal, suggesting that specialized isolation techniques may be required. We plan continued study of possible methods for the generation and isolation of this substance as well as a study of the formation of less strained (and hopefully

Scheme V



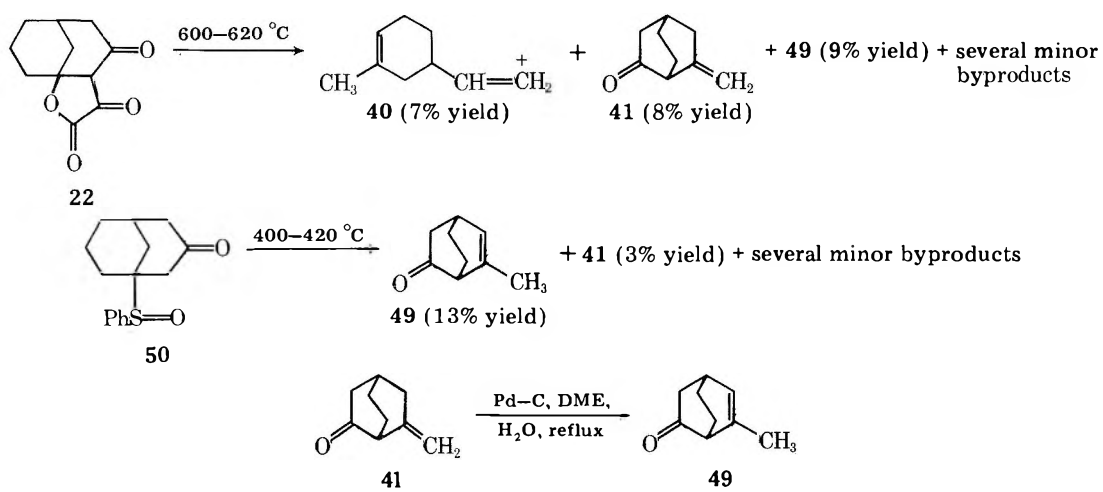
more easily isolated) homologues.

Experimental Section[15]

Preparation of the Dimeric Ketol 4. The enone **5**, prepared as previously described,[16] was obtained as a colorless liquid: bp 89–98 °C (16 mm); n^{25}_D 1.4822 [lit.[16] bp 84–86 °C (9 mm)]; NMR (CCl_4) δ 5.6–5.8 (1 H, m, vinyl CH), 1.7–2.6 (8 H, m, aliphatic CH), and 0.9–1.2 (3 H, m, CH_3). Employing a modification of previous procedures,[17] a mixture of 100 g (0.806 mol) of the enone **5**, 300 g of NaOH, and 150 mL of H_2O was refluxed for 40 min and then poured into ice water and extracted with Et_2O. After the ethereal extract had been washed with H_2O, dried, and concentrated, the residual brown semisolid was triturated with cold hexane to leave 46.5 g of crude yellow solid. Recrystallization from hexane afforded 37.0 g (37%) of a mixture of ketols **4** (NMR analysis) as pale yellow needles, mp 96–110 °C. Fractional recrystallization from hexane separated 16.6 g (17%) of the higher melting ketol **4a** as colorless needles: mp 119–121 °C (lit. mp 116–118,[17b] 120 °C[3]); IR (CCl_4) 3470 (OH), 1650 (conjugated C=O), and 1627 cm^{-1} (conjugated C=C); UV max (95% EtOH) 249 nm (ϵ 9100); NMR (CCl_4) δ 4.93 (1 H, s, OH) and 0.8–2.5 (23 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 248 (M^+, 3), 191 (100), 121 (21), and 41 (11).

The hexane solutions from the trituration and the initial recrystallization were combined, concentrated, and distilled under reduced pressure in a short-path still to separate 34.8 g of pale green viscous liquid, bp 118–135 °C (0.01 mm), that solidified on standing. Recrystallization from hexane separated 17.6 g of colorless solid, mp 83–86 °C that contained (NMR analysis) both ketols **4a** (minor) and **4b** (major). A series of fractional crystallizations from hexane separated

Scheme VI



1.49 g (1.5%) of the pure lower melting ketol **4b** as colorless plates: mp 90–92 °C; IR (CCl_4) 3470 (OH), 1645 (conjugated C=O), and 1627 cm^{-1} (conjugated C=C); UV max (95% EtOH) 248 nm (ϵ 8700); NMR (CCl_4) δ 4.89 (1 H, s, OH) and 0.7–2.7 (23 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity), 248 (M^+, 6), 233 (3), 191 (100), and 121 (20).

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.36; H, 9.77.

Preparation of the Dihydro Ketol 6. To a refluxing solution of 580 mg (76 mg-atom) of Li and 100 mL of Et_2O in 400 mL of liquid NH_3 was added, rapidly with stirring, a solution of 5.35 g (21.6 mmol) of the ketol **4a** and 5.0 mL of *t*-BuOH in 95 mL of Et_2O. After the reaction mixture had been stirred at −33 °C for 45 min, 10 mL of H_2O was added and the NH_3 was allowed to evaporate. The residue was partitioned between Et_2O and H_2O and the organic phase was washed with aqueous NaCl, dried, and concentrated. A cold (0 °C) solution of the residual semisolid in 50 mL of acetone was treated with excess aqueous 8 N H_2CrO_4, and then *i*-PrOH was added to consume the excess oxidant. After the resulting mixture had been neutralized with $NaHCO_3$, it was concentrated and partitioned between H_2O and Et_2O. The ethereal layer was washed with aqueous NaCl, dried, and concentrated to leave 4.96 g of gray-green semisolid. Recrystallization from EtOH afforded 2.50 g of a mixture (IR analysis) of conjugated and nonconjugated ketones as a colorless solid. Chromatography on silica gel with an EtOAc–hexane eluent (1:6 v/v) separated 1.75 g (32%) of the ketol **6** as colorless needles: mp 120–122 °C (lit.[3] mp 124 °C); IR (CCl_4) 3550 (OH) and 1700 cm^{-1} (C=O); UV max (95% EtOH) 294 nm (ϵ 25); ^1H NMR (CCl_4) δ 3.20 (1 H, s, OH) and 0.6–2.8 (25 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity), 250 (M^+ <1), 232 (31), 217 (13), 193 (100), 175 (15), 125 (75), 124 (66), 111 (93), 109 (62), 108 (54), 107 (34), 83 (21), 69 (41), 55 (52), 43 (38), and 41 (53); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 211.3 (s), 70.8 (s), 62.6 (d), 50.1 (t), 49.9 (t), 46.9 (t), 45.4 (t), 43.4 (t), 42.5 (t), 38.2 (d), 34.2 (s), 32.8 (d), 31.9 (q), 28.3 (d), 24.1 (q), and 22.0 ppm (q).

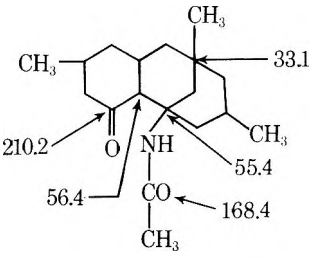
Preparation of the Chloro Ketone 3. A solution of 511 mg (2.04 mmol) of the ketol **6** and 492 mg (4.14 mmol) of $SOCl_2$ in 2.5 mL of $CHCl_3$ (EtOH free) was stirred at 25 °C for 19 h and then concentrated to leave 621 mg of red solid, mp 89–91 °C. Chromatography on silica gel with PhH as the eluent separated 494 mg (92%) of the chloro ketone **3** as a pink solid, mp 93.5–94.5 °C. Recrystallization from MeOH afforded the pure chloro ketone **3** as colorless plates: mp 93.5–94.5 °C; IR (CCl_4) 1725 cm^{-1} (C=O); UV max (95% EtOH) 294 nm (ϵ 40); ^1H NMR (CCl_4) δ 3.33 (1 H, d of d, J = 4.3 and 12.6 Hz), 2.55 (1 H, d, J = 12 Hz), and 0.5–2.4 (23 H, m, aliphatic CH); at 100 MHz, the CH_3 signals in the ^1H NMR spectrum were resolved into a doublet (J = 6.1 Hz) at δ 0.84, a singlet at δ 0.92, and a doublet (J = 5.6 Hz) at δ 1.00; mass spectrum *m/e* (rel intensity) 232 (25), 217 (17), 125 (25), 124 (100), 111 (40), 109 (81), 108 (83), 107 (60), 105 (25), 93 (31), 91 (35), 79 (26), 77 (24), 69 (32), 67 (23), 55 (45), 43 (29), 41 (74), and 39 (27); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 206.3 (s), 69.3 (s), 63.4 (d), 54.6 (t), 51.0 (t), 45.8 (t), 44.8 (t), 44.7 (t), 43.3 (t), 41.1 (d), 35.2 (s), 34.2 (d), 31.6 (q), 29.3 (d), 23.7 (q), and 22.0 ppm (q).

Anal. Calcd for $C_{16}H_{25}ClO$: C, 71.49; H, 9.37; Cl, 13.19. Found: C, 71.48; H, 9.38; Cl, 13.18.

Preparation of the Amino Ketone 8. A cold (−33 °C) mixture of $NaNH_2$ [from 340 mg (15 mg-atom) of Na], 1.00 g (3.73 mmol) of the chloro ketone **3**, 125 mL of liquid NH_3, and 20 mL of THF was stirred for 5 h, during which time the NH_3 was allowed to evaporate. After 5 mL of H_2O had been added, the reaction mixture was partitioned between Et_2O and aqueous NaCl. The ethereal layer was extracted successively with aqueous 1 M HCl and with H_2O and then dried and concentrated to leave 371 mg of colorless viscous liquid containing (TLC, silica gel with an EtOAc–hexane eluent, 1:9 v/v) the starting chloride **3** (R_f 0.58) and two unknown components (R_f 0.0 and 0.74). The acidic aqueous extract was made basic (aqueous NaOH) and extracted with Et_2O. This Et_2O extract was dried and concentrated to leave 451 mg (49%) of the amino ketone **8** as a liquid that solidified on standing, mp 69–71 °C. Recrystallization from pentane afforded the pure amino ketone **8** as colorless prisms: mp 72–73 °C; IR (CCl_4) 3370 (NH) and 1710 cm^{-1} (C=O); NMR (CCl_4) δ 0.7–2.9 (m, NH and aliphatic CH); UV max (95% EtOH) 295 nm (ϵ 23); mass spectrum *m/e* (rel intensity) 249 (M^+, 3), 234 (5), 192 (65), and 124 (100).

Anal. Calcd for $C_{16}H_{27}NO$: C, 77.06; H, 10.91; N, 5.62. Found: C, 77.03; H, 10.95; N, 5.61.

Preparation of the Keto Amide 9. A solution of 52 mg (0.21 mmol) of the amino ketone **8** and 0.5 mL of Ac_2O in 1.0 mL of pyridine was stirred at 25 °C for 11.5 h and then partitioned between Et_2O and aqueous 1 M HCl. The ethereal solution was washed with aqueous 5% NaOH, dried, and concentrated to leave 58 mg (95%) of the crude amide **9**, mp 134–135 °C. Recrystallization from hexane separated the pure keto amide **9** as colorless needles: mp 135–137 °C; IR (CCl_4) 3430 (NH), 1708 (C=O), and 1672 cm^{-1} (amide C=O); UV max (95% EtOH) 293 nm (ϵ 25); ^1H NMR ($CDCl_3$) δ 5.68 (1 H, br, NH), 3.40 (1 H, d, J = 13.2 Hz), and 0.7–2.9 (27 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 291 (M^+, 33), 234 (49), 232 (55), 217 (31), 216 (34), 192 (68), 189 (77), 166 (57), 124 (100), 109 (42), 108 (45), 107 (38), 91 (34), 69 (41), 55 (51), 43 (64), and 41 (82). Although the ^{13}C NMR spectrum ($CDCl_3$ solution) of the keto amide **9** was complicated by restricted rotation of the amide C–N bond that caused a number of ^{13}C signals to appear as two lines, the assignments indicated in the following formula are consistent both with off-resonance decoupling measurements and with the values observed for the structurally related hydroxy ketone **6** and chloro ketone **3**.



Anal. Calcd for $C_{18}H_{29}NO_2$: C, 74.18; H, 10.03; N, 4.81. Found: C, 74.08; H, 10.04; N, 4.79.

Preparation of the Ketol 19. Following a previously described procedure,[8] a solution of 48.7 g (375 mmol) of ethyl acetoacetate and 30.0 g (312 mmol) of 2-cyclohexenone in methanolic NaOMe [from 450 mL of anhydrous MeOH and 7.20 g (313 mg-atom) of Na] was refluxed for 72 h and then cooled to 25 °C and treated with a solution of 43.7 g (797 mmol) of KOH in 120 mL of H_2O. The resulting yellow solution was refluxed for 12.5 h and then concentrated and extracted with CH_2Cl_2. After the organic extract had been washed successively with aqueous 4 M HCl, aqueous NaCl, aqueous $NaHCO_3$, and aqueous NaCl, it was dried and concentrated. The residual yellow semisolid was recrystallized from Et_2O to separate 25.3 g (53%) of the ketol **19** as colorless plates: mp 233–240 °C dec (lit. mp 192–193,[8] 232–239 °C[18]); IR (CCl_4) 3595, 3430 (OH), and 1709 cm^{-1} (C=O); UV max (95% EtOH) 280 nm (ϵ 18); ^1H NMR ($CDCl_3$) δ 3.38 (1 H, s, OH), 2.1–2.7 (5 H, m, aliphatic CH), and 1.1–2.0 (8 H, m, aliphatic CH); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 210.5 (s, C=O), 70.6 (s, COH), 55.1 (t, CH_2), 45.5 (t, CH_2), 41.1 (t, CH_2), 40.2 (t, CH_2), 30.5 (t and d, CH_2 and CH), and 20.0 ppm (t, CH_2); mass spectrum *m/e* (rel intensity) 154 (M^+, 12), 111 (30), 97 (100), 58 (17), 55 (19), 43 (20), and 41 (24).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.08; H, 9.20.

Preparation of the Diketone 20. A solution of NaOEt [from 5 mg (0.2 mg-atom) of Na], 1.10 g (10.0 mmol) of cycloheptenone, and 1.33 g (10.2 mmol) of ethyl acetoacetate in 5 mL of anhydrous EtOH was stirred at 25 °C for 21 h. The solution was then treated with 2 mL of an H_2O solution containing 3.10 mmol of KOH and the resulting mixture was refluxed for 47 h, cooled, and concentrated under reduced pressure. After the reaction mixture had been partitioned between H_2O and CH_2Cl_2, the organic phase was washed successively with aqueous 1 M HCl, with aqueous $NaHCO_3$, and with aqueous NaCl and then dried and concentrated. The residual green liquid (1.17 g) contained (TLC, silica gel coating with an EtOAc–hexane eluent, 1:4 v/v) the diketone **20** (R_f 0.16) and several minor unidentified byproducts (R_f 0.40, 0.33, and 0.03). Chromatography on silica gel with an EtOAc–hexane eluent (1:4 v/v) separated 867 mg (52%) of the diketone **20** as a colorless liquid; $n^{25}D$ 1.4751; IR (CCl_4) 1720 and 1705 cm^{-1} (C=O); UV max (95% EtOH) 280 nm (ϵ 47); NMR (CCl_4) δ 2.35 (6 H, br s, CH_2CO), 2.08 (3 H, s, $COCH_3$), and 1.0–2.1 (7 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 168 (M^+, 8), 111 (100), 110 (37), 83 (64), 67 (22), 58 (30), 55 (59), 43 (82), 42 (24), 41 (36), and 39 (30).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.17; H, 9.68.

Preparation of the Chloro Ketone 21. A mixture of 7.85 g (51.0 mmol) of the ketol **19**, 14.5 g (102 mmol) of anhydrous Na_2HPO_4, and 12.1 g (102 mmol) of $SOCl_2$ in 100 mL of CH_2Cl_2 was stirred at 25 °C for 38 h and then the pale yellow suspension was partitioned between H_2O and CH_2Cl_2. The organic solution was dried and concentrated to leave 8.93 g of yellow-orange semisolid that was chromatographed on silica gel. The fractions eluted with Et_2O–hexane (3:7 v/v) contained 3.16 g (36%) of the chloro ketone **21**: mp 126.5–127.5 °C; TLC R_f 0.41 (silica gel coating with an Et_2O–hexane eluent, 3:7 v/v). Recrystallization from Et_2O afforded the pure chloro ketone **21** as col-

orless plates: mp 126.5–127.5 °C; IR (CCl_4) 1713 and 1722 cm^{-1} (C=O); UV max (95% EtOH) 283 nm (ϵ 22); ^1H NMR (CCl_4) δ 2.82 (2 H, s, CH_2) and 1.2–2.7 (11 H, m, aliphatic CH); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 207.1 (s, C=O), 67.2 (s, CCl), 56.7 (t, CH_2), 45.1 (t, CH_2), 43.3 (t, CH_2), 42.7 (t, CH_2), 31.4 (d, CH), 30.1 (t, CH_2), and 20.9 ppm (t, CH_2); mass spectrum *m/e* (rel intensity) 174 (M^+, 11), 172 (M^+, 36), 137 (100), 136 (26), 121 (21), 95 (54), 94 (56), 93 (39), 81 (26), 79 (32), 67 (30), 55 (22), 41 (23), and 39 (28).

Anal. Calcd for $C_9H_{13}ClO$: C, 62.61; H, 7.59; Cl, 20.53. Found: C, 62.70; H, 7.61; Cl, 20.53.

In a more satisfactory procedure, 8.21 g (69.0 mmol) of $SOCl_2$ was added, dropwise and with stirring during 15 min, to a solution of 9.25 g (60.0 mmol) of the ketol **19** and 7.03 g (69.5 mmol) of Et_3N (distilled from $LiAlH_4$) in 270 mL of Et_2O. The reaction mixture, which warmed to boiling with separation of a white precipitate, was filtered and concentrated to leave the crude product as a red solid. Chromatography on silica gel with an Et_2O–hexane eluent (3:7 v/v) separated 7.40 g of the crude chloro ketone **21** as a yellow solid, mp 114–122.5 °C. Recrystallization from Et_2O afforded 6.44 g (62%) of the previously described pure chloro ketone **21** as colorless plates, mp 126.5–127.5 °C.

Reaction of the Chloro Ketone 21 With NaOMe. A solution of NaOMe, from 32.9 mg (1.43 mg-atom) of Na and 5 mL of anhydrous MeOH, was added, dropwise and with stirring during 50 min, to a refluxing solution of 178 mg (1.03 mmol) of the chloro ketone **21** in 30 mL of anhydrous MeOH. The resulting solution was refluxed for 9 h and then cooled, neutralized with aqueous NH_4Cl, concentrated, and partitioned between Et_2O and H_2O. After the organic layer had been dried and concentrated, the residual yellow liquid [166 mg containing (TLC, silica gel coating with an EtOAc–hexane eluent, 1:4 v/v) the methoxy ketone **24** R_f 0.18] was chromatographed on silica gel with an EtOAc–hexane eluent (2:1 v/v) to separate 158 mg (91%) of the methoxy ketone **24** as a colorless liquid, $n^{25}D$ 1.4887. The product exhibited a single GLC peak (silicone DC-710 on Chromosorb P) corresponding to the methoxy ketone **24** (retention time 34.6 min) under conditions where the retention time for the chloro ketone **21** was 29.4 min. The spectral properties of the methoxy ketone **24** follow: IR (CCl_4) 1712 (C=O) and 1098 cm^{-1} (COC); UV max (95% EtOH) 278 nm (ϵ 21) with weak end absorption (ϵ 103 at 211 nm); ^1H NMR (CCl_4) δ 3.19 (3 H, s, OCH_3) and 0.8–2.7 (13 H, m, aliphatic CH); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 210.9 (s, C=O), 74.9 (s, C-O), 51.3 (t, CH_2), 48.4 (q, OCH_3), 46.1 (t, CH_2), 37.6 (t, CH_2), 35.9 (t, CH_2), 31.1 (t, CH_2), 30.4 (d, CH), and 19.7 ppm (t, CH_2); mass spectrum *m/e* (rel intensity) 168 (M^+, 5), 125 (60), 111 (100), 97 (18), 72 (16), 43 (18), and 41 (29).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.43; H, 9.62.

To demonstrate the rapidity of the reaction of the chloro ketone **21** with NaOMe, a solution of 91.8 mg (0.53 mmol) of the chloro ketone **21** in 3 mL of anhydrous MeOH was treated with 0.15 mL of a MeOH solution containing 0.65 mmol of NaOMe and the resulting solution was stirred at 25 °C for 15 min. After the solution had been neutralized by the addition of 1 mL of saturated aqueous NH_4Cl, the MeOH was evaporated under reduced pressure and the residue was partitioned between Et_2O and H_2O. The ethereal layer was dried and concentrated to leave 80.1 mg (90%) of the methoxy ketone **24** that was identified with the previously described sample by comparison of IR and NMR spectra. To demonstrate the need for NaOMe in this reaction, a solution of 101 mg (0.59 mmol) of the chloro ketone **21** in 3 mL of MeOH was stirred at 25 °C for 15 min and then concentrated under reduced pressure. The recovered chloro ketone **21**, mp 127–127.5 °C, amounted to 100 mg (99%) and was identified with an authentic sample by comparison of IR spectra. However, when a solution of 51.6 mg (0.30 mmol) of the chloro ketone **21** in 10 mL of MeOH was refluxed for 9 h and then concentrated, 37.9 mg (76%) of the methoxy ketone **24** (identified by comparison of IR, NMR, and TLC data) was isolated.

Our attempts to effect the dehydrochlorination of the chloro ketone **21** by reaction with Et_3N in Et_2O for 24 h or by reaction with a suspension of KH (prewashed with pentane) in THF at −3 °C for 40 min or at 23 °C for 18 h resulted in the recovery of 79–94% of the unchanged chloro ketone **21**. Similarly, after a solution of 51 mg (0.29 mmol) of the chloro ketone **21** and 58 mg (0.57 mmol) of Et_3N in 2 mL of heptane had been refluxed (98 °C) for 15 h, all of the starting chloro ketone **21** (IR and TLC analyses) was recovered. After a mixture of 61 mg (0.36 mmol) of the chloro ketone **21** and 2 mL of 2,4,6-collidine had been refluxed for 22 h, the neutral product (55 mg separated in the usual way) again contained (TLC analyses) the starting chloro ketone **21**. Chromatography separated 50 mg (82%) of the pure chloro ketone **21**, mp 126–127 °C.

A solution of NaOMe, from 32.3 mg (1.40 mg-atom) of Na and 0.5 mL of MeOH, was added, dropwise and with stirring during 2 min, to a solution of 183 mg (1.06 mmol) of the chloro ketone **21** in 35 mL of furan. The resulting mixture, from which a precipitate began to separate within a few seconds, was stirred for 25 °C for 16.5 h and then concentrated and partitioned between Et_2O and H_2O. The organic layer was dried and concentrated to leave 154 mg (87%) of the methoxy ketone **24** (IR and NMR analysis) with no other product being detected. In a similar experiment NaOMe [from 32.1 mg (1.40 mg-atom) of Na and 0.5 mL of MeOH] was added to a solution of 175 mg (1.01 mmol) of the chloro ketone **21** in 35 mL of butadiene. The resulting mixture was stirred under reflux for 2 h, allowed to stand overnight, and then subjected to the previously described isolation procedure to separate 158 mg (93%) of the methoxy ketone **24**. When the same procedure was repeated with 1.07 mmol of the chloro ketone **21** and 1.02 mmol (0.95 equiv) of NaOMe, the product again contained (GLC, IR, NMR) mainly the methoxy ketone **24** accompanied by a small amount of the starting chloro ketone **21**. In a similar procedure, 192 mg (1.11 mmol) of the chloro ketone **21** in 50 mL of $EtOCH{=}CH_2$ was treated with 0.26 mL of a MeOH solution containing 1.11 mmol of NaOMe and stirred at 25 °C for 5 h. After following the previously described isolation procedure, an aliquot of the crude product (194 mg of pale yellow liquid) was mixed with a known amount of *n*-$C_8H_{17}Ph$ (an internal standard) for GLC analysis (silicone DC-710 on Chromosorb P, apparatus calibrated with known mixtures). The product contained methoxy ketone **24** (86% yield, retention time 28.4 min) and *n*-$C_8H_{17}Ph$ (20.9 min); the product was identified with an authentic sample of the methoxy ketone **24** by comparison of IR and NMR spectra, GLC retention times, and TLC R_f values (R_f 0.39, silica gel coating with an EtOAc–hexane eluent, 4:6 v/v).

The mixture obtained by the dropwise addition during 60 min of KOBu-*t* [from 55.4 mg (1.42 mg-atom) of K and 5 mL of *t*-BuOH] to a refluxing solution of 177 mg (1.03 mmol) of the chloro ketone **21** in 30 mL of *t*-BuOH was refluxed for an additional 2 h and then cooled, neutralized with aqueous NH_4Cl, concentrated, and partitioned between H_2O and CH_2Cl_2. The organic layer was dried and concentrated to leave 169 mg of a viscous liquid (contains halogen) that appeared to be a mixture of polymeric materials: IR ($CHCl_3$) 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.0–2.8 (m, aliphatic CH including a *t*-BuO singlet at δ 1.27). Very similar crude product mixtures were obtained when a solution of the chloro ketone **21** in *t*-BuOH was added to *t*-BuOK in *t*-BuOH and then stirred at 25 °C and when a solution of the chloro ketone **21** in DME was added to a solution of alcohol-free KOBu-*t* in DME and then stirred at 2–4 °C for 30 min. Comparable crude products were also obtained when the chloro ketone **21** was allowed to react at 25 °C with 2 mol equiv of KOBu-*t* in $CH_2{=}CHOEt$ or with a mixture of 1 mol equiv of PhN_3 and 2 mol equiv of KOBu-*t* in THF. After a solution of 173 mg (1.00 mmol) of the chloro ketone **21** in 20 mL of anhydrous furan had been treated with 271 mg (2.42 mmol) of alcohol-free KOBu-*t*, the resulting suspension was stirred at 25 °C for 4.5 h and then partitioned between CH_2Cl_2 and H_2O. The organic phase was dried and concentrated to leave 147 mg of viscous liquid containing (TLC, silica gel coating with an Et_2O–hexane eluent, 3:7 v/v) mainly the previously described high molecular weight material (R_f 0–0.1) accompanied by a small amount of a more rapidly eluted component (R_f 0.25). Chromatography on silica gel separated 3.7 mg (1.8%) of this component, which may be the adduct **37**, as a colorless liquid: IR (CCl_4) 3070 (vinyl CH) and 1705 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 204 (M^+, 10), 161 (27), 136 (32, M^+ − furan), 119 (32), 118 (41), 108 (55), 94 (23), 91 (30), 82 (100), 81 (20), 79 (23), 68 (38), 57 (24), 56 (20), 55 (25), 43 (26), 41 (44), 40 (36), and 39 (62). Our attempts to obtain larger amounts of this material have thus far been unsuccessful. In an attempt to trap the enone **18** as an α,β-epoxy ketone, a solution of 104 mg (0.602 mmol) of the chloro ketone **21** in 5 mL of *t*-BuOH was treated with 40 mg (3.8 mmol) of aqueous 30% H_2O_2 and 0.61 mL (4.6 mmol) of aqueous 7.3 M NaOH. After the resulting suspension had been stirred at 25 °C for 1 h, it was partitioned between Et_2O and aqueous NH_4Cl. The organic solution was dried and concentrated to leave 79.6 mg (86%) of the crude ketol **19**, mp 232–240 °C dec, that was identified with an authentic sample by comparison of IR spectra and TLC R_f values.

Preparation of the Sulfide 25 and the Sulfoxide 50. To a solution of 193 mg (1.12 mmol) of the chloro ketone **21** and 429 mg (3.9 mmol) of PhSH (freshly distilled) in 5 mL of anhydrous MeOH was added, dropwise and with stirring during 5 min, 1.2 mL of a MeOH solution containing 5.12 mmol of NaOMe. The resulting solution, from which a white precipitate began to separate after two-thirds of the NaOMe solution had been added, was stirred at 25 °C for 2 h and then concentrated under reduced pressure and partitioned between Et_2O and H_2O. The Et_2O solution was dried and concentrated to leave 261 mg of liquid product that solidified on standing and contained (TLC,

silica gel coating with an EtOAc–hexane eluent, 1:9 v/v) an unknown component (R_f 0.41), the keto sulfide **25** (R_f 0.32), and the methoxy ketone **24** (R_f 0.09). Chromatography on silica gel with an EtOAc–hexane eluent (1:9 v/v) separated 247 mg (89%) of early fractions containing the keto sulfide **25**, mp 66–67 °C. This product crystallized from an Et_2O–pentane mixture as colorless plates with the same melting point; IR (CCl_4) 1709 cm^{-1} (C=O); UV max (95% EtOH) 222 (ϵ 11 000) and 267 nm (ϵ 1300); ^1H NMR (CCl_4) δ 7.2–7.8 (5 H, m, aryl CH) and 1.2–2.9 (13 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 246 (M^+, 85), 137 (77), 110 (76), 109 (51), 96 (71), 95 (100), 93 (49), 67 (41), 55 (21), and 41 (29); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 209.9 (s, C=O), 137.3 (d, 2 C atoms), 129.3 (s), 128.9 (d, 2 C atoms), 128.3 (d), 53.0 (t), 49.2 (s), 45.6 (t), 39.3 (t), 38.4 (t), 30.9 (d and t, 2 C atoms), and 20.1 ppm (t).

Anal. Calcd for $C_{15}H_{18}OS$: C, 73.13; H, 7.36; S, 13.01. Found: C, 73.01; H, 7.39; S, 12.96.

To a cold (−70 °C) solution of 547 mg (2.22 mmol) of the keto sulfide **25** in 55 mL of CH_2Cl_2 was added, dropwise and with stirring during 7 min, a solution of 384 mg (2.22 mmol) of freshly purified[19] *m*-$ClC_6H_4CO_3H$ in 16 mL of CH_2Cl_2. After the resulting mixture has been stirred at −70 °C for 10 min, it was partitioned between Et_2O and aqueous Na_2SO_3. The organic layer was washed with aqueous $NaHCO_3$, dried, and concentrated to leave 578 mg of a colorless solid that contained (TLC, silica gel coating with an EtOAc–hexane eluent, 7:3 v/v) the sulfoxide **50** (R_f 0.31) and two minor unidentified impurities (R_f 0.69 and 0.18). This material was chromatographed on silica gel with an EtOAc–hexane (7:3 v/v) eluent to separate 554 mg (95%) of the sulfoxide **50** (a mixture of stereoisomers) as a viscous liquid that crystallized on standing: mp 129–138 °C; IR (CCl_4) 1713 (C=O) and 1053 cm^{-1} (S=O); NMR ($CDCl_3$) δ 7.3–7.7 (5 H, m, aryl CH) and 1.0–3.1 (13 H, m, aliphatic CH); UV max (95% EtOH) 251 nm (ϵ 4700) with end absorption (ϵ 9060 at 211 nm); mass spectrum *m/e* (rel intensity) 262 (M^+, 9), 218 (21), 138 (41), 137 (100), 126 (37), 109 (88), 95 (87), 93 (62), 82 (40), 81 (46), 79 (34), 78 (30), 77 (40), 67 (48), 55 (37), and 41 (32).

Anal. Calcd for $C_{15}H_{18}O_2S$: C, 68.67; H, 6.91; S, 12.22. Found: C, 68.61; H, 6.94; S, 12.18.

Preparation of the Sulfide 26. After a cold (4 °C) solution of 1.73 g (10.0 mmol) of the chloro ketone **21** and 2.00 g (41.6 mmol) of MeSH in 25 mL of MeOH had been treated with 10.3 mL of an MeOH solution containing 54.3 mmol of NaOMe, the resulting mixture was warmed to 25 °C and allowed to stand for 10 h. The resulting mixture was concentrated and partitioned between Et_2O and H_2O. After the organic layer had been dried and concentrated, the residual yellow liquid (1.79 g) was chromatographed on silica gel with an EtOAc–hexane eluent (1:9 v/v) to separate 1.59 g (86%) of the keto sulfide **26** as a pale yellow liquid: $n^{25}D$ 1.5372; IR (CCl_4) 1710 cm^{-1} (C=O); UV max (95% EtOH) 240 (shoulder, ϵ 181) and 287 nm (ϵ 30); ^1H NMR (CCl_4) δ 2.1–2.6 (6 H, m, aliphatic CH) and 1.2–2.1 (10 H, m, aliphatic CH including a CH_3S singlet at δ 2.02); mass spectrum *m/e* (rel intensity) 184 (M^+, 74), 137 (75), 109 (39), 95 (100), 93 (66), 67 (50), and 41 (34); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 209.4 (s), 52.1 (t), 45.7 (t), 44.5 (s), 38.2 (t), 37.7 (t), 30.8 (t and d, 2 C atoms), 19.7 (t), and 9.5 ppm (q).

Anal. Calcd for $C_{10}H_{16}OS$: C, 65.17; H, 8.75; S, 17.40. Found: C, 65.06; H, 8.77; S, 17.36.

Preparation of the Amino Ketone 28. To a refluxing (7 °C) solution of 1.73 g (10.0 mmol) of the chloro ketone **21** in 300 mL of Me_2NH (freshly distilled from Na) was added, dropwise and with stirring during 3 min, 2.35 mL of a MeOH solution containing 10.2 mmol of NaOMe. After the resulting solution had been refluxed for 2 h, the Me_2NH was allowed to evaporate and the residue was partitioned between Et_2O and aqueous 1 M HCl. The aqueous phase was made basic (pH 10) with NaOH and extracted with Et_2O. After this final ethereal extract had been dried and concentrated, the residual pale green liquid was distilled to separate 1.67 g (92%) of the amino ketone **28** as a colorless liquid: bp 79–80 °C (0.05 mm); $n^{25}D$ 1.5049; IR (CCl_4) 1709 cm^{-1} (C=O); UV max (95% EtOH) 215 (ϵ 709) and 279 nm (shoulder, ϵ 60); ^1H NMR ($CDCl_3$) δ 1.2–3.3 (19 H, m, aliphatic CH including a 6 H singlet for the Me_2N group at δ 2.35); mass spectrum *m/e* (rel intensity) 181 (M^+, 58), 139 (20), 138 (100), 124 (84), 110 (21), and 85 (29); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 211.4 (s, C=O), 57.5 (s), 46.7 (t), 46.0 (t), 37.3 (q, 2 C atoms), 36.5 (t, ?), 32.5 (t, ?), 31.1 (t, ?), 30.2 (d, ?), and 19.3 ppm (t).

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.57; N, 7.73. Found: C, 72.77; H, 10.59; N, 7.69.

Preparation of the Ammonium Salts 29 and 30. A solution of 186 mg (1.03 mmol) of the amino ketone **28** and 388 mg (2.73 mmol) of MeI in 3 mL of Et_2O was stirred at 25 °C for 48 h and then filtered to separate 312 mg (94%) of the methiodide **29** as a colorless solid, mp 206–210 °C dec. Recrystallization from EtOH–H_2O afforded the pure methiodide **29** as colorless plates: mp 206–209 °C dec; IR (KBr pellet) 1699 cm^{-1} (C=O); UV (95% EtOH) shoulder at 285 nm (ϵ 25) with end absorption (ϵ 10 700 at 218 nm); NMR (Me_2SO-d_6) δ 1.3–3.4 (22 H, m, aliphatic CH including a Me_3N^+ singlet at δ 3.07).

Anal. Calcd for $C_{12}H_{22}INO$: C, 44.59; H, 6.86; I, 39.26; N, 4.33. Found: C, 44.55; H, 6.88; I, 39.18; N, 4.35.

A mixture of 64.2 mg (0.199 mmol) of the methiodide **29**, 140 mg (0.604 mmol) of Ag_2O, and 1.5 mL of H_2O was stirred at 25 °C for 12 h and then filtered. The filtrate was concentrated under reduced pressure and the residual crude ammonium salt **30** was heated to 150 °C for 4 h in a sublimation apparatus at 20-mm pressure. The sublimate that was collected amounted to 13.5 mg (44%) of the ketol **19**, mp 233–240 °C dec, that was identified with the previously described sample by comparison of IR spectra.

Preparation of the Keto Selenide 27. Following previously described directions,[20] a solution of 2.34 g (7.50 mmol) of PhSeSePh in 100 mL of anhydrous MeOH was treated, portionwise, with 790 mg (20.9 mmol) of $NaBH_4$ and the resulting solution was stirred at 25 °C for 2.5 h. Then 1.73 g (10.0 mmol) of the chloro ketone **21** was added and the resulting solution was stirred while 10 mL of a MeOH solution containing 43.4 mmol of NaOMe was added dropwise during 2 min. The resulting mixture was stirred at 25 °C for 1.5 h and then concentrated under reduced pressure and partitioned between Et_2O and H_2O. The ethereal solution was dried and concentrated to leave 3.04 g of crude yellow liquid product containing (TLC, silica gel coating with an EtOAc–hexane eluent, 1:9 v/v) the selenide **27** (R_f 0.30) and a minor, unidentified impurity (R_f 0.65). Chromatography on silica gel with an EtOAc–hexane eluent (1:9 v/v) separated 2.54 g (87%) of the keto selenide **27** as a pale yellow liquid, $n^{25}D$ 1.6043. The selenide **27** crystallized on standing as yellow plates: mp 49.5–51 °C; IR (CCl_4) 1709 cm^{-1} (C=O); UV max (95% EtOH) 220 (ϵ 12 100) and 280 nm (ϵ 610); ^1H NMR (CCl_4) δ 6.9–7.7 (5 H, m, aryl CH) and 1.0–3.2 (13 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 296 (M^+, 7), 294 (M^+, 22), 292 (M^+, 17), 291 (M^+, 5), 290 (M^+, 6), 157 (52), 137 (100), 109 (54), 95 (95), 93 (73), 81 (35), 77 (45), 67 (65), 55 (47), and 41 (45); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 210.0 (s, C=O), 137.8 (d, 2 C atoms), 128.4 (d, 3 C atoms), 125.4 (s), 53.9 (t), 46.2 (t), 45.6 (s), 40.1 (t), 39.1 (t), 31.4 (d), 30.8 (t), and 20.6 ppm (t).

Anal. Calcd for $C_{15}H_{18}OSe$: C, 61.43; H, 6.19. Found: C, 61.48; H, 6.28.

Preparation of the Keto Acetate 39. A solution of 1.54 g (10.0 mmol) of the ketol **19** and 5 mL of Ac_2O in 10 mL of anhydrous pyridine was stirred for 25 °C for 176 h with additional 2.5-mL portions of Ac_2O being added after 42.5 and 151 h. The resulting mixture was partitioned between Et_2O and H_2O and the ethereal layer was washed with aqueous 1 M HCl and then dried and concentrated to leave 1.25 g of the crude acetate **39** as a yellow solid, mp 59.5–66 °C. Recrystallization from pentane separated 1.09 g (56%) of the pure keto acetate **39** as colorless plates: mp 65.5–67 °C; IR (CCl_4) 1737, 1730 (ester C=O), and 1713 cm^{-1} (C=O); UV (95% EtOH) shoulder at 250 nm (ϵ 45) with weak end absorption (ϵ 140 at 207 nm); NMR (CCl_4) δ 2.85 (2 H, br s, CH_2CO) and 1.1–2.8 (14 H, m, including a CH_3CO singlet at δ 1.93); mass spectrum *m/e* (rel intensity) 196 (M^+, 2), 136 (42), 111 (34), 108 (76), 97 (63), 95 (51), 94 (39), 93 (63), 92 (44), 82 (42), 79 (40), 67 (45), 55 (61), 53 (33), 43 (100), 41 (54), and 39 (55).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.36; H, 8.25.

Preparation of the Diketo Lactone 22. A solution of 1.54 g (10.0 mmol) of the ketol **19** and 1.28 g (10.1 mmol) of freshly distilled $(COCl)_2$ in 25 mL of $CHCl_3$ (alcohol free) was protected from moisture and stirred at 25 °C for 47 h. Evaporation of the volatile materials left a red-brown solid containing (TLC, silica gel coating with an EtOAc–hexane eluent, 2:3 v/v) the diketo lactone **22** (R_f 0.18) and three unidentified components (R_f 0.59, 0.33, and 0.05). The crude product was chromatographed on silica gel with EtOAc–hexane mixtures as the eluent to separate 856 mg of the product **22** as a tacky orange solid. Recrystallization from an Et_2O–$CHCl_3$ mixture separated 728 mg (35%) of the pure diketo lactone **22** (obtained as the enol **23**) as orange plates: mp 180.5–181.5 °C; IR ($CHCl_3$) 3490 (br, OH), 1788, 1777, 1768, 1760 (lactone C=O), 1687 (conjugated C=O), and 1621 cm^{-1} (C=C); UV max (CH_2CN) 270 (ϵ 7170) and 335 nm (ϵ 3260); ^1H NMR ($CDCl_3$) δ 7.91 (1 H, s, OH) and 1.0–3.0 (11 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 208 (M^+, 4), 164 (45), 137 (74), 136 (100), 135 (21), 95 (22), 69 (34), 55 (30), 41 (54), and 39 (36); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 196.0 (s), 164.8 (s), 144.8 (s), 127.2 (s), 83.1 (s), 43.8 (t), 37.8 (t, 2 C atoms), 31.0 (t), 29.7 (d), and 21.3 ppm (t).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.50; H, 5.83.

Formation and Decomposition of the Selenoxide 31. A cold (4 °C) solution of 171 mg (0.58 mmol) of the selenide **27** and 101 mg (0.58 mmol) of purified[19] *m*-$ClC_6H_4CO_3H$ in 12 mL of anhydrous furan was stirred at 4–5 °C for 30 min and then warmed to 25 °C and stirred for 2 h. During this warming the solution acquired a distinct yellow color at ~20 °C. After the reaction mixture had been partitioned between aqueous 10% Na_2CO_3 and CH_2Cl_2, the organic layer was washed with aqueous NaCl, dried, and concentrated. The residual yellow liquid (184 mg) contained (TLC, silica gel coating with an EtOAc–hexane eluent, 1:4 v/v) Ph_2Se_2 (R_f 0.72), the starting selenide **27** (R_f 0.52), the hydroxy selenide **32** (R_f 0.19), and a minor unknown component (R_f 0.04). Chromatography on silica gel with an EtOAc–hexane eluent (1:9 v/v) separated 31 mg of Ph_2Se_2, mp 59–61 °C (lit.[9] mp 60–62 °C, identified with an authentic sample by comparison of IR spectra and mixture melting point determination), 9.6 mg of the starting selenide **27** (IR and mass spectral analysis), and 78.5 mg (44%) of the hydroxy selenide **32** as a colorless solid, mp 94–96 °C. Recrystallization from a PhH–hexane mixture separated the pure hydroxy selenide **32** as colorless plates: mp 97–98 °C; IR (CCl_4) 3500 (br, assoc. OH) and 1700 cm^{-1} (C=O); UV max (95% EtOH) 227 (ϵ 8100) and 325 nm (ϵ 960); ^1H NMR ($CDCl_3$) δ 6.9–8.0 (5 H, m, aryl CH), 3.5–3.9 (1 H, m, COCHSe), and 1.0–3.3 (12 H, m, OH and aliphatic CH); mass spectrum *m/e* (rel intensity) 310 (M^+, 75), 308 (M^+, 39), 214 (61), 212 (34), 171 (59), 169 (45), 159 (53), 158 (71), 157 (100), 156 (56), 155 (83), 154 (61), 153 (50), 117 (44), 97 (77), 95 (34), 91 (42), 79 (40), 78 (55), 77 (81), 69 (39), 65 (44), 55 (62), 51 (51), 50 (44), 43 (75), 41 (55), and 39 (53); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) 206.5 (s, C=O), 134.3 (d, 2 C atoms), 128.7 (d, 3 C atoms), 127.8 (s), 70.6 (s, COH), 66.1 (d, CHSe), 41.3 (t), 39.1 (t), 38.0 (t), 30.5 (t), 29.5 (d), and 19.5 ppm (t). Comparison of the position of the ^{13}C NMR signal for the substituted bridgehead carbon atom (70.6 ppm) with the position of the corresponding signals for the ketol **19** (70.6 ppm) and the keto selenide **27** (45.6 ppm) indicates that our product has the structure **32** and is not the isomeric α-hydroxy-β-phenylseleno ketone.

Anal. Calcd for $C_{15}H_{18}O_2Se$: C, 58.26; H, 5.87. Found: C, 58.33; H, 5.93.

In a similar experiment, 590 mg (2.01 mmol) of the selenide **27** was oxidized with 361 mg (2.09 mmol) of purified[19] *m*-$ClC_6H_4CO_3H$ in 50 mL of CH_2Cl_2 at 1–3 °C for 1 h and then 427 mg (2.67 mmol) of Br_2 was added to the cold solution. After the resulting solution had been warmed to 25 °C and stirred for 1 h, it was washed with aqueous 10% Na_2CO_3 and then dried and concentrated. The residual orange liquid (654 mg) contained (TLC, silica gel coating with an EtOAc–hexane eluent, 1:9 v/v) the bromo ketone **38** (R_f 0.34) and two minor unidentified components (R_f 0.78 and 0.44). Chromatography on silica gel with an EtOAc–hexane eluent (7:93 v/v) separated 240 mg (55%) of the bromo ketone **38**, mp 79–80.5 °C. Recrystallization from hexane afforded the pure bromo ketone **38** as colorless plates: mp 84.5–85.5 °C; IR (CCl_4) 1722 cm^{-1} (C=O); UV max (95% EtOH) 224 (ϵ 426) and 283 nm (ϵ 65); ^1H NMR (CCl_4) δ 2.8–3.2 (2 H, m, CH_2CO), 2.0–2.8 (6 H, m, aliphatic CH), and 0.7–2.0 (5 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 218 (M^+, 2), 216 (M^+, 2), 137 (100), 109 (23), 95 (73), 93 (30), 67 (31), 65 (20), 55 (20), 41 (20), and 39 (25); ^{13}C NMR ($CHCl_3$, multiplicity in off-resonance decoupling) 206.9 (s), 62.3 (s), 58.0 (t), 45.1 (t), 44.5 (t, 2 C atoms), 32.0 (d), 30.0 (t), and 21.6 ppm (t).

Anal. Calcd for $C_9H_{13}BrO$: C, 49.79; H, 6.04; Br, 36.81. Found: C, 49.80; H, 6.04; Br, 36.75.

Vapor-Phase Pyrolysis Studies. A. With the Keto Acetate 39. A solution of 1.55 g (7.90 mmol) of the acetate **39** in 10 mL of CH_2Cl_2 and 40 mL of pentane was added, dropwise during 2.5 h, to the top of a 20-cm vertical glass column packed with glass helices and surrounded by an oven heated to 580–600 °C. During this addition a slow stream of N_2 was passed through the column and the effluent solvent and volatile pyrolysis products were collected in traps cooled with a dry ice–*i*-PrOH mixture. After the effluent liquid had been concentrated, an aliquot of the crude pyrolysate (910 mg of red liquid) was mixed with a known weight of *n*-$C_8H_{17}Ph$ (an internal standard) for GLC analysis (silicone DC-710 on Chromosorb P, apparatus calibrated with known mixtures). The material contained the keto olefin **41** (retention time 18.6 min, 42% yield), the dienone **40** (22.9 min, 16% yield), *n*-$C_8H_{17}Ph$ (54.0 min), and a series of minor unidentified components (1.3, 1.5, 1.7, 2.0, 2.1, 2.6, 3.3, 4.3, 5.4, 6.9, 9.4, 11.4, 14.4, and 15.0 min). A collected (GLC) sample of the keto olefin **41** was obtained as a colorless liquid: $n^{25}D$ 1.5047; IR (CCl_4) 1729 (C=O), 1650 (C=C), and 897 cm^{-1} (C=CH_2); UV max (95% EtOH) 283 nm (ϵ 239); NMR (CCl_4) δ 4.6–5.1 (2 H, m, vinyl CH), 2.6–2.9 (1 H, m, CHCO), and 1.4–2.6 (9 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 136 (M^+, 12), 93 (25), 92 (100), 91 (24), 79 (37), 77 (16), 41 (15), and 39 (20).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.35; H, 8.90.

A collected (GLC) sample of the dienone **40** was obtained as a colorless liquid: $n^{25}D$ 1.4995; IR (CCl_4) 1671 (C=O), 1639 (C=C), and 924 cm^{-1} (CH=CH_2); UV max (95% EtOH) 237 nm (ϵ 9830); NMR ($CDCl_3$ at 100 MHz) δ 5.9 (1 H, m, vinyl CH), 1.9–2.7 (8 H, m, aliphatic CH including a CH_3 singlet at δ 1.98), and a pattern characteristic of a —CH=CH_2 group with signals (total 3 H) at δ 5.82 (d of d of d, J = 6.9, 10.8, and 18.6 Hz), 5.08 (d of d of d, J = 1.4, 1.5, and 18.6 Hz), and 5.06 (d of d of d, J = 1.5, 1.6, and 10.8 Hz); mass spectrum *m/e* (rel intensity) 136 (M^+, 11), 107 (14), 94 (30), 93 (34), 82 (100), 79 (17), 77 (14), 54 (32), 53 (16), 44 (20), 41 (29), and 39 (40).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.29; H, 8.92.

B. With the Keto Lactone 22. A solution of 217 mg (1.04 mmol) of the lactone **22** in 10 mL of CH_2Cl_2 was added, dropwise during 50 min, to the previously described pyrolysis apparatus with the oven heated to 600–620 °C. The crude liquid pyrolysate was 172 mg of red liquid. After an aliquot of this crude product had been mixed with *n*-$C_8H_{17}Ph$ (an internal standard), GLC analysis (silicone DC 710 on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of the enone **49** (retention time 18.5 min, 9% yield), the enone **41** (23.8 min, 8% yield), the dienone **40** (31.5 min, 7% yield), *n*-$C_8H_{17}Ph$ (76.2 min), and a number of minor, unidentified materials (1.1, 1.2, 1.7, 2.0, 2.6, 3.2, 4.4, 5.5, 6.6, 7.5, 8.4, 9.1, 13.4, and 35.3 min). Collected (GLC) samples of ketones **40** and **41** were identified with previously described samples by comparison of IR and mass spectra and GLC retention times. A collected (GLC) sample of the enone **49** was identified with a subsequently described sample by comparison of IR and mass spectra and GLC retention times.

C. With the Sulfoxide 50. A solution of 275 mg (1.05 mmol) of the sulfoxide **50** in 10 mL of CH_2Cl_2 was added, dropwise during 45 min, to the previously described pyrolysis apparatus with the oven heated to 400–420 °C. An aliquot of the crude pyrolysate (511 mg of red liquid) was mixed with *n*-$C_8H_{17}Ph$ for GLC analysis (silicone DC 710 on Chromosorb P). The crude product contained PhSH (retention time 5.5 min), the enone **41** (19.4 min, 3% yield), the enone **49** (15.3 min, 13% yield), an unidentified component [or mixture of components, IR (CCl_4) 1717 cm^{-1}, 29.8 min, ~10% yield], *n*-$C_8H_{17}Ph$ (59.8 min), and a number of minor unidentified components (1.5, 2.0, 2.3, 4.3, 9.8, and 11.7 min). Collected (GLC) samples of PhSH and the enone **41** were identified with authentic samples by comparison of IR and mass spectra and GLC retention times. A collected (GLC) sample of the enone **49** was obtained as a colorless liquid: IR (CCl_4) 1726 (C=O) and 1650 cm^{-1} (weak, C=C); NMR ($CDCl_3$, obtained at 100 MHz) δ 6.07 (1 H, d of d of q, J = 7.1, 1.9, and ~1.7 Hz, vinyl CH), 2.7–3.0 (2 H, m, bridgehead CH), 2.16 (2 H, d, J = 2.9 Hz, CH_2CO), and 1.1–2.1 [7 H, m, aliphatic CH including a CH_3 doublet (J = ~1.7 Hz) at δ 1.82]; mass spectrum *m/e* (rel intensity) 136 (M^+, 12), 94 (75), 93 (12), 91 (14), 79 (100), 77 (16), 41 (11), and 39 (14); calcd for $C_9H_{12}O$, 136.0888; found, 136.0908 [lit.[14a] IR 1715 cm^{-1}; NMR δ 6.02 (d of q, J = ~2 and ~6.5 Hz), 2.84 (br, 2 H), and 1.62 (d, J = ~2 Hz)].

To obtain an authentic sample of the enone **49** a mixture of 204 mg (1.5 mmol) of the enone **41**, 160 mg of 5% Pd/C catalyst, 2 mL of H_2O, and 18 mL of DME was refluxed for a total of 268 h with the reaction being stopped periodically to examine the progress of the isomerization. After the mixture had been filtered and then partitioned between Et_2O and aqueous NaCl, and organic solution was dried and concentrated. The crude liquid product (834 mg) contained (GLC with added internal standard) the enone **49** (26% yield) and the starting enone **41** (27% recovery). Collected (GLC) samples of both enones **41** and **49** were identified with previously described samples by comparison of IR and mass spectra and GLC retention times. The collected sample of enone **49** exhibited a UV maximum (95% EtOH) at 295 nm (ϵ 47) [lit.[14a] UV 294 nm (ϵ 153)].

Degradation of the Keto Olefin 41. To the mixture obtained from 3.9 mg of OsO_4 and 30.9 mg (0.227 mmol) of the keto olefin **41** in 0.75 mL of purified dioxane and 0.25 mL of H_2O was added, portionwise and with stirring during 35 min, 102 mg (0.477 mmol) of $NaIO_4$. After the resulting suspension had been stirred at 25 °C for 3 h, it was partitioned between H_2O and CH_2Cl_2. The organic layer was dried over Na_2SO_4, concentrated, redissolved in an Et_2O–PhH mixture (1:1 v/v), filtered through alumina, and again concentrated to leave 30.7 mg of the crude diketone **46**. Recrystallization from a PhH–hexane mixture afforded 20.8 mg (66%) of the pure diketone **46** as colorless plates: mp 195.5–196.5 °C (lit. mp 188–190,[21] 191,[22] 190–191 °C[23]); IR (CCl_4) 1742 and 1721 cm^{-1} (C=O) [lit.[21] IR (CCl_4) 1745 and 1720 cm^{-1}]; UV max (cyclohexane) 298 (ϵ 103), 307 (ϵ 103), 318 (ϵ 101), and 329 nm (ϵ 73) [lit.[21] UV max (cyclohexane) 300 (ϵ 100), 320 (ϵ 100), and 330 nm (ϵ 75)]; mass spectrum *m/e* (rel intensity) 138 (M^+, 73), 110 (12), 109 (11), 95 (16), 82 (11), 81 (17), 68 (37), 67 (83), 55 (100), 41 (19), and 39 (18).

Isomerization of the Dienone 40. A mixture of 17.1 mg (0.126 mmol) of the dienone **40**, 24 mg of 5% Pd on C, 0.4 mL of H_2O, and 3.6 mL of DME was refluxed for 78 h, at which time isomerization of **40** was practically complete [TLC analysis on silica gel with an EtOAc–hexane eluent (1:4 v/v); **40**, R_f 0.47; **42**, R_f 0.57]. The mixture was diluted with Et_2O, filtered, washed with aqueous NaCl, dried, and concentrated to leave 31.1 mg of crude liquid product. After an aliquot of the crude product had been mixed with a known weight of $PhCH_2CH_2Ph$ (an internal standard), GLC analysis (silicone DC-710 on Chromosorb P, apparatus calibrated with a known mixture) indicated the presence of the phenol **42** (retention time 30.2 min, 30% yield), $PhCH_2CH_2Ph$ (81.1 min), and a number of minor unidentified byproducts. A collected (GLC) sample of the phenol **42** was obtained as a colorless solid, mp 50–51 °C (lit. mp 51,[24] 52–54,[25] 54,[26] 55 °C[27]), that was identified with an authentic sample (Aldrich Chemical Co.) by comparison of IR and mass spectra and GLC retention times. The sample was clearly different from the isomeric phenol **43**.

Following a previously described procedure,[12] 5.04 g (31.1 mmol) of isosafrole (**45**) was added, dropwise and with stirring during 30 min, to a refluxing dispersion of 4.66 g (202 mg-atom) of Na in 35 mL of xylene. Then 45 mL of anhydrous EtOH was added, dropwise and with stirring during 4 h, and the resulting mixture was steam-distilled to remove volatile neutral components. The residual aqueous solution was acidified and extracted with CH_2Cl_2. The organic extract was dried and concentrated and the dark residual liquid (3.38 g) was distilled to separate 1.69 g of colorless liquid, bp 106–109 °C (8 mm), that contained [TLC on silica gel coating, EtOAc–hexane eluent (3:17 v/v)] the phenol **43** (R_f 0.41) and a component believed to be phenol **44** (R_f 0.36). Chromatography on silica gel with an EtOAc–hexane eluent separated early fractions containing 1.04 g (25%) of the phenol **43** as a colorless liquid: n^{25}_D 1.5199 [lit. bp 110 (10 mm),[12] 117–118 °C (11 mm)[28]]; IR (CCl_4) 3590 and 3380 cm^{-1} (OH); NMR (CCl_4) δ 6.2–7.4 (5 H, m, OH and aryl CH), 2.43 (2 H, t, J = 7 Hz, benzylic CH_2), 1.2–2.1 (2 H, m, CH_2), and 0.85 (3 H, t, J = 7 Hz, CH_3); mass spectrum m/e (rel intensity) 136 (M^+, 39), 121 (16), 108 (43), 107 (100), 77 (21), and 39 (13).

Later chromatographic fractions contained 462 mg (11%) of a component believed to be phenol **44** as a colorless liquid: n^{25}_D 1.5748; IR (CCl_4) 3590, 3400 (OH), and 965 cm^{-1} (*trans*-CH=CH); NMR (CCl_4) δ 6.5–7.4 (7 H, m, OH, vinyl and aryl CH) and 1.78 (3 H, d, J = 5 Hz, CH_3); mass spectrum m/e (rel intensity) 134 (M^+, 100), 133 (71), 107 (30), 105 (28), 91 (22), 77 (24), 51 (20), 40 (25), and 39 (22).

Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.31; H, 7.71.

Registry No.—**3**, 66921-72-0; **4**, 17348-81-1; **5**, 1123-09-7; **6**, 66921-73-1; **8**, 66921-74-2; **9**, 66921-75-3; **19**, 20498-02-6; **20**, 66921-76-4; **21**, 66921-77-5; **23**, 66921-78-6; **24**, 66921-79-7; **25**, 66921-80-0; **26**, 66921-81-1; **27**, 66921-82-2; **28**, 66921-83-3; **29**, 67011-17-0; **30**, 66921-84-4; **32**, 66921-85-5; **37**, 66921-86-6; **38**, 66077-98-3; **39**, 66921-87-7; **40**, 66921-88-8; **41**, 66921-89-9; **42**, 698-71-5; **43**, 621-27-2; **44**, 66921-90-2; **45**, 120-58-1; **46**, 66921-91-3; **49**, 53922-17-1; **50** isomer I, 66921-92-4; **50** isomer II, 67009-05-6; ethyl acetoacetate, 141-97-9; 2-cyclohexenone, 930-68-7; cycloheptanone, 1121-66-0; diphenyl diselenide, 1666-13-3.

References and Notes

(1) This research has been supported by Public Health Service Grant R01-GM-20197 from the National Institute of General Medical Science. The execution of this research was also assisted by Institutional Research Grants from the National Science Foundation for the purchase of a mass spectrometer and a Fourier transform NMR spectrometer.

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Mechanism of Pseudobase Disproportionation. Kinetics and Mechanism of the Reaction of the Pseudobases of 2-(Substituted-benzyl)-5-nitroisoquinolinium Cations with the 2-Methylisoquinolinium Cation[1]

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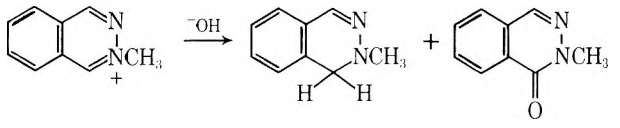
Received March 22, 1978

The rates of reaction of a series of 2-(X-benzyl)-5-nitroisoquinolinium cations (**8**, X = 4-CH_3O, 4-CH_3, H, 3-F, 3-CN, 4-CN) with the 2-methylisoquinolinium cation (**9**) to give the corresponding 2-(X-benzyl)-5-nitro-1-isoquinolinones and 1,2-dihydro-2-methylisoquinoline have been studied in 0.01–0.5 M KOH in 20% acetonitrile–water at 25 °C and ionic strength 1.0. These reactions are strictly first order in each reactant, and the dependence of the second-order rate constant on [$^-$OH] indicates that the reaction involves hydride transfer from the pseudobase anions of **8** to **9**. The correlation line for the pH-independent second-order rate constant, $\log k_2^H = -0.11\sigma + 1.35$, indicates that the transition state is quite "reactant-like". The rates of reaction of the corresponding 1-deuterio-2-(X-benzyl)-5-nitroisoquinolinium cations (**14**, X = 4-CH_3O, H, 3-F, 4-CN) have also been investigated ($\log k_2^D = -0.29\sigma + 1.13$). An X-dependent primary kinetic isotope effect is shown to be consistent with a reactant-like transition state for direct hydride transfer from C-1 of the *N*-benzyl-5-nitroisoquinoline derivatives to **9**. Such direct hydride transfer is confirmed by ^{1}H NMR spectral studies of the reaction of **8** with **9** in D_2O and of **14** with **9** in H_2O. The mechanism of the general disproportionation reaction of heterocyclic pseudobases is discussed in the context of the observed mechanism for the current reaction which can be considered as a "crossed disproportionation".

The disproportionation of heteroaromatic cations in aqueous base has been known for many years.[2–4] For example, fresh organic extracts of basic aqueous solutions of the 2-methylphthalazinium cation (**1**) contain[2,6,7] a mixture of 2-methyl-1,2-dihydrophthalazine (**2**) and 2-methyl-1-phthalazinone (**3**). Similar reactions have been reported for pyridinium,[7] isoquinolinium,[8,9] benzothiopyrylium,[10] quinazolinium,[11] acridinium,[3] xanthylium,[12] thioxanthylium,[12,13] and phenanthridinium[3] cations. In all cases, the cations display spectral changes consistent with pseudobase formation at electronic absorption spectral concentrations (e.g., **1** + $^-$OH ⇌ **4**),[6] with the disproportionation reaction becoming important only at much higher concentrations of the heterocycle. This concentration dependence indicates the bimolecular nature of these reactions, and the 1:1 ratio of oxidized and reduced products, in those cases which have been carefully investigated, is indicative of a true disproportionation reaction.



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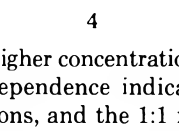

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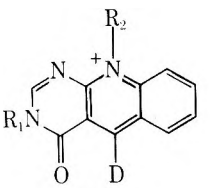
The bimolecular nature of the reaction has also been established[14,15] by deuterium labeling experiments in the case of the pyrimido[4,5-*b*]quinolinium cations **5**. Reduced product **6** is doubly labeled with deuterium; no deuterium is incorporated into the reduced product when the unlabeled cation is allowed to disproportionate in D_2O. Clearly, hydrogen transfer during disproportionation occurs without exchange with solvent protons, and so direct interaction between two heterocyclic molecules is indicated.

Disproportionation for the 2-methylphthalazinium cation occurs only in the range pH 10–13, with the pseudobase, itself, being extracted from more basic aqueous solutions in which the pseudobase alkoxide ion ($pK_{RO^-} = 13.0$) predominates.[6]



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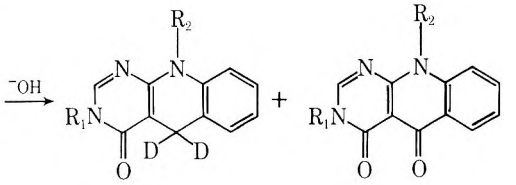

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Although there does not appear to have been a detailed kinetic study of the pH dependence of these disproportionation reactions, these qualitative observations suggest that the rate of disproportionation reaches a maximum value at the pH at which the concentration of the pseudobase is at its maximum value. At first glance, this result seems to suggest that the alkoxide ion is stable toward disproportionation and that this reaction proceeds via the pseudobase itself in aqueous solution but not in organic solvent. However, this interpretation is not consistent with the observed stability of many pseudobases to disproportionation, and it is difficult to conceive of a mechanism for a disproportionation via two molecules of the pseudobase. A kinetically equivalent mechanism for the reaction of two molecules of the pseudobase is the reaction of the pseudobase alkoxide ion with the heterocyclic cation as has been suggested[16] for the disproportionation of the pseudobase of berberine to oxyberberine and dihydroberberine.

Direct spectrophotometric kinetic studies of such disproportionation reactions are difficult because of the relatively high concentrations of heterocycle that are necessary to promote disproportionation and the relative insolubility of both reaction products in aqueous media. For an investigation of the kinetics and mechanism of such reactions, we have chosen to study the "crossed disproportionation" reaction between 2-benzyl-5-nitroisoquinolinium cations (**8**) and the 2-methylisoquinolinium cation (**9**) which react in aqueous base to give the 2-benzyl-5-nitro-1-isoquinolinones (**10**) and 1,2-dihydro-2-methylisoquinoline (**11**). Such a crossed reaction

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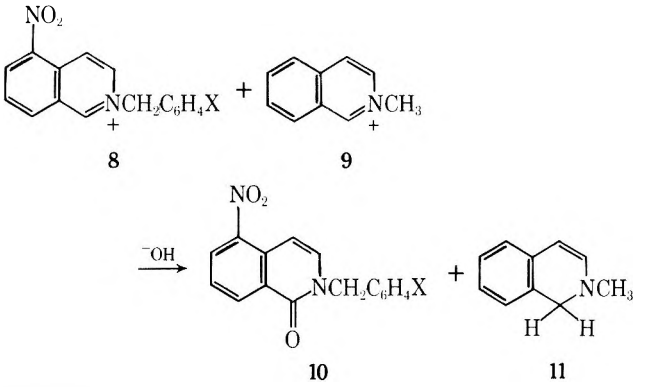
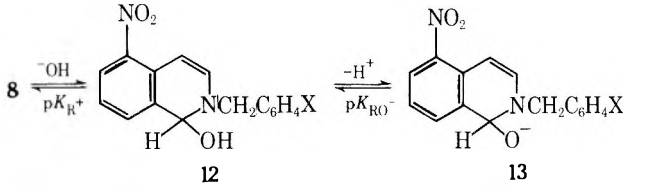


also has the advantage that one can study substituent effects (e.g., X in 8) in the two reacting species individually; the interpretation of substituent effects in a simple disproportionation is complicated by simultaneous substituent variation in both reacting species. The present paper reports a kinetic study of the mechanism of the above reaction via pH–rate dependence, substituent effects, and kinetic isotope effects.

Results

Basic aqueous solutions of 2-benzyl-5-nitroisoquinolinium cations (8) are pink due to the presence of the pseudobases **12** (λ_{max} 450–458 nm) and/or the pseudobase anions 13 (λ_{max} 493–507 nm).[17] Quantitative studies[17,25] of cation–pseudobase equilibration in these systems indicate that the cations 8 are essentially completely converted to their pseudobases **12** at



even the lowest base concentrations (0.01 M KOH) investigated in the current kinetic study. Addition of the 2-methylisoquinolinium cation to such pink solutions ([KOH] = 0.01–0.5 M) produces decolorization at rates which can be conveniently measured by conventional spectrophotometry at room temperature. The time dependence of the visible absorption spectrum of the 2-(4-methoxybenzyl)-5-nitroisoquinolinium cation in 0.5 M KOH in the presence of excess 2-methylisoquinolinium cation is displayed in Figure 1. The presence of a relatively clean isosbestic point at 413 nm is indicative of the occurrence of a single major reaction that does not involve intermediate species in any significant concentration. These spectral changes are consistent with the formation of 2-(4-methoxybenzyl)-5-nitro-1-isoquinolinone (**10**, X = 4-CH_3O) (λ_{max} 367 nm[17]) and 1,2-dihydro-2-methylisoquinoline ($\lambda_{max}(CHCl_3)$ 328 nm[6]) since neither of these products show more than a very weak tail absorption in the vicinity of 500 nm.

These two reaction products were confirmed by H^1 NMR spectral studies of chloroform extracts of a basic solution in which the 2-(4-cyanobenzyl)-5-nitroisoquinolinium and 2-methylisoquinolinium cations had been allowed to react under the conditions described in the Experimental Section. The product spectrum clearly indicated a mixture of **10**, X = 4-CN, and **11**. Repetition of this experiment in basic D_2O, and also the corresponding reaction of the 1-deuterio-2-(4-cyanobenzyl)-5-nitroisoquinolinium (**14**) and 2-methylisoquinolinium cations in H_2O, indicated that there was no detectable incorporation of solvent hydrogen at C-1 of the 1,2-dihydro-2-methylisoquinoline product. Thus direct transfer of hydrogen occurs from C-1 of the *N*-(4-cyanobenzyl)isoquinoline derivative to C-1 of **9**.

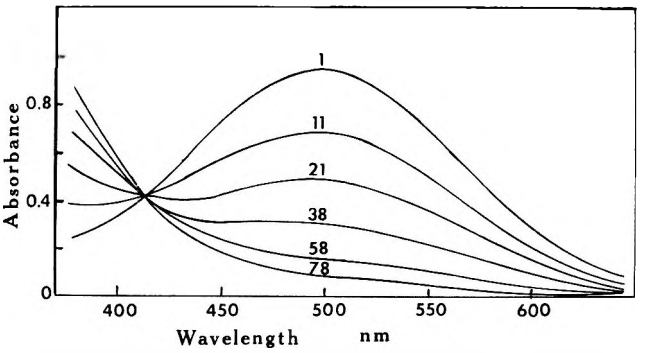


Figure 1. Time dependence of the absorption spectrum of a solution containing 8·Br^- (X = 4-CH_3O) (2.1×10^{-4} M) and 2-methylisoquinolinium bromide (1.7×10^{-3} M) in 0.5 M KOH in 20% CH_3CN–H_2O at 25 °C, ionic strength 1.0. Spectra were recorded at times (min) indicated on each curve.

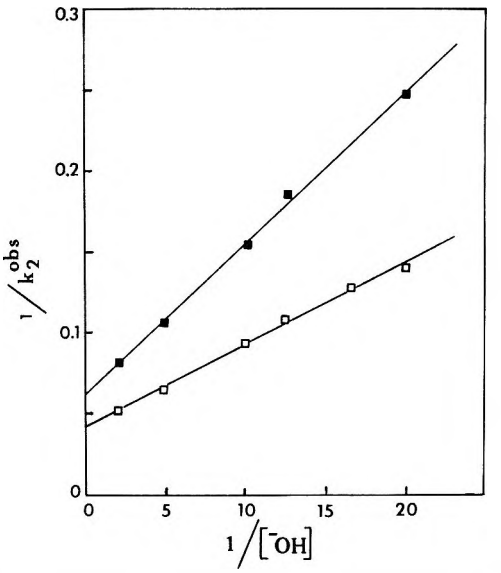
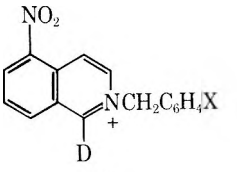


Figure 2. Double reciprocal plot of dependence of k_2^{obsd} on [$^-$OH] for 8·Br^- (X = 4-CH_3O) (□) and 14·Br^- (X = 4-CH_3O) (■). Data at 25 °C, ionic strength 1.0, in 20% CH_3CN–H_2O.



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For each of the *N*-benzyl-5-nitroisoquinolinium cations 8 (X = 4-CH_3O, 4-CH_3, H, 3-F, 3-CN, 4-CN) the change in absorbance at 480 nm was recorded as a function of time in the presence of 50–500-fold molar excesses of 2-methylisoquinolinium cation in the range 0.01–0.5 M KOH in 20% CH_3CN in water at 25 °C, ionic strength 1.0. In all cases the reaction proved to be first order in the 5-nitroisoquinoline derivative for at least 4 half-lives and pseudo-first-order rate constants, k_1^{obsd}, were calculated. Values of k_1^{obsd} were proportional to the concentration of the 2-methylisoquinolinium cation, and thus the kinetics of the reaction are first order in each reactant. The second-order rate constant k_2^{obsd} was evaluated for each X at 6–10 base concentrations in the range [KOH] = 0.01–0.5 M. In each case, plots of $1/k_2^{obsd}$ vs. $1/[^-OH]$ were linear (e.g., Figure 2), and extrapolation of these plots to $1/[^-OH] = 0$ gives $1/k_2^H$, where k_2^H is a second-order rate constant that is independent of [$^-$OH]. The values k_2^H that were evaluated in this way for each 8 from least-squares analysis of the plots in Figure 2 are given in Table I.

Table I. Kinetic Parameters for the Reduction of the 2-Methylisoquinolinium Cation[b] by *N*-Benzyl-5-nitroisoquinolinium Cations[a]

cation	X	registry no.	k_2^H, M^{-1} min^{-1}	k_2^D, M^{-1} min^{-1}	K, M^{-1}
8	4-CH_3O	64840-47-7	23.9 ± 0.2		8.3 ± 0.1
	4-CH_3	64840-46-6	23.1 ± 0.2		8.2 ± 0.1
	H	52166-52-6	22.9 ± 0.2		7.5 ± 0.1
	3-F	64840-45-5	20.7 ± 0.2		10.4 ± 0.1
	3-CN	64840-43-3	18.6 ± 0.4		12.7 ± 0.3
	4-CN	64840-42-2	19.5 ± 0.5		12.7 ± 0.3
14	4-CH_3O	64840-51-3		15.7 ± 0.3	6.8 ± 0.2
	H	64840-50-2		13.6 ± 0.3	7.8 ± 0.2
	3-F	64840-49-9		10.9 ± 0.2	12.8 ± 0.3
	4-CN	64840-48-8		8.5 ± 0.3	10.9 ± 0.3

[a] At 25.0 °C, ionic strength 1.0, 20% CH_3CN–H_2O. [b] Registry no. 33718-23-9.

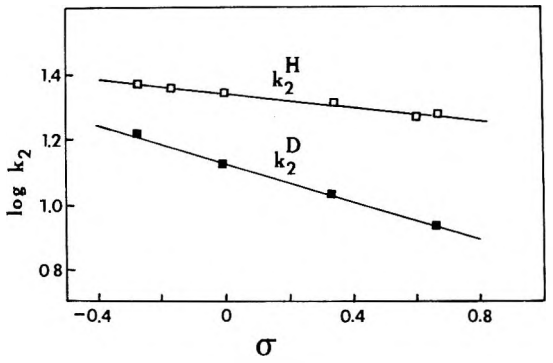


Figure 3. Hammett plots for the dependence of k_2 on X for 8 (k_2^H) and 14 (k_2^D).

The linear relationships in Figure 2 are consistent with eq 1, where K is the equilibrium constant for a rapidly established preequilibrium of the form

$$k_2^H = k_2^{obsd}(1 + 1/K[^-OH]) \quad (1)$$

$$K = [Y]/[Z][^-OH]$$

Values of K were evaluated from the slopes ($= 1/k_2^H K$) of the lines in Figure 2 and are included in Table I. Since the 2-methylisoquinolinium cation is not involved in a base-dependent equilibrium in this region,[6] the equilibrium constant K must be related to a base-dependent equilibrium of the *N*-benzyl-5-nitroisoquinoline derivatives. In fact, it has been established that alkoxide ion (**13**) formation from the pseudobases (**12**) does occur in this region and values of $K_d = [13]/[12][^-OH]$ for this ionization have previously[17] been evaluated spectrophotometrically under the current experimental conditions (except for the absence of the 2-methylisoquinolinium cation). Values of K = 7–12 M^{-1} in Table I are in reasonable agreement with K_d = 9–12 M^{-1} previously reported for these species.

The kinetics of oxidation of four *N*-benzyl 1-deuterio-5-nitroisoquinolinium cations **14** by the 2-methylisoquinolinium cation were also investigated in the same way as described above, and the values of k_2^D and K that were evaluated for these deuterated derivatives are also included in Table I.

In Figure 3, k_2^H and k_2^D are plotted as a function of the Hammett σ constant for the substituent X. Least-squares analysis gives the correlation lines of eq 2 and 3.

$$\log k_2^H = -0.11(\pm 0.04)\sigma + 1.35(\pm 0.01) \quad \text{(corr. coeff. = 0.977)} \quad (2)$$

$$\log k_2^D = -0.29(\pm 0.03)\sigma + 1.13(\pm 0.01) \quad \text{(corr. coeff. = 0.997)} \quad (3)$$

Table II. Kinetic Isotope Effects for the Reduction of the 2-Methylisoquinolinium Cation by *N*-Benzyl-5-nitroisoquinolinium Cations (8 and 14)[a]

X	k_2^H/k_2^D	X	k_2^H/k_2^D
4-CH_3O	1.52	3-F	1.90
H	1.68	4-CN	2.29

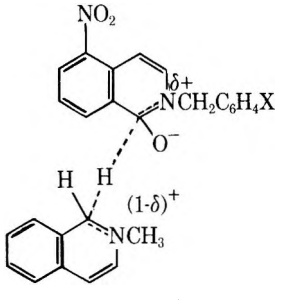
[a] At 25 °C, ionic strength 1.0, in 20% CH_3CN–H_2O.

The difference in the slopes of these correlation lines is significantly greater than the experimental error. In fact the kinetic isotope effect k_2^H/k_2^D shows a clear dependence on the electronic effect of the substituent X (Table II), and from eq 2 and 3 the substituent dependence of this isotope effect can be expressed by eq 4.

$$\log (k_2^H/k_2^D) = 0.18\sigma - 0.23 \quad (4)$$

Discussion

The reaction between the 2-benzyl-5-nitroisoquinolinium cation and the 2-methylisoquinolinium cation in aqueous base results in the oxidation of the former to 2-benzyl-5-nitroisoquinolinone and reduction of the latter to 1,2-dihydro-2-methylisoquinoline. The observed second-order kinetics for this reaction, the rate dependence on base concentration, the absence of a spectroscopically observable intermediate, and the deuterium labeling studies (for both product structure and kinetics) are all consistent with direct hydrogen transfer from the pseudobase anion **13** to the 2-methylisoquinolinium cation. The magnitudes of the kinetic isotope effects (k_2^D/k_2^D in Table II) require C–H bond breaking in the rate-determining transition state. The small negative ρ values (eq 2 and 3) indicate a small decrease in electron density for the *N*-benzylisoquinoline derivative in the transition state relative to the reactant pseudobase anion. All of these experimental data are most readily rationalized in terms of transition state **15** which involves hydride transfer from the pseudobase anion to the 2-methylisoquinolinium cation. The ρ values of eq 2 and 3, upon comparison with $\rho = -1.05$ for the protonation of



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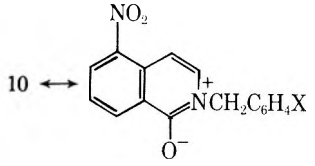
ring-substituted benzylamines,[18] clearly indicate that in the transition state only a small fractional positive charge is developed on the ring nitrogen atom of the *N*-benzylisoquinoline derivative; i.e., a quite "reactant-like" transition state.

The kinetic isotope effects increase with the electron-withdrawing effect of the substituent X and thus show a definite dependence on the nature of X (eq 4). This substituent dependence of k_2^H/k_2^D is the electronic reverse of that recently reported[17] for the oxidation of the same series of alkoxide ions (**13**) by ferricyanide ion. This latter reaction has $\rho(k_2^H) = -1.29$ which corresponds to a quite "product-like" transition state in contrast to the "reactant-like" transition state that is indicated for the present reaction. This dependence of substituent effect for k_2^H/k_2^D on transition state structure can be rationalized in terms of a combination of the theoretical prediction of a transition state dependent kinetic isotope effect[19] and the substituent dependence of transition state structure that is required by the Hammond postulate.[20] This argument has been presented earlier[17] for the product-like transition state in the ferricyanide oxidation of **13**, and will now be briefly enunciated for the reactant-like transition state in the present system.

A reactant-like transition state is consistent with a single-step exothermic reaction as indicated in Figure 4. As discussed previously,[17] the stability of the alkoxide ion **13** is expected to be relatively independent of the substituent X, while the stability of the isoquinolinone products **10**, represented by their zwitterionic resonance contributors **16**, will be more responsive to variations in X. Electron-withdrawing substituents (e.g., X = 4-CN) will lead to the destabilization of **16**, while electron-releasing substituents (e.g., X = 4-OCH_3) will lead to further stabilization of **16**. This situation is represented qualitatively in Figure 4. In such a case, the Hammond postulate predicts that the transition state should gradually become less reactant-like as X is varied from 4-OCH_3 to 4-CN. Theoretical treatments of primary kinetic isotope effects of asymmetric transition states predict that k^H/k^D should increase as the transition state becomes less reactant-like.[19] This prediction is in accord with the observed variation in k_2^H/k_2^D with the substituent X in the present study.



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The substituent dependence of k_2^H/k_2^D observed in this study is particularly interesting, since the substituent effects on the kinetic isotope effect are of similar magnitudes to the substituent effects on the reaction rate (eq 2–4). In this regard, it should be noted that theoretical considerations[19] of the dependence of kinetic isotope effects on transition-state structure predict the steepest dependence of isotope effect on transition-state structure when the transition states are very reactant-like (or very product-like). Such is the case in the present reaction. There appear to be few detailed systematic experimental studies of the transition-state dependence of kinetic isotope effects. Most available experimental data in this area refer to proton transfers, usually with large isotope effects which indicate later transition states (e.g., ref 19d), and so are not directly comparable with the present data.

The products observed for this reaction are exactly analogous to the disproportionation products of heterocyclic cations in aqueous base and strongly suggest that such reactions occur via hydrogen transfer from a pseudobase alkoxide ion to a heterocyclic cation. Such a suggestion was made some years ago by Jeffs[16] but without any supporting experimental evidence. Also consistent with this mechanistic interpretation is the recent observation of Clark and Parvizi[15] that **17** and **18** react to give the products **19** and **20** at pH 10.2 much faster than the self-disproportionation of **17** and **18** individually at this pH. These workers interpret the mechanism of hydride transfer in this reaction as being via transition state **21**; however, the alkoxide ion **22** could act as hydride donor to **17** in a kinetically equivalent mechanism to **21**.

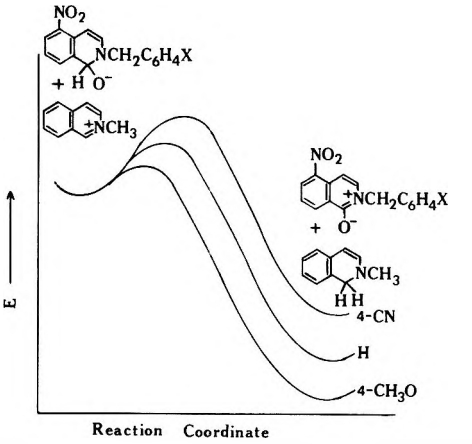
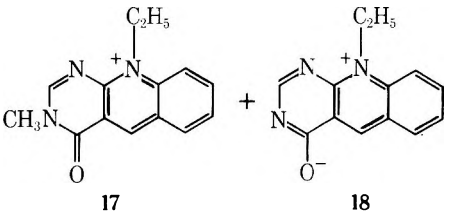


Figure 4. Schematic representation of the substituent dependence of the energy profiles for the reaction of *N*-benzyl-5-nitroisoquinolinium cations with the 2-methylisoquinolinium cation in basic solution. Curves derived as described in text and ref 17.



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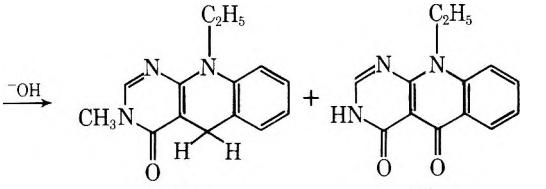

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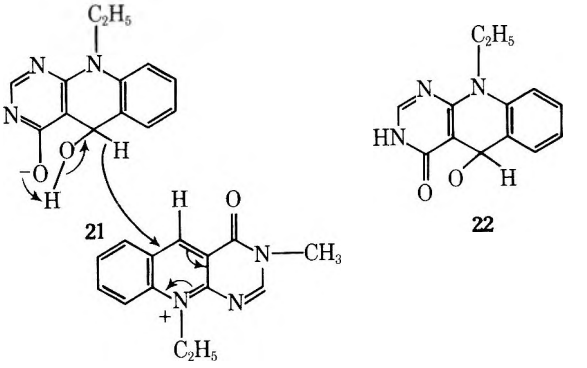

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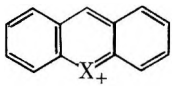
Such disproportionation via hydride transfer from pseudobase alkoxide ion to heterocyclic cation would be expected to occur most readily in those heterocyclic systems in which reasonable concentrations of cation and pseudobase anion can be obtained simultaneously. This implies ready disproportionation for those cations which have pK_{R^+} and pK_{RO^-} of similar magnitude, and particularly in those cases where $pK_{R^+} \geq pK_{RO^-}$. An example of the latter situation is the 1-methylquinolinium cation which irreversibly forms 1-methyl-2-

quinolinone in very basic aqueous solution without undergoing any spectral changes consistent with reversible pseudobase formation.[6] For this cation, pK_{R^+} has been estimated[6] as 16.5, while pK_{RO^-} may be estimated[21] as 14.4.

There are many heterocyclic pseudobases for which disproportionation has not been reported. For systems having $pK_{R^+} \ll pK_{RO^-}$, significant concentrations of heterocyclic cation and pseudobase anion cannot exist simultaneously. Thus, the rate of pseudobase disproportionation via reaction of heterocyclic cation and pseudobase anion would be quite small in such cases. However, it should also be noted that relatively ready disproportionation has been reported[12,13,22] for xanthylium and thioxanthylium cations which have extremely low pK_{R^+} values (e.g., $pK_{R^+} = -0.83$[23] for **23** (X = O) and $pK_{R^+} = -0.21$[23] for **23** (X = S)). These cations are very



23

susceptible to nucleophilic attack, and apparently in these cases the neutral pseudobases are sufficiently reactive to act as hydride donors toward such very reactive cationic hydride acceptors.

Habermehl and Schunk[24] have drawn attention to the analogy between pseudobase disproportionation and the Cannizzarro reaction of aldehydes, which can be considered to be a disproportionation of the aldehyde hydrate to a carboxylic acid and alcohol. This reaction is usually considered to involve hydride transfer from either the mono- or dianion (i.e., **24** or **25**) of the aldehyde hydrate to the carbonyl group of another aldehyde molecule. The anions **24** and **25** are clearly

24 **25**

quite similar electronically to the pseudobase anion which is suggested above to be involved in hydride transfer to a heterocyclic cation in pseudobase disproportionation.

Experimental Section

Salts of the cations **8** and **14** were available from earlier studies.[17,25] 2-Methylisoquinolinium bromide was prepared by treatment of isoquinoline with methyl bromide in a Fisher pressure bottle, and the product was recrystallized several times from aqueous ethanol. Potassium chloride and acetonitrile (spectroscopic) were the best commercially available grades. Potassium hydroxide solutions were prepared by dilution of a standardized 1 M KOH solution.

Kinetic Studies. All kinetic measurements were at 25.0 ± 0.05 °C in 20% (v/v) acetonitrile–water at ionic strength 1.0 (KOH + KCl). Reactions were followed using a Unicam SP1800 spectrophotometer–Unicam AR-25 linear recorder combination at 480 nm in all cases. Concentrations of *N*-benzyl-5-nitroisoquinolinium cations were in the range $2–4 \times 10^{-5}$ M, while concentrations of 2-methylisoquinolinium bromide were in the range $0.2–1.0 \times 10^{-2}$ M. First-order plots were linear for at least 4 half-lives and rate constants were calculated from least-squares fitting of these plots.

Product Studies. A typical experiment is described. A solution (50 mL) containing 2-(4-cyanobenzyl)-5-nitroisoquinolium bromide (2.7×10^{-3} M) and 2-methylisoquinolinium bromide (4.5×10^{-3} M) in 0.1 M KOH and 40% acetonitrile was allowed to react until the pink color of the pseudobase had faded (about 2 h). Acetonitrile was removed on the rotary evaporator at room temperature, and the aqueous solution was extracted with several aliquots of chloroform. Solvent was removed from the combined chloroform extracts on the rotary evaporator at room temperature. The residue was dissolved in $CDCl_3$ and the H^1 NMR spectrum was recorded. The major peaks in this spectrum were readily assigned to a mixture of 2-(4-cyanobenzyl)-5-nitro-1-isoquinolinone[17] and 1,2-dihydro-2-methylisoquinoline.[6] Several other unidentified signals were established by control experiments to be due to decomposition products of 1,2-dihydro-2-methylisoquinoline and/or small amounts of self-reaction products of the 2-methylisoquinolinium cation. Prolonged reaction of the alkaline solution, or the use of temperature above room temperature during the workup, resulted in extensive decomposition of 1,2-dihydro-2-methylisoquinoline.

The above experiment was repeated (a) with 2-(4-cyanobenzyl)-5-nitroisoquinolinium bromide in D_2O–acetonitrile and (b) with 1-deuterio-2-(4-cyanobenzyl)-5-nitroisoquinolinium bromide in H_2O–acetonitrile. In both experiments, the relative intensities of the signals at δ 4.12 (C(1)–H) and 2.69 (CH_3) of 1,2-dihydro-2-methylisoquinoline indicated that, within experimental error, there was no incorporation of solvent hydrogen at C-1.

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Structural Effects in Solvolytic Reactions. 27. Solvolysis of the *exo*- and *endo*-1,2-Diphenyl-2-norbornyl and -1,2-Dimethyl-2-norbornyl *p*-Nitrobenzoates and Chlorides. Definitive Evidence for the Classical Nature of the 1,2-Disubstituted Tertiary 2-Norbornyl Cations and Implications for the Structure of the Parent 2-Norbornyl Cation[1]

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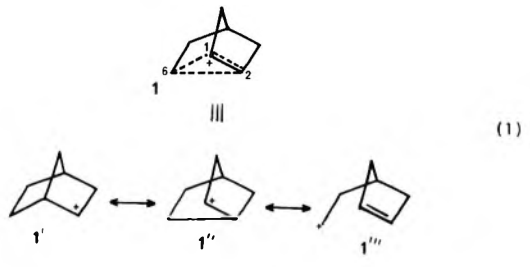
Received March 27, 1978

exo- and *endo*-1,2-diphenyl- and -1,2-dimethyl-2-norbornyl *p*-nitrobenzoates were synthesized and their rates of solvolysis determined in 80% aqueous acetone. The tertiary chlorides were also synthesized and their rates of solvolysis measured in 100% ethanol. The exo/endo rate ratios for the solvolysis of 1,2-diphenyl-2-norbornyl *p*-nitrobenzoates (350) and of 1,2-dimethyl-2-norbornyl *p*-nitrobenzoates (564) are similar to the ratios observed for the corresponding tertiary 2-phenyl and 2-methyl derivatives, as well as to those for the secondary 2-norbornyl tosylates. Similarly, the exo/endo ratio observed for the 1,2-dimethyl-2-norbornyl chlorides (178) is similar to the value previously determined for the epimeric 2-norbornyl chlorides (170). Consequently, the presence of substituents at the 2 position or at the 1,2 positions has little effect upon the observed exo/endo rate ratios. The introduction of a 1-phenyl substituent into the 2-phenyl-2-norbornyl *p*-nitrobenzoate does not increase, but decreases significantly the rate of solvolysis (by factors of 21 in the exo and 58 in the endo). A 1-methyl substituent, introduced into 2-methyl-2-norbornyl *p*-nitrobenzoate, increases the rate. The effect is the same in both the exo (8.5) and the endo (8.6). Similar effects were realized for the ethanolysis of the corresponding tertiary chlorides. The effects of the 1-phenyl and 1-methyl substituents reveal the absence of significant charge delocalization from the 2 to the 1 position in the solvolytic process. It is concluded that these tertiary derivatives must undergo solvolysis without σ bridging and accompanying charge delocalization to the 1 position associated with such bridging. Yet the free-energy diagram for the solvolysis of 1,2-dimethyl-2-norbornyl *p*-nitrobenzoate is remarkably similar to 2-methyl-2-norbornyl *p*-nitrobenzoate and to 2-norbornyl tosylate. It does not appear reasonable to attribute such similar behavior to the operation of totally different physical phenomena. Yet such has been claimed. Three such proposals which have been advanced are considered and refuted on the basis of available experimental data. Comparison of the rate of solvolysis of 2-methyl-*endo*-norbornyl chloride with that for *endo*-norbornyl chloride reveals a relative rate of 53 000. Ignoring minor differences in the ground state energies, this yields a difference in the energies of the tertiary and secondary transition states of 6.5 kcal mol^{-1}. This corresponds to an estimated difference in energy of the 2-methyl-2-norbornyl cation and 2-norbornyl cation under stable ion conditions of 7.5 kcal mol^{-1} and a difference in the calorimetric heats of ionization of 2-methyl-*exo*-norbornyl chloride and of *exo*-norbornyl chloride in SO_2ClF of 7.4 kcal mol^{-1}. These results establish that the magnitude of the positive charge at the developing cationic center in these transition states must approach that in the intermediate ions or ion pairs, providing strong support for the validity of the Hammond postulate as applied to solvolytic processes. The similarity in the tertiary/secondary rate ratio for the exo isomers to the value for the endo isomers supports the absence of any significant nonclassical resonance contribution to the rate of solvolysis of *exo*-norbornyl derivatives. These data yield essentially identical values of 2-Me/2-H, 5.3×10^4 for endo and 5.5×10^4 for exo, incompatible with the presence of major nonclassical resonance contributions in the exo secondary and its reduction or absence in the exo tertiary. Other approaches for extrapolating from the tertiary derivatives to the secondary fail to support the presence of a major nonclassical resonance contribution in the exo secondary, absent in the endo secondary and in the exo and endo tertiary derivatives, as postulated in some current proposals.

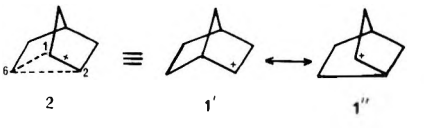
The proposed nonclassical structure (1) for the 2-norbornyl cation distributes positive charge from the 2 position to the 1 and 6 carbon atoms[4] (eq 1). The nonclassical ion (1)



(1)

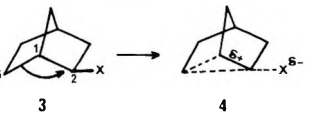
was considered to be a resonance hybrid of the three canonical structures, 1′, 1″, and 1‴. In this interpretation, the charge is not delocalized from the cationic center by hyperconjugation, but involves a specific σ bridge, converting the unsymmetrical classical structure (corresponding to 1′) into the nonclassical structure (1) with a plane of symmetry.

It was later suggested that this last structure (1‴) does not contribute significantly to the resonance hybrid.[5] Consequently, only canonical structures 1′ and 1″ need now be considered as significant contributors to the resonance hybrid (eq 2).



(2)

This structure implies that significant portions of the positive charge of the carbocation are distributed equally to C-1 and C-2. The transition state for a solvolytic process leading to such an intermediate is believed to be close to the carbocation produced.[6] Consequently, in the transition state (4) for the solvolysis of an *exo*-norbornyl derivative (3), a significant portion of the developing positive charge at C-2 should be delocalized to C-1 (eq 3). On the other hand, in the



(3)

endo isomer (5) the 1,6-bonding pair is postulated to be stereoelectronically unfavorable for such participation (eq 4).

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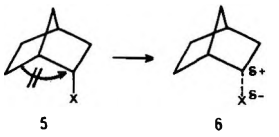


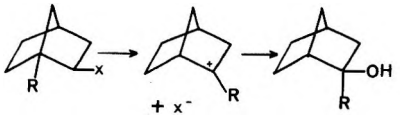
(4)

5 6

Consequently, the mechanism for the delocalization of charge from C-2 to C-1, which operates in the exo isomer, cannot be effective in the transition state for the endo isomer (**6**). It follows that there should be far less delocalization of charge from C-2 to C-1 in **6**, as compared to **4**. Accordingly, a reasonable test of the nonclassical proposal for 2-norbornyl would appear to be an examination of the relative magnitudes of the charge delocalization from C-2 in the transition states for the solvolysis of appropriate *exo*- and *endo*-norbornyl derivatives.

A frequently used test of this kind is the introduction of a phenyl or methyl group into the position being probed.[1b] These substituents provide electron density on demand to satisfy electron deficiencies at the carbon atoms to which they are attached. The 2 position in the transition state for a solvolyzing *endo*-norbornyl derivative should possess a far higher electron deficiency than the 2 position of the corresponding exo isomer, partially satisfied as the latter would be by electronic contributions from the 1,6-bonding pair. Therefore, 2-Me or 2-Ph should exhibit considerably greater activating effects on the endo isomers than on the corresponding exo isomers.

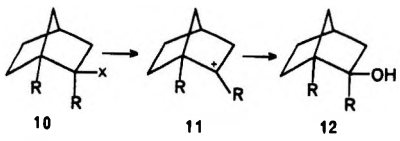
It is not possible to test in this way for such charge delocalization at C-1. The introduction of a phenyl or methyl group at C-1 produces a species (**7**) which undergoes solvolysis only with rearrangement to the tertiary cation[7] (**8**), subsequently converted to the tertiary derivatives (**9**) (eq 5). Consequently, such derivatives contain an internal driving force to produce in the solvolysis the more stable tertiary cation, so that it becomes difficult to utilize the effect of substituents at C-1 as a probe of the magnitude of the charge delocalization to C-1.



(5)

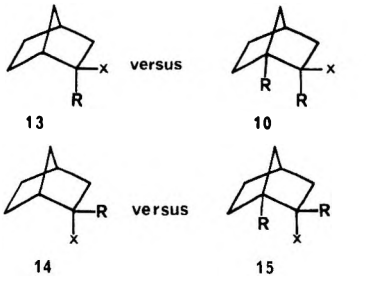
7 8 9

Fortunately, these difficulties can be avoided by introducing the substituent into the related 2-substituted-2-norbornyl derivative. This structural modification converts the molecule into a system (**10**) which undergoes solvolysis into a tertiary cation (**11**), without rearrangement to a more stable structure (eq 6). We are now in a position to observe whether a phenyl or methyl substituent, represented by R, introduced into the exo isomer (**13** → **10**) is far more effective than the same substituent introduced into the endo isomer (**14** → **15**) (eq 7 and 8).



(6)

10 11 12



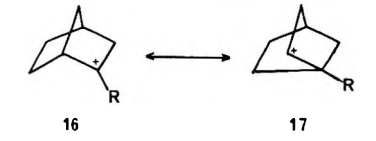
(7)

(8)

13 10 14 15

Note that the predicted effects of introducing such groups at C-2 are opposite to those for introducing the groups at C-1 for systems involving nonclassical resonance. At C-2 the rate-enhancing effect of the groups should be larger for the endo isomer. At C-1 the rate-enhancing effects of the groups should be larger for the exo isomer. *In the absence of nonclassical resonance, similar effects of such groups would be anticipated for both epimers.*

There was still another question we wished to answer. It has been argued that resonance is possible in the 2-norbornyl cation because the two canonical structures (**1′** and **1″**) are equivalent with identical energies (eq 2). On the other hand, in a tertiary cation, such as 2-phenyl- or 2-methyl-2-norbornyl (**16**), the two canonical structures (**16** and **17**) differ greatly in energies. Whatever the level of resonance stabilization in a nonclassical 2-norbornyl system (**1** ≡ **1′** ↔ **1″**), it should be much less[8] in **16** (eq 9). However, in symmetrically disubstituted 1,2-norbornyl cations, the two canonical structures (**18′** and **18″**) are again equivalent (eq 10). Will nonclassical resonance, of the kind postulated to be present in 2-norbornyl (eq 2), now return? If so, the 1-R substituent should exhibit an enormously greater effect in the exo isomer (eq 7) compared with the endo isomer (eq 8).



(9)

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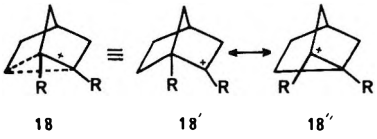


(10)

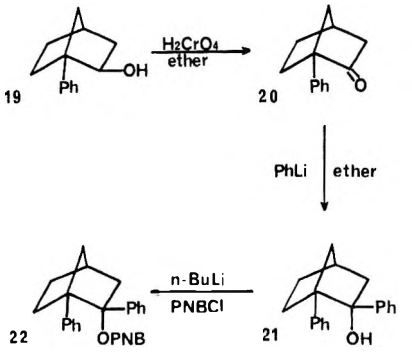
18 18′ 18″

Accordingly, we undertook to synthesize and to determine the rates of solvolysis of *exo*- and *endo*-1,2-diphenyl-2-norbornyl and 1,2-dimethyl-2-norbornyl *p*-nitrobenzoates in 80% aqueous acetone and the corresponding chlorides for solvolysis in 100% ethanol.

Finally, attention is called to the study of the related 1,2-di-*p*-anisyl-2-norbornyl,[9] 1,2-diphenyl-2-norbornyl,[10] and 1,2-dimethyl-2-norbornyl[11] cations under stable ion conditions, and to the highly pertinent studies on the solvolysis of optically active 1,2-dimethyl-2-norbornyl derivatives.[12,13] These studies will be incorporated into the discussion of the present results.

Results

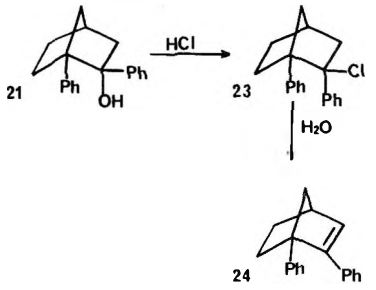
Synthesis. 1-Phenyl-*exo*-norbornanol[14] (**19**) was oxidized to 1-phenylnorbornanone (**20**) by aqueous chromic acid, utilizing the two-phase oxidation procedure.[15] Addition of phenyllithium in ether provided 1,2-diphenyl-*endo*-norbornanol[14] (**21**), converted to the *p*-nitrobenzoate (**22**) by treatment with *n*-butyllithium and *p*-nitrobenzoyl chloride in THF[16] (eq 11).



(11)

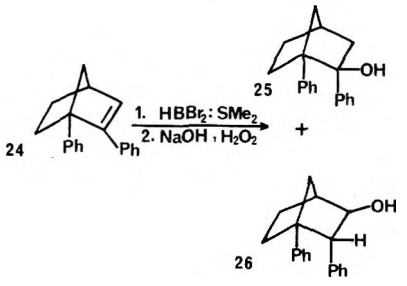
19 20 22 21

Major problems were encountered in the synthesis of the exo isomer. The standard procedure to obtain the exo isomer through solvolysis of the exo chloride (**23**) or the endo OPNB (**22**) failed. Only the corresponding olefin, 1,2-diphenylnorbornene (**24**), was produced (eq 12). Attempts to hydrate **24**



(12)

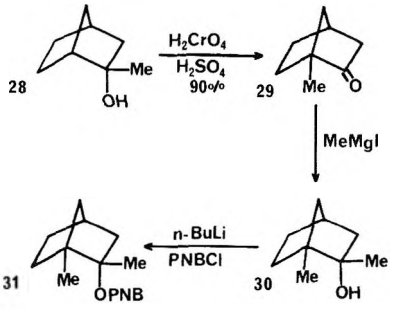
by oxymercuration–demercuration[17] or by synthesis of the epoxide[18] followed by reduction[19] failed. However, hydroboration of **24** by $HBBr_2/SMe_2$[20] followed by oxidation with alkaline hydrogen peroxide gave a mixture of approximately 10% of the desired 1,2-diphenyl-exo-norbornanol (**25**) with the isomeric secondary alcohol (**26**) (eq 13). The alcohol



(13)

mixture was converted into the mixed *p*-nitrobenzoates and most of the secondary isomer was removed by fractional crystallization. The resulting product, containing approximately 40% of the *p*-nitrobenzoate (**27**) of **25**, proved satisfactory for the solvolytic study. The secondary *p*-nitrobenzoate showed no evidence of undergoing solvolysis under the conditions used to solvolyze the desired tertiary isomer.

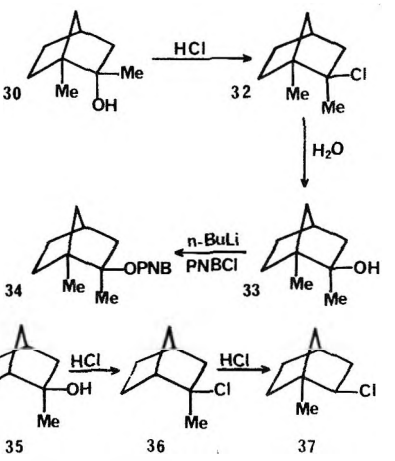
2-Methyl-*endo*-norbornanol (**28**) was converted to 1-methylnorbornanone (**29**) by means of a combined isomerization–oxidation technique. The ketone (**29**) was treated with methylmagnesium iodide to form 1,2-dimethyl-*endo*-norbornanol[21] (**30**). The alcohol was then converted into the *p*-nitrobenzoate (**31**) by the usual procedure[16] (eq 14). The endo



(14)

alcohol (**30**) was converted into the exo chloride (**32**) by treatment with hydrogen chloride in an automatic hydrochlorinator.[22] The chloride was then hydrolyzed in buffered aqueous acetone to yield 1,2-dimethyl-*exo*-norbornanol (**33**), which was converted into the *p*-nitrobenzoate[16] (**34**) (eq 15).

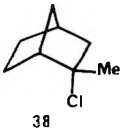
Treatment of 2-methyl-*exo*-norbornanol (**35**) with hydrogen chloride yields 2-methyl-*exo*-norbornyl chloride[21,23] (**36**). On further contact with hydrogen chloride rearrangement occurs to the secondary chloride[24] (**37**) (eq 16). There appears



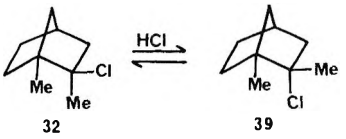
(15)

(16)

to be no method now available to prepare 2-methyl-*endo*-norbornyl chloride (**38**).



Fortunately, treatment of 1,2-dimethyl-*exo*-norbornyl chloride (**32**) with hydrogen chloride takes another course. Here, isomerization to the secondary chloride is not feasible. Instead, there is an isomerization to another isomer, identified as 1,2-dimethyl-*endo*-norbornyl chloride (**39**) (eq 17).



(17)

The formation of the second isomer can be followed by the appearance of two new methyl peaks in the ^1H NMR spectrum and by the formation of an isomer which undergoes solvolysis at a rate $^1/_{178}$ that of the original chloride. Both isomeric chlorides, which were not separated, undergo hydrolysis to the same alcohol (**33**). At equilibrium the two chlorides are present in the ratio 70% **32**/30% **39**.

Equilibration of 1,2-Dimethyl-2-norbornanols. The exo and endo alcohols, **30** and **33**, were dissolved in cyclohexane (0.2 M solutions) and isomerized under the influence of 6 M sulfuric acid at room temperature. GC analysis of aliquots revealed an equilibrium distribution of 72% exo and 28% endo, similar to the equilibrium distribution for the chlorides, 70% **32** and 30% **39**.

Rates of Solvolysis. The rates of solvolysis of the *p*-nitrobenzoates were determined in 80% aqueous acetone by the titrimetric procedure.[16] In our earlier studies,[1a] we had utilized 60% aqueous dioxane as the solvolytic medium, following Bartlett and Stiles.[25] However, we observed that this medium was not a satisfactory solvent for the slower compounds. Competitive reaction with oxygen produced acid, resulting in erratic, somewhat high values for the slower endo derivatives. Accordingly, we shifted to aqueous acetone on the recommendation of R. C. Fort and P. v. R. Schleyer and this has proven to be a far superior medium. Accordingly, we redetermined the kinetic data for the isomeric 1,2-dimethyl-2-norbornyl *p*-nitrobenzoates utilizing aqueous acetone and only these data are here reported. The pertinent rate data are summarized in Table I.

The rates of solvolysis of the tertiary chlorides were determined in 100% ethanol. The differential method was employed for determining the rate constants for 1,2-dimethyl-*exo*- and -*endo*-norbornyl chlorides.[26] The available rate data for the

Table I. Rates of Solvolysis of 1,2-Dimethyl-2-norbornyl and 1,2-Diphenyl-2-norbornyl *p*-Nitrobenzoates and Related Derivatives in 80% Aqueous Acetone

OPNB	isomer	$k_1 \times 10^6$ s^{-1} T_1, °C	T_2, °C	25 °C	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	exo/endo, 25 °C	rel rate, 25 °C	
2-CH_3[a]	exo	94.6 (100)	6.94 (75)	0.010[b]	26.3	−7.0	885	1.00	
	endo	54.7 (150)	5.41 (125)	1.13×10^{-5} [b]	30.1	−7.5			1.00
1,2-$(CH_3)_2$	exo[e]	40.0 (75)	1.91 (50)	5.45×10^{-2} [b] (8.44×10^{-2})[c]	26.6	−2.5	564 (875)[c]	5.45 (8.5)[c]	
	endo[f]	41.4 (125)	3.11 (100)	9.67×10^{-5} [b]	30.0	−3.8			8.6
2-Ph[d]	exo		179 (50)	7.56	23.6	−2.7	127	1.00	
	endo	364 (100)	30.2 (75)	0.059[b]	25.1	−7.4			1.00
1,2-Ph_2	exo[g]	168 (75)	9.86 (50)	0.36[b]	24.8	−4.9	350	0.048	
	endo[h]	204 (125)	17.9 (100)	1.03×10^{-3} [b]	28.2	−5.2			0.0174

[a] Reference 47. [b] Calculated from data at higher temperatures. [c] Values in parentheses are k_α values, $k_\alpha/k_t = 1.55$ in 90% aqueous acetone at 25 °C (ref 12), assumed to be the same in 80% aqueous acetone. [d] Reference 46. [e] Registry no.: 13351-32-1. [f] Registry no.: 13351-31-0. [g] Registry no.: 67162-93-0. [h] Registry no.: 67162-94-1.

Table II. Rates of Ethanolysis for Norbornyl Chlorides

system	isomer	registry no.	$k_1 \times 10^{-6}$ s^{-1} T_1, °C	T_2, °C	25 °C	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	exo/endo
2-norbornyl	exo[a]	765-91-3	175 (99.7)[b]	38.8 (85)[c]	0.0236[d] (5.42×10^{-4})[f]	26.6	−4.8	170[e]
	endo[a]	2999-06-6		0.56 (85)[c]	1.40×10^{-4} [g] (3.2×10^{-6})[f]			
2-methyl-2-norbornyl	exo	19138-54-6		0.754 (0)	30.0	23.3	−1.2	
	endo	6196-86-7			0.168[h]			178
1,2-dimethyl-2-norbornyl	exo	35033-23-9		6.03 (0)	210	22.6	−0.6	
	endo	6564-96-1			1.18			178
2-phenyl-2-norbornyl	exo	16166-72-6		9080 (0)	158000	17.9	−2.2	
1,2-diphenyl-2-norbornyl	exo	67162-95-2		542 (0)	11300	19.1	−3.5	
2-*p*-anisyl-2-norbornyl	exo[i]				2.55×10^8			

[a] In 80% ethanol. [b] Reference 27b. [c] Reference 27a. [d] Calculated from data at higher temperatures. [e] Calculated from the exo/endo rate ratio at 85 °C (70) assuming constant entropy. [f] Rate constant in ethanol. Calculated from the rate of chloride in 80% ethanol using the factor for the tosylates, $k_{1,\ 80\%\ EtOH}/k_{1,\ EtOH} = 43.5$; M.-H. Rei, Ph.D. Thesis, Purdue University, 1967. [g] Calculated from the exo/endo rate ratio of 170 at 25 °C. [h] Calculated from the rate of 1,2-dimethyl-*endo*-norbornyl chloride, assuming the effect of the 1-methyl substituent to be the same as in the exo isomers ($k_{1,2\text{-dimethyl-}exo\text{-}}/k_{2\text{-methyl-}exo\text{-}} = 7.0$). This assumption appears to be valid; see text. [i] H. C. Brown and K. Takeuchi, *J. Am. Chem. Soc.*, 88, 5336 (1966).

ethanolysis of the tertiary and secondary 2-norbornyl chlorides are summarized in Table II.

We wished to compare the rates of ethanolysis of *exo*- and *endo*-norbornyl chlorides at 25 °C with our values for the tertiary chlorides. Data were available for the solvolysis in 80% ethanol of *exo*-norbornyl chloride at 85 and at 99.7 °C and of *endo*-norbornyl chloride at 85 °C.[27] The exo/endo rate ratio of 70 at 85 °C calculates to be 170 at 25 °C, in good agreement with the value of 178 for 1,2-dimethyl-2-norbornyl chloride. The rate constant for the unknown 2-methyl-*endo*-norbornyl chloride was calculated from the rate for 1,2-dimethyl-*endo*-norbornyl chloride by assuming that the effect of the 1-methyl substituent was the same as in the exo isomers ($k_{1,2\text{-dimethyl-}exo\text{-}}/k_{2\text{-methyl-}exo\text{-}} = 7.0$). These values are included in Table II.

Alternatively, we could have estimated the rates for *exo*- and *endo*-norbornyl chlorides by proceeding from the tosylates, correcting from tosylate to chloride.[1b] Similarly, we could have proceeded from the rate constant for 2-methyl-*endo*-norbornyl *p*-nitrobenzoate (Table I) to the value for the chloride by correcting for the leaving group.[28] In fact, the values are very similar. However, the procedure adopted involves much smaller corrections. It also avoids the uncertainty involved in the usual assumption of a constancy in the correction factors for different leaving groups.[29,30]

Discussion

As was pointed out earlier, the nonclassical 2-norbornyl cation (2) is stabilized by resonance involving two equivalent canonical structures (1′ and 1″). Such resonance should be considerably lower in tertiary 2-norbornyl cations where the two canonical structures (16 and 17) differ considerably in their energies.[8] It was a major objective of the present study to examine the possibility that the introduction of a substituent at C-1, identical with that at C-2 (18), would again provide two equivalent canonical structures (18′ and 18″), resulting in an increase of the nonclassical resonance in the system. Such an increase could readily be detected in the transition state by comparing the effect of the substitutent at C-1 in the exo isomer as compared to that produced in the endo isomer.

The rate constant for ethanolysis of 2-methyl-*endo*-norbornyl chloride is 53 000 times that for *endo*-norbornyl chloride (Table II). Ignoring small differences in the ground-state energies, this means that the transition state for the solvolysis of the tertiary chloride must be 6.5 kcal mol^{-1} more stable than that for the corresponding secondary chloride.

To the extent that solvent participation contributes to the transition state for the secondary chloride, the difference will be even larger. However, recent studies have revealed that solvent participation is not significant in the solvolysis of both *exo*- and *endo*-norbornyl derivatives.[31,32] Consequently, it appears reasonable to ignore what can only be quite minor contributions of this kind by the usual solvolytic media.

According to the Hammond postulate, the transition state for solvolysis should be close to the first intermediate, the corresponding free ion or ion pair.[6] Therefore, the secondary

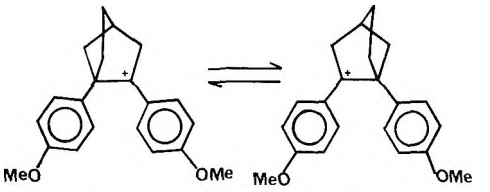
and tertiary 2-norbornyl cations (or ion pairs) should differ in energy by a quantity somewhat larger than 6.5 kcal mol^{-1}.

Under stable ion conditions, the tertiary 2-methyl-2-norbornyl cation is estimated to be some 7.5 kcal mol^{-1} more stable than the secondary 2-norbornyl cation.[33] Similarly, the difference in the calorimetric heats of ionization of 2-methyl-*exo*-norbornyl and *exo*-norbornyl chlorides in SO_2ClF has recently been determined to be 7.4 kcal mol^{-1}.[34] These values are in excellent agreement with the value derived from the relative rates and the Hammond postulate.[6] Resonance involving canonical structures which differ in energies by 6.5–7.5 kcal mol^{-1} should not be large.

In the same way, the two canonical structures for 2-phenyl-2-norbornyl cation (**16**, R = Ph) can be estimated to differ in energies by somewhat more than 12 kcal mol^{-1}. The corresponding structures for the 2-*p*-anisyl-2-norbornyl cation should differ in energies by some 15 kcal mol^{-1}.

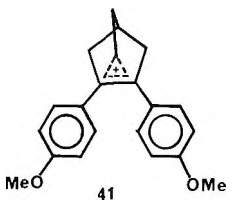
Consider the consequences of introducing a substituent at C-1, identical with the substituent at C-2 (eq 10). In the endo isomer, the substituent will have little effect, since σ bridging is postulated not to occur in the endo isomer (eq 8). However, in the exo isomer (eq 7), return of all or part of the resonance energy should bring about rate increases of 10^3–10^6 or even greater. Thus we should observe large unambiguous effects of the 1-R substituent in systems where nonclassical resonance returns or increases.

The 1,2-Di-*p*-anisyl-2-norbornyl System. We did not undertake an examination of this interesting system. It had been examined under stable ion conditions and unambiguous evidence had been obtained for its classical nature[9] (eq 18).



40 40′ (18)

The ion was generated in concentrated sulfuric acid. The UV spectrum was similar to that of the 2-*p*-anisyl-2-norbornyl cation, without the changes anticipated for extended conjugation in a symmetrical σ-bridged cation (**41**).



41

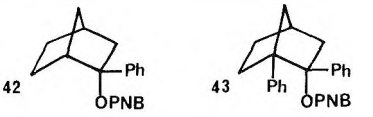
The 2-*p*-anisyl-2-norbornyl cation is half formed from the carbinol in 41% sulfuric acid. To form the ion **40** ⇌ **40′** requires more (51%), not less concentrated sulfuric acid. This is not in accord with greater stabilization of the cation by the cumulative effect of two *p*-anisyl groups, as in **41**.

The 2-*p*-anisyl-2-norbornyl cation does not react easily with bromine, evidently because the *p*-anisyl group is conjugated with the cationic center. The 1,2-di-*p*-anisyl cation takes up bromine in <1 min, corresponding to the presence of a nonconjugated *p*-anisyl group, as in **40** ⇌ **40′**.

Finally, on cooling solutions of the cation to low temperatures (−70 °C), changes in the ^1H NMR spectrum are observed which indicate impending nonequivalence of the two aryl rings.

It has been argued that these results should not be generalized to other systems. First, steric effects could prevent the two *p*-anisyl groups from being coplanar for optimum conjugation in **41**.[35,36] (However, such steric difficulties do not prevent the three *p*-anisyl groups in the more crowded tri-*p*-anisylmethyl cation from stabilizing the system: pK_R for *p*-An_3C^+ 0.82; *p*-An_2CH^+ −1.24).[37] Second, Winstein has suggested that highly stable 2-norbornyl cations, stabilized by extreme groups, such as 2-*p*-anisyl, should be classical.[38] However, he implied that less stabilizing groups, such as phenyl and methyl, could provide nonclassical cations. Accordingly, these were the focus of our studies.

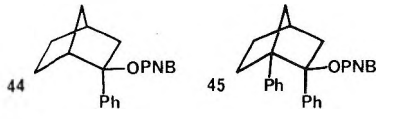
The 1,2-Diphenyl-2-norbornyl System. The introduction of a phenyl group at the 2 position of norbornyl increases the rate of hydrolysis over the parent compound by a factor of approximately 10^9 (Table II). The introduction of a phenyl group into the 1 position (**43**) in 2-phenyl-*endo*-norbornyl *p*-nitrobenzoate (**42**) does not increase the relative rate (RR), but decreases it by a factor of 58 (eq 19). Evidently, the combined inductive and steric effects of the 1-Ph substituent are responsible; no significant electronic contribution is anticipated for this isomer. The critical case is the exo isomer.



42 43 (19)

RR(25°C) 1.00 1/58

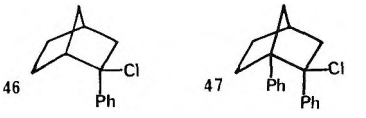
The presence of a 1-Ph substituent in 1,2-diphenyl-*exo*-norbornyl *p*-nitrobenzoate (**45**) does not result in any enhanced rate. Indeed, there is an actual decrease by a factor of 21 over the parent compound (**44**) (eq 20).



44 45 (20)

RR(25°C) 1.00 1/21

In the corresponding chlorides (**46** and **47**), the factor is similar, 16 (eq 21).

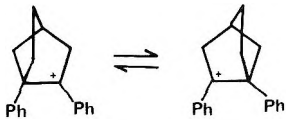


46 47 (21)

RR(25°C) 1.00 1/16

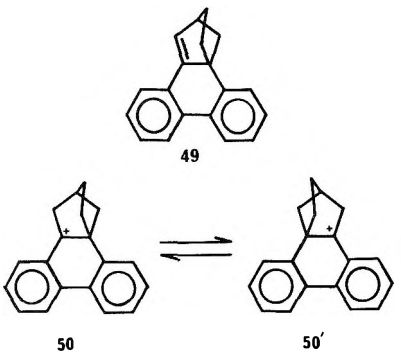
The exo/endo rate ratio for **45**/**43** is 350, slightly larger than the value of 127 realized for the parent system **44**/**42**. This increase in the exo/endo rate ratio arises not from any increase in the rate of the exo isomer (**45**), but from a comparative decrease in the rate of the endo isomer (**43**). Possibly, the decrease arises from the enhanced steric difficulties afforded by the 1-Ph substituent to the departure of the endo leaving group.[39]

Examination of the 1,2-diphenyl-2-norbornyl cation (**48**) by NMR has confirmed the conclusion that the system is best described as a pair of rapidly equilibrating classical cations[10] (eq 22).



48 48′ (22)

The steric argument for the failure of both aryl groups in **41** and its equivalent phenyl derivative to conjugate and thereby stabilize the nonclassical structure is rendered questionable by a study of the behavior of the phenanthrene derivative[40] (**49**) (eq 23). This olefin **49** dissolves in fluorosulfonic acid to give a pair of classical equilibrating cations,

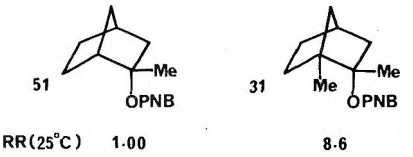


(23)

50 ⇌ **50′**, recognizable by the UV and ^{1}H NMR spectra.[40]

The 1,2-Dimethyl-2-norbornyl System. Aryl groups can, on occasion, be treacherous as a probe for electron delocalizations. If the system makes only a small demand on the aryl substituent for electrons, the −I effect of the aryl group can predominate over the +R effect.[41] As discussed earlier, steric inhibition to resonance can also be a factor.[42] However, methyl substituents appear to be free of these ambiguities. They exert consistent electron-supplying effects, +I and +R, and these effects do not appear to be susceptible to steric influences. Accordingly, the study of the 1,2-dimethyl-2-norbornyl system was emphasized.

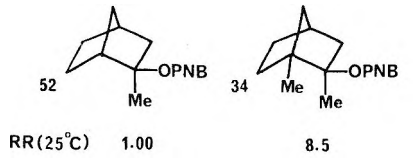
The introduction of a methyl group into the 1 position of the endo isomer (**51**) increases the rate of solvolysis of the *p*-nitrobenzoate (**31**) by a factor of 8.6 (eq 24). Presumably,



(24)

the increase is the result of the combined steric and inductive effects of the 1-methyl substituent.

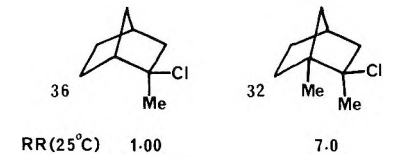
The question is the effect of a 1-methyl substituent (**34**) on the exo isomer (**52**). If the 1-methyl group were to induce the return or increase of nonclassical resonance to the cation and to the transition state modeling the cation,[6] such stabilization should result in a major rate enhancement, as high as 10^3–10^6. However, this is not observed. The rate enhancement (eq 25)



(25)

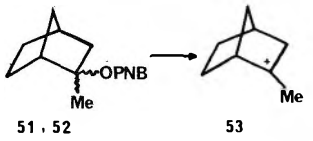
is identical with that observed for the endo isomer (eq 24).

1,2-Dimethyl-*exo*-norbornyl chloride (**32**) exhibits a rate enhancement over **36** by a comparable factor (eq 26).

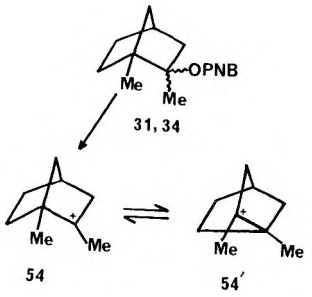


(26)

We took advantage of this constancy in the effect of the 1-Me substituent to convert the rate constant for 1,2-dimethyl-*endo*-norbornyl chloride into the rate constant for the presently unknown 2-methyl-*endo*-norbornyl chloride by dividing the rate constant for the former (**39**) by the factor 7 (Table II). These results clearly establish the absence of significant charge delocalization from C-2 to C-1 in the transition state for solvolysis of the 2-methyl-*exo*-norbornyl *p*-nitrobenzoate (**52**). Clearly the solvolyses of the 2-methyl (**51** and **52**) and the 1,2-dimethyl (**31** and **34**) derivatives must proceed without significant participation of the 1,6-bonding pair, leading to the formation of the corresponding classical cations, **53** and **54** ⇌ **54′** (eq 27 and 28).

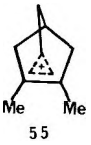


(27)



(28)

This conclusion is supported by results of Goering and his co-workers. Thus the solvolysis of optically active 1,2-dimethyl-*exo*-norbornyl *p*-nitrobenzoate (**34***) in 90% aqueous acetone gives alcohol with 9% retention.[12] Similarly, methanolysis of optically active 1,2-dimethyl-*exo*-norbornyl chloride (**32***) gives the methyl ether with 14% retention.[13,43] Clearly the cation produced cannot be the symmetrical σ-bridged species (**55**). The authors conclude that they are trapping the



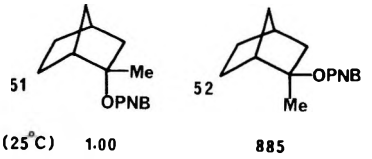
rapidly equilibrating classical cation or ion pair before complete equilibration has been achieved (eq 28).

MINDO/3 calculations indicate that in the gas phase the classical form of 2-norbornyl (**1′**) is more stable than the nonclassical form (**2**) by approximately 2 kcal mol^{-1}.[44a] A much larger energy difference, 12 kcal mol^{-1}, favors the classical structure for the 2-methyl-2-norbornyl cation[44a] (**53**). MINDO/3 calculations reveal that solvation stabilizes the classical structure over the nonclassical.[44b] Consequently, there can be little reason to question at this time the interpretation that 2-methyl-*exo*- and 1,2-dimethyl-*exo*-norbornyl derivatives undergo solvolysis through classical (unbridged) transition states to classical cations (eq 27 and 28) or ion pairs.

Even under stable ion conditions, the 1,2-dimethyl-2-norbornyl cation exists as a rapidly equilibrating pair of classical cations (**54** ⇌ **54′**).[11,45] Consequently, we can extend our position to accept the existence of both 2-methyl-2-norbornyl and 1,2-dimethyl-2-norbornyl cations in classical form in solvolytic media, in superacids, and in the gas phase.

Exo/Endo Rate Ratios. In the case of 1,2-diphenyl-2-norbornyl *p*-nitrobenzoates (**45/43**), the exo/endo rate ratio is 350, as compared with values of 127 for the parent 2-phenyl derivatives[46] (**44/42**) and 280 for the acetolysis of 2-norbornyl tosylate.[5] (Corrected for internal return both the first and last of these would increase modestly.) As discussed earlier, the small increase in the exo/endo rate ratio for **45/43** arises primarily because of a decrease in the rate of the endo isomer, **43**. This could arise from a increase in steric effects hindering the departure of the endo leaving group.[39]

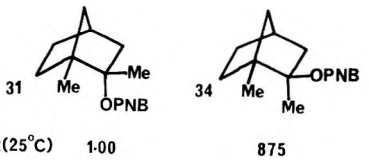
The exo/endo rate ratio in the solvolysis of 2-methyl-2-norbornyl *p*-nitrobenzoates (**52/51**) is 885[47] (eq 29). Under the same conditions, the exo/endo rate ratio in the solvolysis of the corresponding 1,2-dimethyl derivatives (**34/31**) is 564 (Table I). Corrected for internal return,[12] this becomes 875



(29)

RR(25°C) 1.00 885

(eq 30). Hence, a methyl substituent in the 1 position has essentially no effect on the exo/endo rate ratio, further evidence

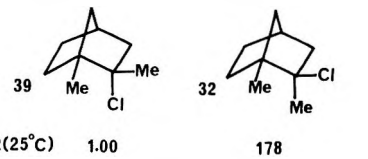


(30)

RR(25°C) 1.00 875

for the absence of σ bridging and charge delocalization in the transition state for the solvolysis of the exo isomer **34**.

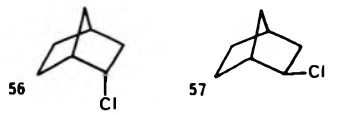
The ethanolysis of 1,2-dimethyl-2-norbornyl chlorides (**32/39**) gives an exo/endo rate ratio of 178 at 25 °C (eq 31).



(31)

RR(25°C) 1.00 178

This is similar to the exo/endo ratio of 170 for the solvolysis of *exo*- and *endo*-norbornyl chloride (**57/56**) in 80% ethanol (Table II) (eq 32).



(32)

RR(25°C) 1.00 170

All efforts to obtain independent evidence for σ bridging in the transition state for the solvolysis of 2-methyl- and 1,2-dimethyl-2-norbornyl derivatives have failed. How then are we to account for exo/endo rate ratios as large as 885 and 875 (eq 29 and 30)? Clearly, high exo/endo rate ratios can no longer be considered to require σ bridging.

Free-Energy Diagrams. We are now in position to examine the properties of such classical tertiary 2-norbornyl cations and to compare them with the corresponding properties of the secondary derivatives. The Goering–Schewene diagram provides a quantitative representation of the relationship between the ground-state energies of the exo and endo isomers, the exo/endo rate ratio, and the exo/endo product ratio.[48]

In the case of the secondary tosylate (Figure 1) the difference in the free energies of the exo and endo transition states is 5.8 kcal mol^{-1}. (Because of the greater precision we utilize the free energies rather than the derived enthalpies.[48]) The nonclassical ion interpretation accounts for the lower energy of the exo transition state in terms of its stabilization via σ bridging as the system proceeds along the reaction coordinate to the σ-bridged cation **1** or the equivalent ion pair. The endo isomer is proposed to be stereoelectronically unfavorable for such σ bridging so that ionization proceeds to the classical ion or ion pair.

Since the two transition states differ by 5.8 kcal mol^{-1}, the fully developed nonclassical cation (or ion pair) and the classical cation (or ion pair) must differ by more than 5.8 kcal mol^{-1}. On the basis of the Hammond postulate, fully supported by the experimental data of the present study, the increment need not be large; an estimate of 7 kcal mol^{-1} may be considered reasonable for the difference in energy between the nonclassical and classical structures of the 2-norbornyl cation (solvated). (The difference in energy for the unsolvated ions in the gas phase should be even larger.)[44b] The present study establishes that the solvolysis of 1,2-dimethyl-*exo*-norbornyl *p*-nitrobenzoate proceeds without detectable σ bridging (with accompanying charge delocalization from the 2 to the 1 position). It appears, therefore, appropriate to construct a free-energy diagram for the solvolysis of the 1,2-dimethyl-2-norbornyl *p*-nitrobenzoates for comparison.

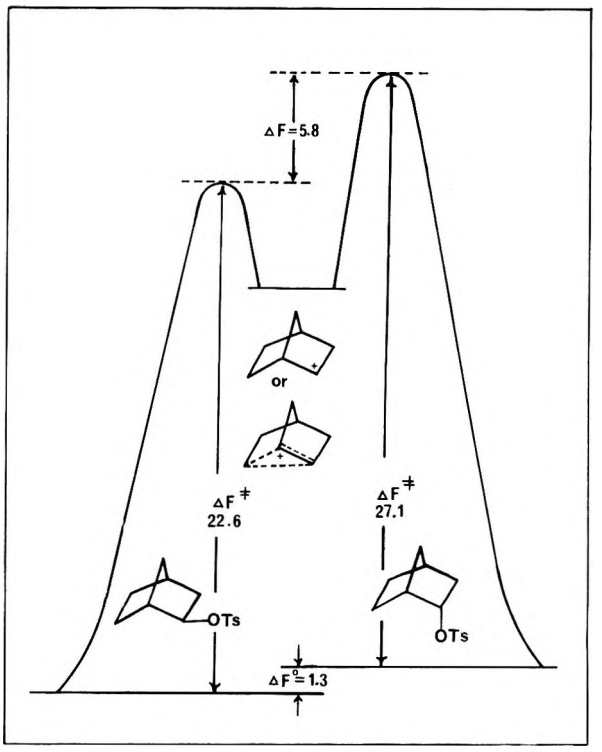


Figure 1. Free-energy diagram for the solvolysis of 2-norbornyl tosylates in acetic acid at 25 °C.

The free energy of activation for the solvolysis of 1,2-dimethyl-*exo*-norbornyl *p*-nitrobenzoate, corrected for internal return, is 27.2 kcal mol^{-1}; the corresponding value for the endo isomer is 31.1 kcal mol^{-1}. Equilibration of the two epimeric alcohols yields a distribution of 72% *exo*-OH and 28% of *endo*-OH. This establishes that the ground-state energy of the endo isomer is higher than that of the exo isomer by a relatively small quantity, 0.6 kcal mol^{-1}. These data yield a diagram (Figure 2) with a difference in the energies of the two transition states of 4.5 kcal mol^{-1}. Such a difference predicts that the cationic intermediate will distribute itself between exo and endo product in the ratio of 99.8% exo/0.2% endo. Experimentally the observed distribution is ≥99.7% exo/≤0.3% endo.

The free-energy diagram for this tertiary system (Figure 2) is remarkably similar to the diagram for the parent secondary system (Figure 1).[48,49]

The high exo/endo rate ratio or the difference in energies between the two transition states for 1,2-dimethyl-2-norbornyl (Figure 2) cannot be attributed to σ bridging and charge delocalization in the exo isomer. The present study has established the absence of these effects in the 1,2-dimethyl system. Consequently, we must find some other explanation. Steric hindrance to ionization has been proposed.[50]

There is now some acceptance of this interpretation (steric hindrance to ionization) of slow rates for the tertiary *endo*-norbornyl system,[51] but a reluctance to extend this interpretation to the parent secondary system.[51,52] Yet is it reasonable to utilize two very different explanations for phenomena which appear so similar? Yet such has been the case. In a later section we shall consider in detail three different proposals of this kind which have been advanced. However, first we shall

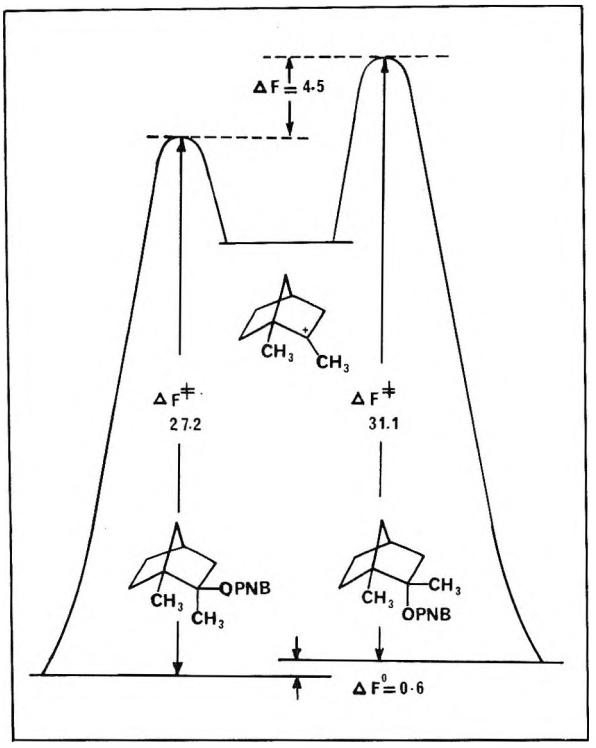


Figure 2. Free-energy diagram for the solvolysis of 1,2-dimethyl-2-norbornyl *p*-nitrobenzoates in 80% aqueous acetone at 25 °C.

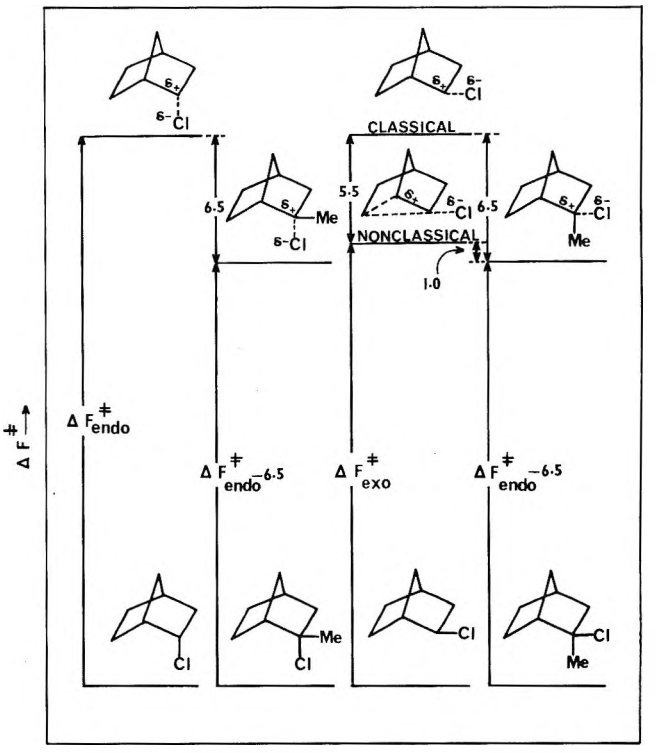


Figure 3. Free energies of activation for the epimeric 2-norbornyl chlorides and 2-methyl-2-norbornyl chlorides assuming the presence of 5.5 kcal mol^{-1} nonclassical stabilization in the exo secondary and its absence in the exo tertiary.

subject to critical test the proposal that the transition state for *exo*-norbornyl solvolysis is resonance stabilized by some 5.8 kcal mol^{-1} (from the Goering–Schewene diagram) as compared to *endo*-norbornyl.

Comparative Energies of Exo and Endo Transition States for Secondary and Tertiary Systems. In recent years there has been a number of attempts to define the stabilities of carbocations in the gas phase[53-55] and in superacids.[33,34,56] Thus it has been observed recently that the calorimetric heat of ionization of 2-propyl chloride (−15.3 ± 0.9 kcal mol^{-1}) is less than that of *tert*-butyl chloride (−25.4 ± 0.8) by some 10.1 kcal mol^{-1}.[34] On the other hand, the values for *exo*-norbornyl chloride (−23.6 ± 0.8) is less than that of 2-methyl-*exo*-norbornyl chloride (−31.0 ± 1.5) by some 7.4 kcal mol^{-1}.[34] Similarly, the difference between 2-propyl chloride and 2-phenyl-2-propyl chloride (−30.3 ± 0.3) is 15.0 ± 1.2 kcal mol^{-1}, whereas the difference between *exo*-norbornyl chloride and 2-phenyl-*exo*-norbornyl chloride (−37.0 ± 1.2) is 13.4 ± 2.1 kcal mol^{-1}.[34]

This change in the secondary–tertiary energy difference for simple alkyl derivatives and the corresponding 2-norbornyl compounds,[57] 2.7 kcal mol^{-1} for the methyl and 1.6 kcal mol^{-1} for the phenyl derivatives, can be interpreted to indicate a modestly higher stability of the secondary 2-norbornyl cation. However, the question must be raised: does such higher stability require σ bridging in the 2-norbornyl cation?

Although such results have been so interpreted in the past, the fact is that this change in the secondary–tertiary energy difference does not require that the secondary 2-norbornyl cation be σ bridged. The 2-norbornyl cations contain a rigid three-dimensional structure which can well delocalize charge from the 2 position by mechanisms other than the σ bridging inherent in the nonclassical interpretation.

Solvolytic data would appear to be more capable of providing an unambiguous answer. The nonclassical concept was introduced in large part to account for the high exo/endo rate ratio in the solvolysis of 2-norbornyl derivatives.[4] Now numerous high exo/endo rate ratios have been observed in the solvolyses of many tertiary 2-norbornyl derivatives where σ bridging has been demonstrated to be absent.[58] There can now be no question but that high exo/endo rate ratios can be realized in stabilized tertiary 2-norbornyl systems not involving σ bridging. The point requiring settling is whether the high exo/endo ratios in 2-norbornyl itself can be accounted for in the same way, or whether we still require σ bridging to account for the parent secondary derivative.

The advantage of the solvolytic approach is that it distinguishes between exo and endo, in contrast to work with the actual ions in superacids. It is a fundamental requirement of the nonclassical phenomenon that σ bridging plays a major role in the solvolysis of the exo isomer, but not of the endo isomer.

As a first approximation, let us ignore the minor differences in the ground-state energies of *exo*- and *endo*-norbornyl chloride (**57** and **56**) and 2-methyl-*exo*- and -*endo*-norbornyl chloride (**36** and **58**). The exo transition state for the solvolysis of representative secondary 2-norbornyl derivatives is more stable than the corresponding endo transition state by some 5.5 kcal mol^{-1}.[59] The introduction of a methyl group into *endo*-norbornyl chloride increases its rate of solvolysis by a factor of 53 000 (Table II). This indicates that the methyl group stabilizes the transition state for the solvolysis of 2-methyl-*endo*-norbornyl chloride by 6.5 kcal mol^{-1}. The introduction of a methyl group into *exo*-norbornyl chloride provides a species which undergoes solvolysis to the classical 2-methyl-2-norbornyl cation. Consequently, the stabilization resulting from the 2-methyl substituent, ~6.5 kcal mol^{-1}, is counterbalanced by the loss of the 5.5 kcal mol^{-1} nonclassical σ bridging in the transition state. There is a net gain in stabilization of only 1.0 kcal mol^{-1}, a factor of only 5!

This analysis predicts that the rate of solvolysis of 2-methyl-*exo*-norbornyl chloride will be faster than *exo*-norbornyl chloride by a factor of only 5. In actual fact, the experimental relative rate is 55 000, almost identical with that of the endo isomers.

The analysis is represented graphically in Figure 3.

α-Methyl/Hydrogen Ratios in 2-Norbornyl. Schleyer

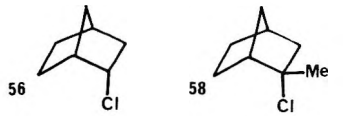
and his co-workers have proposed utilization of α-methyl/hydrogen rate ratios as a diagnostic tool to test for nonclassical resonance stabilization.[60,61] They argued that the limiting value (in the absence of anchimeric and nucleophilic solvent assistance) should be in the neighborhood of 10^8.[60] We had earlier reported that α-methyl/hydrogen ratios for the solvolysis of *exo*-norbornyl chlorides in ethanol at 25 °C is $10^{4.8}$.[1b,62] This diminished value was attributed by other workers to anchimeric assistance (σ bridging) in secondary *exo*-norbornyl[60,63] (solvent assistance is quite unlikely) which increases the rate of the exo isomer "by several powers of 10".

The α-methyl/hydrogen ratio in the solvolysis of *endo*-norbornyl bromides has been reported as 10^5.[61] The diminished ratio for the endo isomers was then accounted for in terms of an enhanced rate for the secondary endo derivatives resulting from large nucleophilic solvent contributions (k_S).[61]

Both Harris, Mount, and Raber[31] and we,[32] by means of independent experimental approaches, have now concluded that the solvolyses of *endo*-norbornyl derivatives proceed without significant solvent participation (k_c). *exo*-Norbornyl derivatives were also shown to solvolyze without significant solvent participation (k_c or k_Δ). In view of this development, we undertook to reexamine the α-methyl/hydrogen ratios in the solvolysis of *exo*- and *endo*-norbornyl chlorides. We restricted ourselves to the chlorides because of growing evidence that there can be large front strain effects in the solvolysis of tosylates and *p*-nitrobenzoates.[29,30]

The fact that we were successful in synthesizing for the first time 1,2-dimethyl-*endo*-norbornyl chloride and determining its rate of solvolysis made it possible to estimate the rate for 2-methyl-*endo*-norbornyl chloride (Table II) with reasonable confidence, without the need for large corrections for different leaving groups.

The α-methyl/hydrogen ratio of 5.3×10^4 for *endo*-norbornyl raises a serious question as to the earlier proposal of 10^8 for this ratio in the absence of either solvent or anchimeric assistance[61] (eq 33). It is probable that this ratio varies with

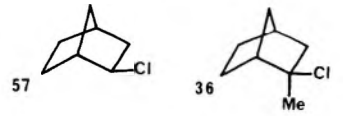


(33)

RR(25°C) 1.00 5.3×10^4

structure, influenced by steric effects, similar to the large variations in the α-*tert*-butyl/α-methyl ratios which have been observed.[64] Harris and his co-workers have come to the same conclusion.[31]

The question now is the magnitude of the α-methyl/hydrogen ratio for *exo*-norbornyl chloride. Will it be a far smaller value, corresponding to the oft postulated σ bridging? In fact the value is 5.5×10^4, almost identical with that for the endo isomer (eq 34).



(34)

RR(25°C) 1.00 5.5×10^4

The close similarity in the α-methyl/hydrogen rate ratios in *exo*- and *endo*-norbornyl chlorides essentially rules out a k_Δ process for the solvolysis of the exo isomer. The remarkable constancy of the exo/endo rate ratio over an exceptionally wide range of solvents and the similarity in the effects of solvent on the rates of solvolysis of *exo*- and *endo*-norbornyl with those of 2-adamantyl[65] (a model k_c process) argues strongly for the conclusion that *exo*-norbornyl must also undergo solvolysis by a process that is essentially k_c.[32]

These results call for a revision of the previous interpretations that the α-methyl/hydrogen ratio in 2-norbornyl indicates large anchimeric assistance for the solvolysis of *exo*-norbornyl and large solvent assistance for the solvolysis of *endo*-norbornyl derivatives.[63,66] The results are interpreted far more simply in terms of essentially k_c processes in both cases. It should be pointed out that Farcasiu earlier pointed out that α-methyl/hydrogen ratios are not reliable criteria for σ bridging in complex systems.[67]

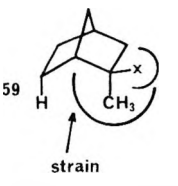
It is appropriate to call attention to the fact that over the years numerous criteria have been advanced in support of σ bridging in the solvolysis of *exo*-norbornyl derivatives. One by one these proposals have crumbled under critical examination. Now the α-methyl/hydrogen criterion joins this growing graveyard.[68]

Effect of Substituents at C-1 and C-2. In the Introduction we pointed out that the presence of σ bridging and accompanying electron delocalization in the exo isomers should result in markedly different effects of substituents at C-1 and C-2. Thus a substituent such as methyl at C-2 should exhibit a much higher activating effect in the endo isomer than in the exo (Figure 2), if charge were delocalized in the latter by a σ bridge. Contrariwise, such a substituent at C-1 would be much more activating in the exo isomer than in the endo isomer. On the other hand, in the absence of nonclassical resonance energy, both in the secondary and tertiary derivatives, we should expect essentially identical effects of substituents, both at C-2 and C-1, in each exo and endo isomer pair.

We have seen that Me/H at C-1 is 8.6 for the endo isomer (eq 24) and 8.5 for the exo isomer (eq 25). We have also seen that Me/H at C-2 is 5.3×10^4 for the endo isomer (eq 33) and 5.5×10^4 for the exo isomer (eq 34). Clearly the observed effects correspond to the absence of a σ-bridged nonclassical species in the transition state for the solvolysis of the exo isomer.

Factor Responsible for the High Exo/Endo Rate Ratios in Secondary and Tertiary 2-Norbornyl Systems. Three different proposals have been advanced to account for the evident similarity in the Goering–Schewene diagrams for secondary and tertiary 2-norbornyl derivatives (Figures 1 and 2) without accepting a common physical origin. (In an earlier section we asked the question: "Is it reasonable to propose two very different explanations for phenomena which appear so similar?" This was answered emphatically by Paul Schleyer: "Yes, it certainly is!")[69]

Proposal No. 1. It was originally proposed back in 1965–1966 that steric effects in the tertiary 2-methyl-2-norbornyl derivatives would be very large, with the steric requirements of the methyl substituent far exceeding the acyloxy group. On this basis large steric strains were estimated for the *endo*-methyl substituent (**59**). Such strain would be relieved during



ionization.[70] The smaller strain assumed for the isomer in which the 2-methyl substituent is exo would be less effective in increasing the rate.

On this basis, the high exo/endo rate ratio in secondary 2-norbornyl was attributed to an enhanced exo rate, resulting from carbon assistance, with a normal endo rate, whereas the high exo/endo rate ratio in tertiary 2-norbornyl was attributed to a greatly enhanced exo rate, resulting from relief of steric strain, with a comparatively normal endo rate.

This proposal requires that 2-methyl-*endo*-norbornanol be far more stable than 2-methyl-*exo*-norbornanol. However, equilibration experiments soon revealed that the two isomers possess comparable stabilities.[1c]

Proposal No. 2. A later proposal was that the solvolysis of *endo*-norbornyl tosylate is enhanced by large solvent participation comparable in magnitude to carbon participation in the exo isomer. Thus, one of two alternatives considered to account for the 2-Me/2-H reactivity ratios was: "These $\approx 10^5$ values can be rationalized by the postulation of anchimeric assistance in the exo and solvent assistance in the endo secondary cases . . .".[61] This position was adopted and fully discussed by J. M. Harris and S. P. McManus in their interesting attempt to extrapolate from tertiary to secondary 2-norbornyl rates.[63]

However, as was pointed out earlier in the present paper, both J. M. Harris and we, in independent studies, have now concluded that solvent participation is not a significant factor in the solvolysis of *endo*-norbornyl tosylate in solvents of moderate or low nucleophilicities.[31,32]

Proposal No. 3. In "The Nonclassical Ion Problem", Paul Schleyer also discusses another interpretation.[50] He accepts steric hindrance to ionization in the tertiary 2-methyl-*endo*-norbornyl system. However, he argues that such steric hindrance to ionization should not be important in the secondary 2-norbornyl system.[71]

In fact, a careful consideration of the molecular models reveals that even 2-H can serve to trap the anion in the endo cavity.[52] In addition, the ion pair which is presumably the first intermediate in such solvolyses should be far tighter for the secondary system than the stabler tertiary system. This factor may serve to compensate for the smaller size of 2-H.

However, there appears to be little point to a discussion of this proposal on theoretical grounds, when experimental data are available to settle the question. As was pointed out earlier, the nonclassical interpretation of the Goering–Schewene diagram (Figure 1) requires that the nonclassical 2-norbornyl cation be more stable than classical 2-norbornyl cations by some 7 kcal mol^{-1}. However, comparison of the heats of ionization for 2-propyl, *tert*-butyl, and *tert*-cumyl chlorides with 2-norbornyl, 2-methyl-2-norbornyl, and 2-phenyl-2-norbornyl chlorides reveals a total stabilization that is in the neighborhood of 1–2 ± 2 kcal mol^{-1}.

There appears at the present time to be no sound basis to attribute totally different physical causes to the essentially similar behavior of secondary and tertiary 2-norbornyl derivatives (Figures 1 and 2).

Conclusions

The essentially identical effect of a 1-phenyl and a 1-methyl substituent in the solvolysis of the exo and endo isomers of 1,2-diphenyl- and 1,2-dimethyl-2-norbornyl *p*-nitrobenzoates rigorously precludes σ bridging as a significant factor in the rates of solvolysis of the exo isomers. The high exo/endo rate ratios in the solvolysis of 1,2-diphenyl- and 1,2-dimethyl-2-norbornyl derivatives cannot be the result of σ bridging. The close similarity in the Goering–Schewene diagrams for the solvolysis of 1,2-dimethyl-2-norbornyl, 2-methyl-2-norbornyl, and 2-norbornyl itself suggests the operation of similar physical factors. Steric hindrance to ionization of the tertiary 2-norbornyl derivatives offers a reasonable explanation of the high exo/endo rate ratios in the demonstrated absence of σ bridging. The problem is the extension of the analysis to the secondary 2-norbornyl. It is pointed out that the Goering–Schewene diagrams and the exo/endo rate ratios are remarkably similar for both secondary and tertiary 2-norbornyl derivatives. The α-methyl/hydrogen ratio is essentially identical for both *exo*- and *endo*-2-norbornyl. It is no longer possible to account for this in terms of rate enhancements of comparable magnitudes arising from solvent participation in the endo and carbon participation in the exo. The results are more simply accounted for in terms of solvolysis proceeding through essentially k_c processes for both exo and endo secondary and tertiary 2-norbornyl derivatives.

Experimental Section

All melting points are uncorrected. The ^1H NMR spectra were recorded on a Varian A60A or T-60 spectrophotometer.

1-Methylnorbornanone (29). 2-Methyl-*endo*-norbornanol **(28)** (51 g, 400 mmol) was oxidized with a solution of chromic acid prepared from sodium dichromate (107 g), sulfuric acid (274 g), and water (840 mL) at 90 °C for 3 h in a 2-L, three-neck, round-bottom flask equipped with mechanical stirrer, condenser, and an additional funnel.

1-Methylnorbornanone (32 g, 65% yield) was isolated by steam distillation. The crude product was redistilled to yield 25.4 g of ketone, $n^{20}D$ 1.4676 [lit.[21] $n^{20}D$ 1.4674].

1,2-Dimethyl-*endo*-norbornanol (30). 1-Methylnorcamphor (25 g, 200 mmol) in ether (150 mL) was treated with 10% excess methyllithium solution in ether. The reaction mixture was decomposed with cold saturated ammonium chloride and extracted with ether. The solvent was removed and the alcohol was purified by distillation. The endo alcohol **(30)** was obtained in 85% yield, bp 50 °C (2 mm).

1,2-Dimethyl-*exo*-norbornyl Chloride (32). The endo alcohol **(30)** (19 g, 135 mmol) was treated with hydrogen chloride in an automatic hydrochlorinator.[22] Chloride (20 g, 93% yield) was obtained: mp 120–122 °C [lit.[16] mp 122–123 °C]; ^1H NMR (CCl_4) δ 1.23, 1.57 (2 methyls). This "β-chloride" on storing for 6 months at room temperature under hydrogen chloride atmosphere exhibited two additional methyl signals at δ 1.12 and 1.50 due to the formation of an "α isomer." This α isomer was identified as 1,2-dimethyl-*endo*-norbornyl chloride from the ethanolysis studies of the two isomers. The amount of endo chloride in the isomerized crude mixture was approximately 30%.

1,2-Dimethyl-*exo*-norbornanol (33). The tertiary chloride (20 g, 126 mmol) was dissolved in acetone (120 mL) and stirred with 10% sodium bicarbonate (120 mL) for 2 h at 0 °C. The acetone was removed using a rotary evaporator and the organic material was extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate and solvent was evaporated. The residual material was crystallized from hexane to give pure exo alcohol (14.2 g, 80% yield), mp 111–112 °C [lit.[21] mp 112–113 °C].

1,2-Dimethyl-*endo*-norbornyl *p*-Nitrobenzoate (31). This compound was obtained by treating the endo alcohol **(30)** with *n*-butyllithium and *p*-nitrobenzoyl chloride in THF in 81% yield: mp 144–145 °C [lit.[21] mp 146–146.5 °C]; ^1H NMR (CCl_4) δ 1.22, 1.51 (2 methyls).

1,2-Dimethyl-*exo*-norbornyl *p*-Nitrobenzoate (34). This *p*-nitrobenzoate was obtained from the exo alcohol **(33)** in the usual manner in 72% yield: mp 133–134 °C [lit.[21] mp 132.5–133 °C]; ^1H NMR (CCl_4) δ 1.30, 1.58 (2 methyls).

1-Phenylnorbornanone. 1-Phenyl-*exo*-norbornanol (18.9 g, 100 mmol) in ether (50 mL) was oxidized with a solution of chromic acid (100% excess) at 0 °C.[15] The crude material was purified by distillation to give the pure ketone (79% yield), bp 118–120 °C (0.5 mm). This material solidified on standing, mp 41–42 °C [lit.[14] mp 41–42 °C].

1,2-Diphenyl-*endo*-norbornanol (21). Phenyllithium (0.5 M solution in 1:1 ether/benzene mixture, 220 mL) was added to a solution of 1-phenylnorbornanone (19 g, 100 mmol). The reaction mixture was refluxed overnight and then worked up in the usual manner. Crystallization of the crude product from hexane gave 21.1 g (80% yield) of the tertiary alcohol, mp 109–110 °C [lit.[14] mp 109–110 °C].

1,2-Diphenyl-*endo*-norbornyl *p*-Nitrobenzoate (22). This *p*-nitrobenzoate was obtained in 82% yield in the usual manner: mp 162–163 °C; ^1H NMR (CCl_4) δ 8.23 (4 H, aromatic), 7.17, 6.92 (10 H, 2 phenyls), 3.05 (1 H, bridgehead), and 1.37–2.51 (8 H, remaining protons).

Anal. Calcd for $C_{26}H_{23}NO_4$: C, 75.54; H, 5.57; N, 3.39. Found: C, 75.49; H, 5.54; N, 3.41.

1,2-Diphenyl-exo-norbornyl Chloride. The endo alcohol (5.5 g, 21 mmol) dissolved in methylene chloride (20 mL) was treated with hydrogen chloride in an automatic hydrochlorinator at ice-bath temperature.[22] After the reaction was complete, removal of solvent yielded a light yellow residue. This crude material was crystallized from hexane to yield pure exo chloride (74% yield), mp 65–66 °C.

Anal. Calcd for $C_{19}H_{19}Cl$: C, 80.7; H, 6.75; Cl, 12.55. Found: C, 80.82; H, 6.57; Cl, 12.36.

Solvolysis of 1,2-Diphenyl-*exo*-norbornyl Chloride. The exo chloride (5.25 g, 20 mmol) was solvolyzed in 80% aqueous acetone (100

mL) containing 10% molar excess of sodium bicarbonate. The reactants were stirred overnight at 0 °C and acetone was removed using a rotary evaporator. The residue was extracted with ether, the ether extracts were dried over anhydrous magnesium sulfate, and the solvent was evaporated. The material was crystallized from hexane to give 4.42 g (80%) of 1,2-diphenyl-2-norbornene: mp 97–98 °C [lit.[14] mp 95.4–98 °C]; ^{1}H NMR (CCl_4) δ 7.17, 6.90 (10 H, aromatic), 6.24 (1 H, olefinic), 3.04 (1 H, 4-bridgehead), 1.32–2.22 (6 H, remaining protons).

Anal. Calcd for $C_{19}H_{18}$: C, 92.6; H, 7.36. Found: C, 92.53; H, 7.68.

Hydroboration–Oxidation[20] of 1,2-Diphenyl-2-norbornene. In a 250-mL flask equipped with a reflux condenser, a magnetic stirring bar, and a septum inlet was placed the olefin (5.52 g, 20 mmol) dissolved in methylene chloride (20 mL). The hydroboration was achieved by the dropwise addition of $BHBr_2{\cdot}SMe_2$ (20.6 mmol). After the addition, the reaction mixture was stirred for 10 min and 1 equiv of BBr_3 was slowly dripped in over a period of 4–5 min to induce fast hydroboration. After stirring at room temperature for 1.5 h, the organoborane was oxidized by the addition of aqueous sodium hydroxide (3 N, 43 mL) and hydrogen peroxide (8.5 mL). The temperature was maintained below 40 °C. The reaction mixture was refluxed for 1 h and the aqueous layer was saturated with K_2CO_3 and the organic layer separated. Removal of solvent furnished a solid, mp 84–94 °C. Most of the secondary alcohol was crystallized out from the crude material (mp 108.5–109.5 °C). The *p*-nitrobenzoate of the crude product (after removing the secondary alcohol) was prepared in the usual manner. The secondary OPNB could be crystallized out from the crude OPNB mixture (mp 154.5 °C) and the rest of the material which contained approximately 40% of *tert*-*p*-nitrobenzoate was used for solvolytic studies. The *tert*-OPNB could not be obtained in a pure state.

Solvolytic Products of 1,2-Dimethyl-*exo*-norbornyl *p*-Nitrobenzoate. The *exo*-*p*-nitrobenzoate (5 mmol) was solvolyzed in buffered 60% aqueous acetone at 75 °C. After 5 half-lives, acetone was removed and the solvolysis products were extracted with ether. The ether extract was analyzed by capillary GC. 1,2-Dimethyl-*endo*-norbornanol (0.35 ± 0.05%) was detected among other components, i.e., exo alcohol and hydrocarbons. The same results were obtained in 80% aqueous acetone.

Equilibration of *exo*- and *endo*-1,2-Dimethyl-2-norbornanols. The exo alcohol (10 mL, 0.2 M solution in cyclohexane) was stirred with 10 mL of sulfuric acid (6 M) at room temperature. At appropriate time intervals, 1 mL of organic solution was withdrawn and analyzed by gas chromatography (Perkin-Elmer 226 gas chromatograph, fitted with a 150 ft × 0.01 in. Quadrol column, operated isothermally at 150 °C under a pressure of 20 psi was used for the analysis) until a constant ratio was found for isomeric alcohols. The equilibrium distribution for 1,2-dimethyl-*exo*- and -*endo*-norbornanols was found to be 72% tertiary exo and 28% tertiary endo.

Kinetic Measurements. The rates of solvolysis of the *p*-nitrobenzoates in 80% acetone and the tertiary chlorides in ethanol were determined by the titrimetric method.[16] Sealed ampule technique was used for measuring the rates at higher temperatures. In the case of 1,2-dimethyl-*exo*- and -*endo*-norbornyl chlorides, separate rates were calculated by the differential method.[26] The rate data for the solvolysis of the *p*-nitrobenzoates in 80% aqueous acetone are summarized in Table I and data for the solvolysis of the chlorides in ethanol are tabulated in Table II.

Registry No.—**19,** 14182-93-5; **20,** 7485-54-3; **21,** 67162-96-3; **24,** 67162-97-4; **25,** 67162-98-5; **26,** 67162-99-6; **26** *p*-nitrobenzoate, 67163-00-2; **29,** 10218-04-9; **28,** 3212-16-6; **30,** 13429-45-3; **33,** 23351-29-3; *p*-nitrobenzoyl chloride, 122-04-3; phenyllithium, 591-51-5; $BHBr_2{\cdot}SMe_2$, 55671-55-1.

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Solvolysis of *p,p'*-Dichlorobenzhydryl Chloride in Ethanol–2,2,2-Trifluoroethanol Mixtures

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Received April 25, 1978

The solvolysis of *p,p'*-dichlorobenzhydryl chloride (1) in the nearly isodielectric EtOH–TFE mixtures gives a Grunwald–Winstein *m* value of 1.30. The solvolysis is subject to common ion rate depression and the mass law constants α increase with the increase in the mole fraction of TFE. A k_{TFE}/k_{EtOH} ratio of ~0.025 was calculated from the product distribution by assuming reaction of the solvent components with a free cationic intermediate. Ionizing power parameters *Y* for EtOH–TFE mixtures were calculated from the solvolysis of 1 and from the solvatochromic shifts of the charge-transfer band of 1-(*p*-hydroxyphenyl)-2,4,6-triphenylpyridinium betaine. It is suggested that the reaction proceeds via a selective free *p,p'*-dichlorobenzhydryl cation.

Solvent effects on solvolytic displacement reactions involve several solvent properties such as nucleophilicity, electrophilicity, and dielectric constant. A linear free energy relationship for describing these reactions (eq 1) was suggested by Winstein, Grunwald, and Jones,[1] where *k* and k_0 are the rate constants in a certain solvent and in 80% EtOH, and *Y* and *N* are the solvent ionizing power and nucleophilicity, respectively, *m* and *l* being the sensitivities to these parameters.

$$\log (k/k_0) = mY + lN \quad (1)$$

$$\log (k/k_0) = mY \quad (2)$$

However, in the absence of a scale of *N* values a more restricted form (eq 2)[2] is usually applied where the nucleophilicity is either assumed to be unimportant (k_c process[3]) or nearly constant in the solvents studied. Only recently have scales of *N* values become available.[4] Schleyer and co-workers who presented an extensive list of *N* values[4d] showed the superiority of eq 1 over eq 2 in analyzing solvent effects in solvolysis.[4d]

A useful way to gradually change the solvent properties is by studying binary solvent mixtures. Only one solvent property may be changed significantly as in aqueous EtOH mixtures where the change in *N* is small compared with the change in *Y*.[4d] On the other hand, in aqueous TFE mixtures both *N*[4,5] and *Y*[4b,6] (which are based on solvolytic data) increase with the increase of the water content.

The ionization power parameter *Y* involves contributions from two solvent properties: from the dielectric constant which is related to electrostatic solvation and from electrophilic solvation, mainly via hydrogen bonding to the leaving group. In aqueous EtOH the two effects are in the same direction since water has a higher dielectric constant and a higher electrophilicity than EtOH. In aqueous TFE the two properties operate in opposite directions since water has higher dielectric constant, but TFE is probably a better electrophilic solvator.[7] The nonlinear log *k* vs. *Y* plots found for solvolysis of α-arylvinyl derivatives in aqueous TFE were ascribed to this reason.[7]

The different bulk of the solvent components in a binary mixture was invoked for explaining the selectivity in the product-forming process in terms of different stabilities of solvent separated ion pairs.[8]

It is therefore surprising that more attention was not paid to the binary solvent mixtures EtOH–TFE. Mukherjee and Grunwald showed that these are nearly isodielectric mixtures, where the dielectric constants of TFE (26.14) and EtOH (24.32) are the extremes.[9] The bulk of the two solvents is also very similar. On the other hand, the nucleophilicity of TFE is much lower[4d] and its acidity[10] and probably its electrophilicity are higher than those of EtOH. Nevertheless, only three solvolytic studies in EtOH–TFE mixtures appeared so far.[11–13] da Roza, Andrews, and Keefer measured several *Y* and *N* values and studied the solvolyses of several benzyl halides.[11] They found that *Y* increases and *N* decreases on increasing the molar fraction of TFE in EtOH–TFE and that eq 2 gives nonlinear correlations, as expected since the *lN* term was neglected. From the dependence of the shape of these plots, of the product distribution, and of the k_{Br}/k_{Cl} ratios on the substituent in the aryl ring, the extent of solvent involvement as a nucleophile and an electrophile in the transition state was probed.[11] Ando and Tsukamoto used the product distribution in the solvolysis of 1- and 2-adamantyl systems in 50% EtOH–TFE as a tool for evaluating various proposals concerning the product-forming selectivities in binary mixtures.[12] Kaspi and Rappoport[13] found a nearly linear *N* vs. *Y* correlation in the region of 20–90% TFE with a slope of −0.83.

0022-3263/78/1943-3678$01.00/0

Table I. Kinetic Data for the Solvolysis of *p,p'*-Dichlorobenzhydryl Chloride in EtOH–TFE[a]

% TFE in EtOH–TFE	X_{TFE}[b]	$10^5 k_{obsd}$, s^{-1} at 0 °C	at 25 °C	at 50 °C	$\Delta H^{\ddagger}$, kcal mol^{-1} [c]	$\Delta S^{\ddagger}$, eu[c]
0	0		0.81[d]			
10	0.083		2.68 ± 0.004	36.7 ± 0.1	19.4 ± 0.03	−14.2 ± 0.1
20	0.168		4.70 ± 0.003	69 ± 0.1	19.9 ± 0.03	−11.4 ± 0.1
30	0.257		11 ± 0.1[e]	145 ± 0.2	19.2 ± 0.2	−12.2 ± 0.6
40	0.349		29 ± 0.03	308 ± 6[e]	17.5 ± 0.3	−16.1 ± 1.0
50	0.447		68 ± 0.1	664 ± 23[e]	16.8 ± 0.5	−16.6 ± 1.9
60	0.548	11.6 ± 0.01	176 ± 0.3		17.0 ± 0.02	−14.1 ± 0.1
70	0.652	31 ± 0.06	478 ± 7[e]		17.1 ± 0.2	−11.8 ± 0.7
80	0.763	113 ± 0.1	1291 ± 42[e]		15.2 ± 0.4	−16.2 ± 1.5
90	0.880	349 ± 22[e]	3751 ± 71[e]		14.8 ± 0.8	−15.5 ± 2.8
95	0.940	567 ± 29[e]	6561 ± 792		15.2 ± 1.6	−12.8 ± 5.5

[a] $[Ar_2CHCl]$ = 3.5–4.2 mM. [b] Mole fraction of trifluoroethanol. [c] The errors were calculated by the method of R. C. Peterson, J. H. Markgraf, and S. D. Ross, *J. Am. Chem. Soc.*, **83**, 3819 (1961). [d] S. Nishida, *J. Org. Chem.*, **32**, 2695 (1967). [e] Average of two experiments.

Since the solvolyses of most of the compounds studied so far involve either nucleophilic participation or product formation from ion pairs it was of interest to apply eq 1 and 2 and to determine the product distribution for a substrate more prone to react via a k_c route, where products are derived from a free cation. We therefore studied the solvolysis of *p,p'*-dichlorobenzhydryl chloride (**1**), a substrate likely to solvolyze via the k_c route, in EtOH–TFE mixtures. Several new *Y* values for EtOH–TFE mixtures were also derived by two independent methods.

$(p\text{-}ClC_6H_4)_2CHCl$

1

Results

Solvolysis of 1 in EtOH–TFE Mixtures. Solvolysis of **1** in EtOH–TFE mixtures containing 5–90% EtOH was followed by the conventional conductometric technique. The solvolysis rate in pure TFE was higher than the dissolution rate of **1** and meaningful rate constants were not obtained. Several measurements were conducted in the fast solvents containing 5–30% EtOH and average values of the rate constants are given. In the other mixtures duplicate experiments were conducted whenever the correlation coefficient of the first-order plot was <0.999. Activation parameters were calculated from the data at 0 and 25 °C for the fast reactions and at 25 and 50 °C for the slow reactions. The first-order constants obtained at ca. 4 mM concentrations of **1** and the derived activation parameters are given in Table I.

Clean first-order constants were obtained at 4 mM concentrations of **1**. However, since benzhydryl chlorides show common ion rate depression in other solvents,[14] several experiments were conducted in which the concentration of the substrate was increased in some TFE-rich mixtures to 20 or 50 mM in order to detect a possible decrease in the rate constant during the run caused by the formed chloride ion. A slight decrease was detected in some cases but it was sufficiently small so that attempts to treat it with the usual computer programs which were successful in treating common ion rate depression in vinylic systems[7,15] gave meaningless results. However, by addition of a large excess of external chloride ion, as the tetraethylammonium salt, a rate decrease of 9–58%, which was larger in the TFE-rich mixtures, was observed. An appreciable error may be involved in these experiments since the conductivity could be measured only after 5 min which was the time required to attain equilibrium. By this time a significant part of the reaction (up to 30% for the fast reactions) took place.

In order to evaluate the part of the salt effect which is not due to common ion rate depression, parallel experiments were conducted in the presence of tetraethylammonium bromide. A small rate decrease was found in the fast solvents and this was ascribed to the difficulties mentioned above. A small rate increase was found in the slower solvent, 50% EtOH. The solvolysis data for high concentrations of **1** and for reactions in the presence of added salts are given in Table II.

Table II. Solvolysis of 1 in the Presence of Added Salts[a]

% TFE in EtOH–TFE	added salt	*T*, °C	$10^5 k_{obsd}$, s^{-1}
100		0	319 ± 105
80		0	139 ± 1.2
	0.020 M Et_4NCl	0	72.3 ± 3.4
	0.040 M Et_4NCl	0	57.6 ± 2.8
	0.041 M Et_4NBr	0	154.7 ± 14
70		25	460 ± 20[b]
	0.020 M Et_4NCl	25	375 ± 2.2
	0.039 M Et_4NCl	25	341 ± 1.6
	0.021 M Et_4NBr	25	436 ± 3.5
	0.041 M Et_4NBr	25	427 ± 3.1
50		25	70 ± 1.2[c]
	0.022 M Et_4NCl	25	60.7 ± 0.2
	0.037 M Et_4NCl	25	59.0 ± 0.2
	0.020 M Et_4NBr	25	66.2 ± 0.1
	0.040 M Et_4NBr	25	64.1 ± 0.3
30		25	12.0 ± 1.4[c]
	0.026 M Et_4NCl	25	10.9 ± 0.02

[a] [1] = 0.02 M. [b] [1] = 0.06 M. [c] [1] = 0.02–0.05 M.

The extent of common ion rate depression was evaluated from the simplified solvolysis scheme (Scheme I)[16] which involves only one intermediate, the free carbonium ion **2**. The rate equation is eq 3, and the mass law constant $\alpha = k_{-1}/k_2$ was calculated from eq 4 where k_d is the depressed rate constant in the presence of added salt from Table II, and $k_{obsd'}$ is the undepressed rate constant corrected for the expected rate increase by the "normal" salt effect according to eq 5.[17] The *b* value is taken to be identical for Et_4NBr, a noncommon ion salt, and for Et_4NCl, the common ion salt.

$$k_{obsd} = k_1/(1 + (k_{-1}/k_2)[X^-]) \quad (3)$$

$$\alpha = (k_{obsd'}/k_d - 1)/[X^-] \quad (4)$$

$$k_{obsd'} = k_{obsd}(1 + b[Et_4NX]) \quad (5)$$

The extent of product formation from the free ion **2** is given by eq 6 and the values should be regarded as lower limits since no attempt was made to investigate whether the reaction shows a limit to the rate depression by added salt. The values are given in Table III.

Table III. α Values for $(p\text{-ClC}_6H_4)_2CHCl$ in EtOH–TFE

% TFE in EtOH–TFE (v/v)	T, °C	α, L mol^{-1}	% of product from the free R^+
80	0	40.8 ± 5.3[a]	≥58.5
70	25	10.0 ± 1.2[b]	≥26.0
50	25	5.9 ± 0.9[b]	≥15.7
30	25	4.0	≥9.2

[a] Average of four experiments. [b] Average of two experiments.

Scheme I

$$\underset{1}{RCl} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{2}{R^+} + Cl^-$$

$$\underset{2}{R^+} \xrightarrow{SOH,\ k_2} ROS$$

% of products formed from the free ion

$$= ((k_{obsd'} - k_d)/k_{obsd'})\cdot 100 \quad (6)$$

It is obvious that the α values are highly sensitive to the $k_{obsd'}$ (or the k_{obsd}) value and this is demonstrated by the α values of 40.8 and 20.6 which are based on the k_{obsd} values at 20 and 4 mM, respectively, in 20% EtOH–80% TFE.

The solvolysis products are 4,4′-dichlorobenzhydryl ethyl ether (**3**) and 4,4′-dichlorobenzhydryl trifluoroethyl ether (**4**). The product distribution was obtained by gas chromatography, using an appropriate calibration curve. Relative rate constants for capture of the intermediate **2** were calculated by assuming that the competition for **2** depends on the molar concentrations of the nucleophilic solvent components (reaction 7).

$$\underset{1}{(p\text{-ClC}_6H_4)_2CHCl} \rightarrow \underset{2}{(p\text{-ClC}_6H_4)_2CH^+} \begin{cases} \xrightarrow[k_{EtOH}]{EtOH} (p\text{-ClC}_6H_4)_2CHOEt \\ \xrightarrow[k_{TFE}]{TFE} (p\text{-ClC}_6H_4)_2CHOCH_2CF_3 \end{cases} \quad (7)$$

The ratio of the rate constants was calculated from eq 8 where [TFE], [EtOH], [$ROCH_2CH_3$], and [$ROCH_2CF_3$] are the molar concentrations of the solvents and the products, respectively.

$$k_{TFE}/k_{EtOH} = ([EtOH]/[TFE])\cdot([ROCH_2CF_3]/[ROCH_2CH_3]) \quad (8)$$

The k_{TFE}/k_{EtOH} ratios which are given in Table IV are low, being 0.017–0.032, and the trend is for a higher ratio in EtOH-rich medium. However, if the large experimental error in the ratio at 60% TFE is considered, the ratios are remarkably constant over an appreciable region of solvent composition.

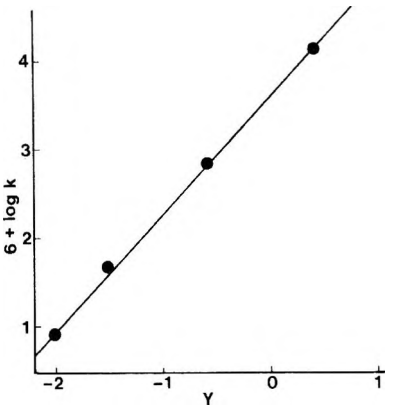
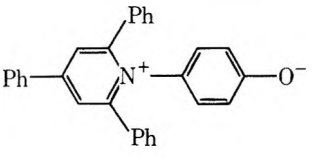


Figure 1. log k_{obsd} vs. Y plot for the solvolysis of **1** in EtOH–TFE at 25 °C.

***E*$_T$ Values of EtOH–TFE Mixtures.** An independent measure of the ionizing power of the medium was sought by measuring the position of the maximum of the internal charge transfer band of 1-(*p*-hydroxyphenyl)-2,4,6-triphenylpyridinium betaine (**5**) (Dimroth's Betaine 1[18]) as a function of



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the solvent composition. Triethylamine (0.1 M) was added to this mixture since otherwise protonation of the betaine oxygen resulted in the disappearance of the charge transfer band. The spectral data and the derived values of the transition energies, E_T, are given in Table V.

Other Benzhydryl Derivatives. Preliminary experiments showed that the solvolysis rate of benzhydryl chloride in solvent mixtures rich in TFE is too high to be measured accurately by conventional conductometric methods. For example, k_{obsd} is ca. 0.027 s^{-1} in pure TFE at 0 °C. On the other hand, the much less reactive benzhydryl 3,5-dinitrobenzoate was not sufficiently soluble in TFE-rich mixtures in order to enable kinetic measurements.

Discussion

The solvent effect, the common ion rate depression, and the products distribution are consistent with a k_c solvolysis mechanism for **1** which initiates by a C–Cl bond heterolysis.

The Solvent Effect. When k_{obsd} values at 25 °C for **1** were plotted against the Y values for 20, 50, and 80% EtOH–TFE from the work of da Roza, Andrews, and Keefer[11] and the value for pure EtOH,[2] a linear plot (Figure 1) was obtained with a slope m = 1.30 ± 0.02 (r = 0.99964). This is the first example of a linear Grunwald–Winstein plot in EtOH–TFE

Table IV. Solvolysis Products of *p,p′*-Dichlorobenzhydryl Chloride in EtOH–TFE at 25 °C

% TFE (v/v) in EtOH–TFE	[TFE]/[EtOH][a]	% $ROCH_2CF_3$	[$ROCH_2CF_3$]/[ROEt][a]	$100k_{TFE}/k_{EtOH}$[b]
60	1.21	3.7 ± 1	0.0384	3.18 ± 0.90
70	1.89	4.8 ± 1	0.0504	2.67 ± 0.58
80	3.23	7.6 ± 1	0.0823	2.55 ± 0.36
90	7.27	15.0 ± 1	0.176	2.43 ± 0.20
95	15.36	21.0 ± 1	0.266	1.73 ± 0.10

[a] Molar ratio. [b] From eq 8.

Table V. UV Spectra and $E_T(1)$ Values for 1-(*p*-Hydroxyphenyl)-2,4,6-triphenylpyridinium Betaine in EtOH–TFE[a]

% TFE (v/v) in EtOH–TFE	X_{TFE}[b]	Y[c]	λ_{max}, nm	ϵ	λ_{max}, nm	ϵ	E_T, kcal mol^{-1}
0	0	−2.033	305	28 200	468	1960	61.2
10	0.083		305	27 200	455	1740	62.8
20	0.168	−1.515	305	27 000	445	1690	64.3
30	0.257		305	27 300	436	1760	65.6
40	0.349		306	27 400	426	1830	67.1
50[d]	0.447	−0.588	306	27 500	419	1870	68.3
60	0.548		306	27 300	408	1780	70.0
70	0.652		306	27 600	405	2090	70.6
80	0.763	0.406	306	27 200	399	2120	71.7
90	0.880		305	27 700	393	2180	72.8
100	1.000	1.147	306	27 900	389[e]	2270	73.5

[a] Measurements in the presence of 0.1 M Et_3N; [5] = 5.6–6.0 × 10^{-4} M. [b] Mole fraction of TFE. [c] From ref 11. [d] Without Et_3N: λ_{max} 308 nm (ϵ 22 000). No absorption was observed at 419 nm. [e] Reported[7] 390 nm (ϵ 2900).

Table VI. Ionizing Power Parameters (Y) in EtOH–TFE Mixtures

% TFE (v/v) in TFE–EtOH	Y from log k_{obsd}	Y from $E_T(1)$	Y from *t*-BuCl[a]
100			1.147[b]
90	0.77	0.80	
80			0.406
70	0.07	0.06	
60	−0.27	−0.28 (−0.12)[c]	
50			−0.588
40	1−0.87	−0.90	
30	−1.22	−1.24	
20			−1.515
10	−1.69	−1.68	
0			−2.033[d]

[a] From ref 11. [b] From ref 6. [c] Value from Table V (see text). [d] From ref 2.

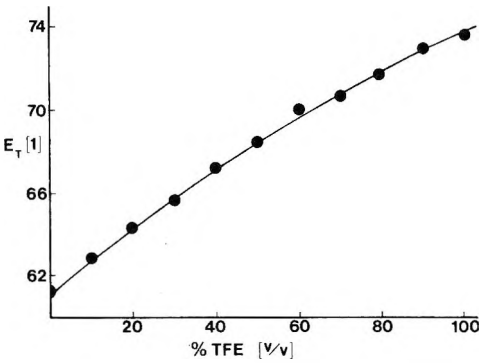

Figure 2. Change of $E_T(1)$ values with the percent volume of TFE in EtOH–TFE.

since the solvolyses of substituted benzyl halides in the same media gave curved relationships.[11] The m value is one of the highest known and points to the absence of a significant solvent participation in the solvolysis in the entire solvent range. Values of m higher than unity were found for other solvolyses which proceed via the k_c route, e.g., 1.20 for 1-adamantyl bromide[19] in aqueous EtOH and 1.20 for α-phenylethyl chloride[20] and 1.71 for benzhydryl chloride[1b] in AcOH–HCOOH mixtures.

The actual m value which measures the sensitivity to Y alone, when contribution from the solvent nucleophilicity is excluded (m of eq 1), may be even higher than 1.30. We recently showed that a linear relationship of N and Y (eq 9) holds for several binary solvent mixtures.[13] Combination of eq 1 and 9 gives eq 10.

$$N = aY + b \tag{9}$$

$$m(\text{eq 1}) = m\ (\text{calcd by eq 2}) - al \tag{10}$$

The EtOH–TFE mixtures are unique among the mixtures investigated in that a of eq 9 is negative and appreciable, being $a = -0.83$, since increase in the TFE content increases Y but decreases N. Consequently, since $l \geq 0$ the m value of eq 1 is ≥ 1.30.

By applying eq 1 we obtained $m = 1.41 \pm 0.14$, $l = 0.16 \pm 0.2$, and $r = 0.994$. The low value and the high error in l show that the addition of the nucleophilicity parameter does not improve significantly the correlation, i.e., the higher rates in TFE-rich media are due to the higher ionizing power.

High m values of eq 2 (1.65–2.08) were found recently for the solvolysis of several substituted benzhydryl bromides in TFE–C_6H_6 mixtures.[21] These values were interpreted as due to increased ion pair return with the increase in the molar fraction of the less ionizing solvent. The gap between the observed rate constant k_t and the ionization rate constant k_{ion} in benzene is therefore larger than in TFE. Consequently, the observed m from the log k_t vs. Y plot is higher than the expected value for a log k_{ion} vs. Y plot. A similar explanation does not apply to our high m value since if the ion pair return increases on decreasing the nucleophilicity it will be more pronounced in solvent mixtures richer in TFE. The m value of the log k_{ion} vs. Y plot would then be expected to be higher than the observed value of 1.30. While we have no independent evidence for ion pairs in our system, the linearity of the mY plot suggests that if ion pairing during the solvolysis of **1** is important, its extent is either proportional to that in the solvolysis of *tert*-butyl chloride or it is linear with Y in the EtOH–TFE mixtures studied.

***Y* Values in EtOH–TFE Mixtures.** Only a few Y values in EtOH–TFE mixtures are available from the solvolysis of *t*-BuCl. The linearity of Figure 1 suggests that the solvolysis of 4,4'-dichlorobenzhydryl chloride can serve as a secondary source for additional Y values for TFE–EtOH mixtures. By using the data of Table I and Figure 1, the new Y values of Table VI were obtained.

An enormous difference between the Y values which are based on solvolytic data and those based on the solvatochromic changes of the betaine **5** were observed in TFE–H_2O mixtures.[7] It was therefore of interest to evaluate the polarity of EtOH–TFE mixtures by a nonkinetic approach which is based on the solvatochromic shift of the internal charge transfer band of the betaine **5**. Table V shows that by this approach TFE is much more polar than EtOH. Plots of $E_T(1)$ values vs. the percent volume of TFE in the mixture (Figure 2) or vs. Y (Figure 3) are nonlinear, but they can be used for evaluating unknown $E_T(1)$ and Y values. Comparison of the Y values which were obtained from Figures 1 and 3 (Table VI) shows a very good agreement between the two sets of values.

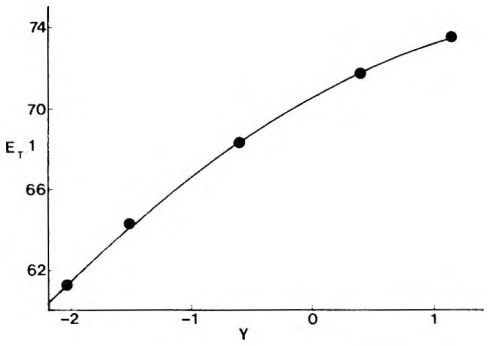

Figure 3. Change of $E_T(1)$ values with Y in EtOH–TFE.

The only discrepancy is in the Y value at 60% TFE–40% EtOH, but Figure 2 shows deviation of the measured E_T value at this composition. When the E_T value from the plot of Figure 2 is used for calculating the Y value from Figure 3, the value agrees with that based on the solvolysis data.

The correspondence between the two sets of Y values which are based on completely different model processes strengthens the case for their use for correlation purposes. Moreover, since the spectroscopic model does not distinguish implicitly between the several possible intermediates, we conclude that ion pair return is either unimportant in the solvolyses of **1** and *tert*-butyl chloride, or that its extent is proportional to Y.[22]

In view of the complex behavior showed in the solvolysis of 7-methyl-7-norbornyl-OTs[23] and several α-arylvinyl derivatives[7] in TFE–H_2O mixtures, it is gratifying that the behavior of all the compounds studied so far is accounted for by eq 1. Substrates solvolyzing via the k_c route, such as **1**, 1-(*p*-methoxyphenyl)-2-methylpropen-1-yl tosylate,[24] and adamantyl bromide,[24] give linear log k vs. Y plots with m = 0.89–1.50. For benzyl halides which give curved log k vs. Y plots and interpolated low and even negative m values, eq 1 gives m (eq 1) values which are expected for benzyl substituted derivatives when the lN term is taken into account.[13] The apparent less complicated behavior in EtOH–TFE media is probably due to a lower number of variable solvent parameters than in TFE–H_2O, since the structures and the dielectric constants of the two pure components are very similar. These mixtures therefore seem suitable for studying solvent effects when N and Y change gradually at almost isodielectric conditions.

Comparison of the $E_T(1)$ values in EtOH–TFE and in TFE–H_2O[7] reveal an interesting behavior. The $E_T(1)$ value of pure TFE is the highest and addition of either EtOH or water decreases the $E_T(1)$ value, although this effect is more pronounced on addition of EtOH. Apparently, the higher acidity of TFE[10] which results in high hydrogen bonding donor ability is more important in solvatochromic changes of the betaine **5** than changes in the dielectric constant. It is impossible at present to evaluate the generality of this behavior since E_T values in acidic media are not available.

Selectivity of the 4,4′-Dichlorobenzhydryl Cation 2. The appearance of common ion rate depression is a compelling evidence for the intermediacy of a free ("dissociated") carbonium ion intermediate.[16b,c] The mass law constant α measures the selectivity of the cation toward Cl^- and the solvent. Within structurally related substrates α increases with the lifetime and the stability of the cationoid intermediate.[14,16a]

Common ion rate depression was amply demonstrated in the solvolysis of substituted benzhydryl chlorides in aqueous acetone. For example, α = 10 and 33 for benzhydryl chloride and *p*-methylbenzhydryl chloride in 80% acetone[14a] and 2.1 and 0.7 for benzhydryl chloride and *p*-nitrobenzhydryl chloride, respectively, in 70% acetone.[14b] Substituent and solvent effects showed that α increases with the electron donating ability of the substituents and decreases with the increase in the water content of the medium.[14]

Tables II and III show that the common ion depression in the solvolysis of **1** is appreciable. For example, addition of 40 mmol of Cl^- in 20% EtOH–80% TFE (Y = 0.41) at 0 °C reduces k_{obsd} by 58% while k_{obsd} for benzhydryl chloride decreases by only 13% on addition of 0.1 M of LiCl in 80% acetone (Y = 0.67) and extrapolation gives a 5.5% decrease in k_{obsd} by addition of 40 mmol of Cl^-.

In order to enable a closer comparison with previous data we applied the linear free energy relationship in substituent effects suggested by Mindl and Věčěra[25] for disubstituted benzhydryl bromides and estimated that the relative solvolysis rate ratio k_{obsd} (**1**)/k_{obsd}(Ph_2CHCl) is 0.085 at 0 °C. From the semiquantitative relationship between k_{obsd} and α values in 70% acetone,[14b] **1** should have an α value of 1.5–2 in 70% acetone. Since the Y value of 70% acetone (0.13)[2] is close to that of 70% TFE–30% EtOH (0.06) while the α value for **1** in this solvent is 10 we conclude that the selectivity of **1** is higher in TFE–EtOH than in aqueous acetone of the same ionizing power. This is not surprising since the nucleophilicity of 70% TFE–30% EtOH[24] is much lower than that of 70% acetone[4d] and the lifetime of **2** before irreversible collapse with the solvent should be longer.

Table III shows that α decreases with the increase of the ethanol content of the media, and this is reminiscent of the decrease of α for 1-(*p*-methoxyphenyl)-2-methylpropen-1-yl bromide with the increase of the water content in aqueous TFE.[7] The effect of a binary nucleophilic solvent on the α values was discussed in this later case. It was suggested that α will increase on enhancing the cation solvation and decrease by enhanced anion solvation, by increasing the concentration of the more nucleophilic component and by increasing the dielectric constant. Since the dielectric constant does not change significantly in our media, and TFE is a better anion solvator than EtOH, the higher α values in the TFE-rich media are due to the reduced nucleophilicity of the medium which more than compensates for the reduced nucleophilicity of the better solvated Cl^- [26] and for the reduced cation solvation.[26]

Table III also gives the extent of product formation from the free ion **2**, as calculated by eq 6. The difficulty associated with measurement of a small conductivity change in the presence of a large amount of added salt prevented the use of higher salt concentrations so that the values of Table III are minimum values for the extent of product formation from the free ion. While we believe that the actual values are much higher, at present it can be concluded that a large fraction, e.g., 59% of the products in 80% TFE–20% EtOH, is derived from the free *p,p′*-dichlorobenzhydryl cation. Ion pairs can still be involved in an internal return process.[27]

Another measure of selectivity of the ion **2** are the product distributions given in Table IV. The lower nucleophilicity of TFE is expected to result in a k_{TFE}/k_{EtOH} ratio lower than unity, but the observed ratios of ca. 0.025 are much lower than the values of 0.8–2.6 obtained for the 1-adamantyl system[12,24] or the values of 0.8–1.4 for the 2-adamantyl system,[12] and lower than the values for the substituted benzyl halides.[11] This can be understood if products are formed in these systems from collapse of solvent separated ion pairs.[8,28] In this case the stability of the TFE and EtOH separated ion pairs will be at least as important as the nucleophilicities of the solvent components.

Our k_{TFE}/k_{EtOH} value can be tentatively taken as a ratio for capture of a free cation by the two solvents. Since N(EtOH) − N(TFE) = 2.87[4d] and log (k_{EtOH}/k_{TFE}) = 1.6, the selectivity of **2** toward EtOH and TFE is lower than the coresponding selectivity of methyl tosylate, but it is still ap-

preciable. Consequently, by the product distribution criterion, as well as by the kinetics, the ion **2** is relatively long lived.

The selectivity of substituted benzhydryl chlorides in aqueous EtOH was determined from the product distribution. The k_{EtOH}/k_{H_2O} ratios were found to increase on increasing the water content of the medium.[29] Three possible explanations for this effect were proposed: (a) a greater stabilization of the intermediates in the more polar solvent with a consequent increased selectivity; (b) an increased dissociation to more selective free ions; (c) enhanced nucleophilicity of ethanol in the more polar media. The k_{TFE}/k_{EtOH} ratios for **2** are nearly constant at $X_{TFE} = 0.65$–0.88. However, there is a trend for lower ratios in the TFE-rich media, i.e., for a relatively higher rate for the faster nucleophile (higher selectivity) in a medium of higher ionizing power. Explanation (b) can be excluded for our system where **2** is already a free ion, but either (a) or (c) can account for the trend in the k_{TFE}/k_{EtOH} ratios. Further decision between these two alternatives is difficult. A more general question is to what extent the k_{TFE}/k_{EtOH} ratios which were derived by assuming that eq 7 and 8 hold reflect the selectivities of the ion at different compositions of TFE–EtOH. TFE–EtOH mixtures show severe deviations from ideal solution behavior[9] and the presence of a mixed hydrogen bond species, probably $CF_3CH_2OH\cdots OHCH_2CH_3$, was shown by the infrared spectra. The stability of this species in CCl_4 is higher than either that of the TFE dimer or the EtOH dimer.[9] Consequently, the concentrations of the three hydrogen-bonded species and probably of the monomers and of higher aggregates and their respective nucleophilicities should be considered when discussing the product-forming step. Hence, caution should be exercised when small differences in the k_{TFE}/k_{EtOH} ratios calculated only from the stoichiometric concentrations and nucleophilicities of EtOH and TFE are used as mechanistic probes.

Experimental Section

Melting points were determined with a Fisher instrument and are uncorrected. NMR spectra were recorded with Varian HA-100 or T-60 instruments, IR spectra were recorded with a Perkin-Elmer 337 instrument, and mass spectra were recorded with a MAT-311 instrument.

Materials. 4,4'-Dichlorobenzhydryl chloride, mp 61–63 °C (lit.[30a] mp 62.5–63.5 °C), was prepared from 4,4'-dichlorobenzhydrol and hydrogen chloride according to Nishida.[30b] Benzhydryl 3,5-dinitrobenzoate was prepared by refluxing benzhydrol (25 g, 0.135 M) and 3,5-dinitrobenzoyl chloride (27 g, 0.11 M) in a mixture of benzene (200 mL) and pyridine (21.5 g) for 2 h, extracting first with dilute aqueous hydrochloric acid and then with dilute aqueous sodium bicarbonate solution, drying ($MgSO_4$), and evaporating the solvent. The recrystallized material had mp 144–146 °C (lit.[31] mp 142 °C).

Solvents. β,β,β-Trifluoroethanol (Halocarbon) was refluxed for 2 h over a mixture of 8:1 of anhydrous $CaSO_4$ and anhydrous K_2CO_3. The fraction boiling at 70–74 °C was used for the kinetic experiments. Absolute ethanol (Frutarom) was purified according to Lund and Bjerrum,[32] 2,6-lutidine and triethylamine were distilled from solid potassium hydroxide, and 2,6-lutidinium hydrochloride was prepared by dissolving the base in HCl and evaporation of the water.

4,4'-Dichlorobenzhydryl Ethyl Ether (3). To a solution of 4,4'-dichlorobenzhydryl chloride (1.01 g, 3.72 mM) in absolute ethanol (40 mL), sodium (0.39 g, 17 mM) in absolute ethanol (5 mL) was added, and the mixture was refluxed for 4 days. The sodium chloride was filtered, the solvent was evaporated to dryness, and the remainder was separated by chromatography over alumina using petroleum ether (60–80 °C). The fraction which contained the ether was distilled and the material boiling at 165–172 °C (8 mm) was collected and repurified by gas chromatography. The purified ether has δ (CCl_4) 1.25 (3 H, t, Me), 3.45 (2 H, q, CH_2), 5.18 (1 H, s, CH), 7.18 (8 H, s, Ar); ν_{max} (KBr) 2990, 1600, 1090, 820, 795, 530 cm^{-1}; *m/e* 284, 282, 280 (M, 1, 6, 9), 254, 252, 250 (Ar_2CO^+, 3, 15, 22), 239, 237, 235 (Ar_2CH^+, 5, 25, 37), 171, 169 (ArCHOEt, 7, 17), 165 (Ph_2CH^+, 30), 141, 139 ($ArCO^+$, 38, 100), 113, 111 (C_6H_5Cl, 19, 42).

Anal. Calcd for $C_{15}H_{14}Cl_2O$: C, 64.07; H, 5.01; Cl, 25.2; OEt, 16.02. Found: C, 63.98; H, 5.04; Cl, 24.5; OEt, 15.1.

Another fraction from the distillate gave a solid, mp 146–148 °C, which was identified as 4,4'-dichlorobenzophenone by melting point, mixture melting point, IR (ν_{max} 1655 cm^{-1}, C=O), and NMR (CCl_4) δ 7.55 (AA'BB' q)). 4,4'-Dichlorobenzophenone was also obtained from reaction mixtures which remained for a few days before workup, from recrystallized sample of 4,4'-dichlorobenzhydryl chloride, from the ether **3** after long standing, from several attempts to prepare **3** by reaction of 4,4'-dichlorobenzhydryl chloride in absolute ethanol containing sodium ethoxide or a catalytic amount of concentrated sulfuric acid, as well as from attempts to prepare the ether **4** from **1** in trifluoroethanol/sodium trifluoroethoxide.

4,4'-Dichlorobenzhydryl β,β,β-Trifluoroethyl Ether (4). 4,4'-Dichlorobenzhydryl chloride (0.47 g, 1.73 mM) was added to a suspension of potassium carbonate (0.26 g, 2.6 mM) in trifluoroethanol (20 mL) at room temperature. The mixture was warmed for a few minutes until a complete dissolution of the benzhydryl chloride took place, the inorganic salts were filtered, and the solvent was evaporated. The remaining oil was chromatographed over alumina using petroleum ether (40–60 °C) as the eluent. One fraction was identified as 4,4'-dichlorobenzhydryl β,β,β-trifluoroethyl ether (**4**) from its analysis and spectra: ($CDCl_3$) δ 3.78 (2 H, q, CH_2), 5.45 (1 H, s, CH), 7.21 (8 H, s, Ar); ν_{max} 2940, 1600, 1495, 1415, 1280, 1170, 1120, 1090, 1015 cm^{-1}; *m/e* 338, 336, 334 (M, 4.5, 27, 40), 301, 299 (M − Cl, 15, 41), 254, 252, 250 ($(p\text{-}ClC_6H_4)_2CO$, 0.6, 3, 5), 239, 237, 235 ($(p\text{-}ClC_6H_4)_2CH^+$, 11, 66, 100), 225, 223 (M − ClC_6H_4, 16, 44), 201, 199 (M − Cl − OCH_2CF_3, 11, 27), 165 (fluorenyl$^+$, 68), 141, 139 ($p\text{-}ClC_6H_4CO^+$, 33, 91), 113, 111 ($C_6H_4Cl^+$, 14, 39).

Anal. Calcd for $C_{15}H_{11}Cl_2F_3O$: C, 53.76; H, 3.31; F, 17.00; Cl, 21.15. Found: C, 53.75; H, 3.18; F, 16.71; Cl, 21.12.

Product Analysis. The product distribution was determined on a 5% SE-30 column on 60/80 Chromosorb W (5 ft × ⅛ in.) at 170 °C at 1.3 atm of He. The retention times under these conditions were 7 min for the trifluoroethyl ether and 10.5 min for the ethyl ether. The solutions were prepared from reaction mixtures which were kept for 10 half-lives at 25 °C. Calibration curves of the purified products were used to obtain the correct product analysis.

E_T Values. These values were calculated from the spectra of the betaine **5**, determined with a Gilford 2400-S spectrophotometer.

Kinetic Work. The substrate was dissolved in absolute ethanol which was kept for 15 min at the reaction temperature. The appropriate amount of TFE was added at the reaction temperature and the solution was introduced after mixing to a conductance cell at the reaction temperature. The resistance of the solution was measured with a Pye Conductance Bridge. When solutions of the tetraethylammonium salts were added, the salts were dried at low pressure for 1 day and dissolved in TFE before the beginning of the measurements. It was found that the conductance was linear with the concentration of either 2,6-lutidinium hydrochloride or of hydrochloric acid in 80% EtOH. The first-order rate constants were calculated from the logarithms of the conductivity difference at the beginning and at the end of the reaction, by using the KINDAT program.[33]

Acknowledgment. We are indebted to Dr. Addy Pross for a preprint of ref 29.

Registry No.—**1**, 782-08-1; **3**, 57070-99-2; **4**, 66922-40-5; **5**, 17658-06-9; benzhydryl 3,5-dinitrobenzoate, 21573-83-1; benzhydrol, 91-01-0; 3,5-dinitrobenzoyl chloride, 99-33-2; β,β,β-trifluoroethanol, 75-89-8; ethanol, 64-17-5; 4,4'-dichlorobenzophenone, 90-98-2.

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Kinetics of the Acid-Catalyzed α-Bromination of Aliphatic Acids

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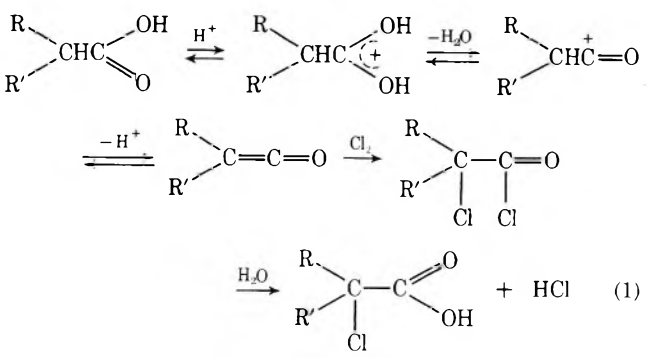
Received March 22, 1978

Aliphatic acids were found to be easily α-brominated in good yields (78–95%) by molecular bromine in the presence of chlorosulfonic acid as a catalyst in 1,2-dichloroethane as a solvent at 84 °C. Kinetic study shows that the rate is expressed as: $v = k_{obsd}[RCO_2H][Br_2]$, where k_{obsd} is proportional to the initial concentration of chlorosulfonic acid at an early stage. The substituent effect fits Taft's equation with little steric effect, giving $\rho^* = -0.97$ at 60 °C, which suggests that the reaction is accelerated by electron-releasing groups, thus the reactivity increases as follows: $CH_3CO_2H < CH_3CH_2CO_2H < CH_3CH_2CH_2CO_2H < (CH_3)_2CHCH_2CO_2H < (CH_3)_2CHCO_2H < (CH_3CH_2)_2CHCO_2H$. The mechanism involving ketene intermediates is discussed.

Ketones and aldehydes are α-halogenated by molecular halogen in the presence of acid or base catalysts;[2] the reaction mechanism is said to involve the corresponding enol which is in equilibrium with the keto form. The rate-determining step in most cases is the enolization, hence the rate is independent of the concentration and nature of halogen, i.e., chlorination, bromination, and iodination under the same conditions proceed at the same rate irrespective of their concentration.[2b,3]

In the Hell–Volhard–Zelinsky reaction the aliphatic acids are α-halogenated by halogen in the presence of phosphorus halides.[4] Little et al. have proposed that this reaction proceeds via enol or ketene intermediate with little evidence,[5] but most workers prefer the intermediacy of enol.[4] Only one kinetic study for the Hell–Volhard–Zelinsky reaction was reported, in which the rate was said to depend on the concentration of bromine,[4c] in contrast to the behavior of ketones.

We have reported previously that aliphatic acids can be α-chlorinated by a Cl_2–O_2 mixture in the presence of a strong acid such as chlorosulfonic or fuming sulfuric acid,[6] and we suggested that the reaction intermediate may be ketene on the basis of NMR and laser-Raman spectral data, deuterium tracer study, and trapping by aniline forming acetanilide.[7] However, no kinetic study could yet be done because of the low solubility of chlorine.

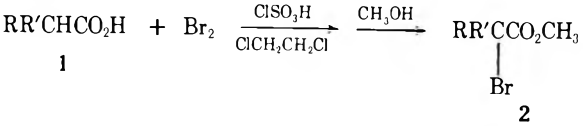


(1)

The present paper reports the application of this chlorination method to bromination of aliphatic acids and also the kinetics of bromination which presents further support and detailed information for the mechanism of reaction.

Results and Discussion

α-Bromination. It was found that aliphatic acids could also be easily α-brominated by molecular bromine in 1,2-dichloroethane using a strong acid catalyst, chlorosulfonic acid, as in the case of chlorination, but the presence of a radical trapper such as molecular oxygen was unnecessary. The yields and physical properties for identification of esters of α-bromo acids are listed in Tables I and II, respectively. The yields are satisfactory (78–95%) under these conditions except for bromination of acetic acid.



(2)

Kinetics of α-Bromination. The rate of α-bromination of isobutyric acid in 1,2-dichloroethane at 60 °C using 0.05 M chlorosulfonic acid as a catalyst fits eq 3.

$$v = k_{obsd}[RR'CHCO_2H][Br_2] \quad (3)$$

The first-order dependence of rate on bromine concentration was confirmed at various concentrations of bromine (Table III). Equation 3, which depends on $[Br_2]$, suggests that

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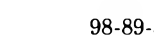
Table I. Yields of Esters of α-Bromo Acids by the Reaction of Aliphatic Acids with Br_2 in 1,2-Dichloroethane at 85 °C[a]

	registry no.	substrate acid	yield, %
1a	64-19-7	CH_3CO_2H	10.9
1b	79-09-4	$CH_3CH_2CO_2H$	78.1
1c	107-92-6	$CH_3CH_2CH_2CO_2H$	85.9
1d	503-74-2	$(CH_3)_2CHCH_2CO_2H$	83.5
1e	79-31-2	$(CH_3)_2CHCO_2H$	95.3 15.1[b]
1f	88-09-5	$(CH_3CH_2)_2CHCO_2H$	92.4
1g	98-89-5		90.4

[a] Substrate acid (10 mmol) was treated with bromine (10 mmol) in the presence of chlorosulfonic acid (10 mmol) in 1,2-dichloroethane (50 mL) at 85 °C for 2 h and refluxed with methanol (30 mL) for 10 h. [b] Concentrated sulfuric acid (18 mmol) was used in place of chlorosulfonic acid.

bromine adds to ketene intermediate **3** at the rate-determining step.

Effect of Concentration of Chlorosulfonic Acid. The initial rate constant k_{obsd} for bromination of isobutyric acid was found to be proportional to the initial concentration of chlorosulfonic acid (Figure 1).

Hence, the rate in eq 3 can be rewritten as follows, where $[\ ]_0$ means initial concentration.

$$v = k[ClSO_3H]_0[RR'CHCO_2H][Br_2] \quad (4)$$

Mechanism. As stated above, there are evidences for the formation of ketenes from aliphatic acids in $ClSO_3H$ or fuming H_2SO_4.[7] These results may be explained by the following scheme.

$$RR'CHCO_2H + ClSO_3H \overset{\text{fast}}{\rightleftarrows} RR'C{=}C{=}O + HCl + H_2SO_4 \quad (5)$$

$$RR'C{=}C{=}O + Br_2 \xrightarrow{k_6} RR'CBrCOBr \quad (6)$$

$$RR'CBrCOBr + CH_3OH \rightarrow RR'CBrCO_2CH_3 + HBr \quad (7)$$

Step 5 for formation of ketene is irreversible or at least shifts greatly to the right side and this reaction competes with other reactions of aliphatic acids such as the formation of $RR'CH(OH)_2^+$, $RR'CHCO^+$, $RR'C(SO_3H)CO_2H$, $RR'CHCOOSO_3H$, and ketene dimer as discussed below. At an early stage of the reaction, the concentration of ketene may be proportional to the initial concentration of $ClSO_3H$. If the rate is determined by eq 6, then the above mechanism leads to the observed rate equation as shown below.

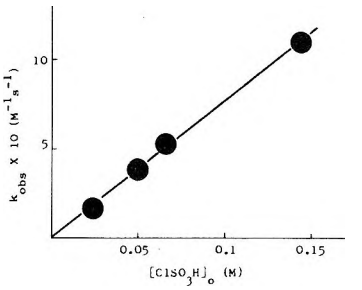


Figure 1. Correlation between concentration of chlorosulfonic acid and rate constant (k_{obsd}) for bromination of isobutyric acid at 60 °C.

$$v = k_6[RR'C{=}C{=}O][Br_2] = k[ClSO_3H]_0[RR'CHCO_2H][Br_2] \quad (8)$$

There may be the following steps before formation of ketene.

$$RR'CHCO_2H + ClSO_3H \rightleftarrows RR'CHC(OH)_2^+ + ClSO_3^- \quad (9a)$$

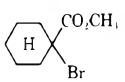
$$RR'CHC(OH)_2^+ + ClSO_3H \rightleftarrows RR'CHCO^+ + HCl + H_2SO_4 \quad (9b)$$

$$RR'CHCO^+ \rightleftarrows RR'C{=}C{=}O + H^+ \quad (9c)$$

Aliphatic acid is readily converted to the corresponding oxonium ion $RR'CHC(OH)_2^+$ in concentrated sulfuric acid but hardly to the corresponding acylium ion $RR'CHCO^+$.[13] On the other hand, aliphatic acid in fuming sulfuric acid is rather easily converted to the acylium ion.[13] Since the acidity of chlorosulfonic acid is analogous to fuming sulfuric acid,[14] chlorosulfonic acid can also convert aliphatic acid to acylium ion and thence to ketene by deprotonation. This lower acidity of sulfuric acid[14] may be the reason why sulfuric acid as a catalyst in α-halogenation gave yields far less than chlorosulfonic or fuming sulfuric acid (Table I and ref 6).

An equimolar amount of sulfuric acid, which should be a large enough amount for converting aliphatic acid to the oxonium ion $RR'CHC(OH)_2^+$, gave only poor yield, while an

Table II. Physical Properties for Identification of Methyl Esters of α-Bromo Acids

ester	registry no.	bp, °C (mm)	NMR chemical shift,[a] δ (J in Hz)	IR[b] $\nu_{C=O}$, cm^{-1}
$CH_2BrCO_2CH_3$	96-32-2	72–73 (40)[c]	3.73 (s, 3 H, CO_2CH_3), 3.79 (s, 2 H, CH_2)	1740
$CH_3CHBrCO_2CH_3$	5445-17-0	62–63 (36)[d]	1.80 (d, J = 6.8, 3 H, β-H), 3.74 (s, 3 H, CO_2CH_3), 4.29 (quart, J = 6.8, 1 H, 7α-H)	1745
$CH_3CH_2CHBrCO_2CH_3$	3196-15-4	76–77 (42)[e]	1.02 (t, J = 7.2, 3 H, γ-H), 2.04 (quart, J = 6.8, 2 H, β-H), 3.74 (s, 3 H, CO_2CH_3), 4.08 (t, J = 7.0, 1 H, α-H)	1735
$CH_3CH(CH_3)CHBrCO_2CH_3$	26330-51-8	82–83 (42)[f]	1.03 (d, J = 7.2, 3 H, γ-H),[h] 1.10 (d, J = 7.2, 3 H, γ′-H),[h] 2.14 (oct, J = 6.5, 1 H, β-H), 3.72 (s, 3 H, CO_2CH_3), 3.92 (d, J = 7.2, 1 H, α-H)	1740
$CH_3C(CH_3)BrCO_2CH_3$	23426-63-3	81–82 (70)[g]	1.89 (s, 6 H, β-H), 3.73 (s, 3 H, CO_2CH_3)	1745
$CH_3CH_2C(CH_3)CH_2BrCO_2CH_3$	2399-18-0	104–105 (42)	0.97 (t, J = 6.9, 6 H, γ-H), 2.09 (quart, J = 6.8, 4 H, β-H), 3.75 (s, 3 H, CO_2CH_3)	1735
	3196-23-4	123–124 (34)	1.03 (br, 6 H, γ, δ-H), 2.13 (t, J = 6.5, 4 H, β-H), 3.76 (s, 3 H, CO_2CH_3)	1740

[a] CCl_4. [b] Neat. [c] Lit.[8] bp 63.4–64.4 °C (33 mm). [d] Lit.[9] bp 56.5 °C (21 mm). [e] Lit.[10] bp 165–172 °C. [f] Lit.[11] bp 64–65 °C (11 mm). [g] Lit.[11] bp 52.2 °C (21 mm). [h] γ and γ′ protons are not equivalent magnetically.[12]

Table III. Effect of Concentration of Bromine on Second-Order Rate Constant (eq 3) for α-Bromination of Isobutyric Acid in 1,2-Dichloroethane at 60 °C[a]

$[Br_2]_0$, M	k_{obsd}, M^{-1} s^{-1}
0.025	3.89×10^{-3}
0.050	3.98×10^{-3}
0.100	3.93×10^{-3}

[a] Initial concentration of $ClSO_3H$, 0.05 M.

Table IV. Initial Rate Constants for α-Bromination of Aliphatic Acids in 1,2-Dichloroethane at 60 °C

	substrate acid $RR'CHCO_2H$		relative rate constant k, M^{-2} s^{-1}	k_{rel}	log k_{rel}
	R	R′			
1a	H	H	0.037	0.046	−1.330
1b	CH_3	H	0.256	0.321	−0.492
1c	CH_3CH_2	H	0.362	0.454	−0.342
1d	$(CH_3)_2CH$	H	0.458	0.575	−0.240
1e	CH_3	CH_3	0.796	1.000	0.000
1f	CH_3CH_2	CH_3CH_2	1.242	1.560	0.193
1g	hexahydrobenzoic acid		1.224	1.537	0.186

equimolar chlorosulfonic acid gave a pretty high yield. This fact suggests that the actual intermediate for bromination would not be the corresponding enol $RR'C{=}C(OH)_2$, because these geminal alcohols should easily be dehydrated in strong acids such as $ClSO_3H$ to form ketene in analogy with the other gem alcohols. Other cationic species, which may exist in equilibrium with ketene, e.g., $RR'CHCO^+$ and $RR'CH(OH)_2^+$, would not be attacked by electrophilic bromine, whereas ketene bearing a double bond is known to add easily to molecular halogen in the gas phase to form α-haloacyl halide,[15] which is confirmed also by us in a solution.[16]

The rate constant decreases with the proceeding of the reaction, which suggests the disappearance of chlorosulfonic acid by the reaction with water[17] produced during formation of ketene (eq 10a) and α-sulfonation of aliphatic acid (eq 10b).[18]

$$H_2O + ClSO_3H \longrightarrow HCl + H_2SO_4 \qquad (10a)$$

$$RR'CHCO_2H \xrightarrow{ClSO_3H} RR'C(SO_3H)CO_2H \qquad (10b)$$

Substituent Effect. The rates of bromination of a number of aliphatic acids were measured in a homogeneous solution of 1,2-dichloroethane at 60 °C (Table IV).

A plot of relative rates (log k_{rel}) vs. summation of Taft's σ* values ($\Sigma\sigma^*$)[19] gave a straight line with a slope (ρ*) of −0.97 (Figure 2).

The negative ρ* value suggests that acid-catalyzed α-bromination is accelerated by an electron-releasing group; the negative ρ value is expected for rate-determining electrophilic addition of bromine to the carbon–carbon double bond of ketene. A similar behavior was reported in the addition of bromine to alkene (ρ = −4.1 in 2,2,4,4-tetrachloroethane at 25 °C).[20] The reactivity of ketene may depend mostly on the inductive effect, but little on the steric hindrance effect.

The observed small steric effect on our reaction, which is rather different from the behavior in the addition of bromine to alkenes,[20,21] may be explained as follows: Addition of bromine to ketene may also proceed via a bromonium ion intermediate **4** as in the bromine addition to alkenes.[22] As postulated for the epoxidation of alkyl-substituted alkenes, an electrophilic oxygen atom should attack on the less hindered

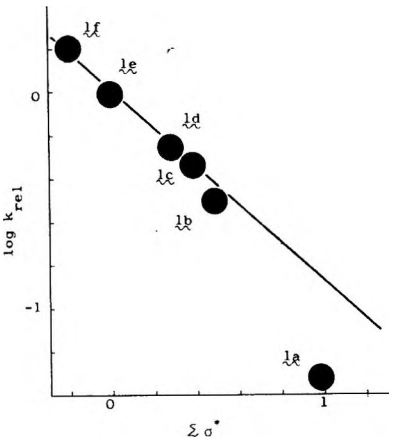
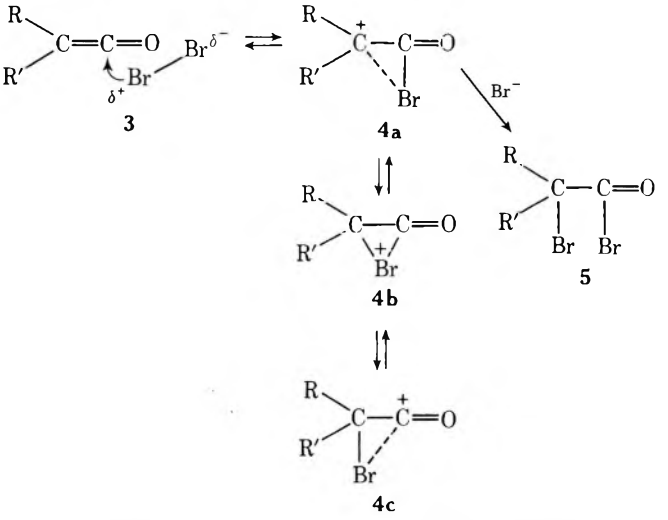


Figure 2. Plot of log k_{rel} vs. summation of Taft's σ* value.

site of the double bond in view of both less steric hindrance and more stabilization of developing positive charge.[23] Similarly, Br^+ should attack primarily on the carbonyl carbon to produce bromonium ion (**4a**) which is stabilized by steric and polar effects. Since **4b** and **4c** are less stable than **4a**, the path via **4a** is favored, thus exerting little steric hindrance. A bromide ion attack on **4** gives α-bromoacyl bromide (**5**).



Lower aliphatic acids show less reactivity than that expected from Taft's equation;[19] this tendency is remarkable with acetic acid. This may be due to the higher association or lower solubility of ketene $RR'CHC(OH)_2^+$ and $RR'CHCO^+$ formed from acetic acid in 1,2-dichloroethane compared with those of the other acids which have larger alkyl groups.

In conclusion, the rates of reaction increase in the following order.

$$CH_3CO_2H \ll CH_3CH_2CO_2H < CH_3CH_2CH_2CO_2H < (CH_3)_2CHCH_2CO_2H < (CH_3)_2CHCO_2H < (CH_3CH_2)_2CHCO_2H$$

Experimental Section

Materials. Commercial first-grade acetic [bp 118 °C], propionic [bp 73–75 °C (53 mm)], *n*-butyric [bp 163 °C], isovaleric [bp 175–177 °C], isobutyric [bp 86–88 °C (48 mm)], diethylacetic [bp 124 °C (38 mm)], hexahydrobenzoic [bp 86–87 °C (1.3 mm)], and chlorosulfonic [bp 86–88 °C (33 mm)] acids were distilled before use.

Kinetics. 1,2-Dichloroethane (100 mL) containing a mixture of aliphatic acid (5 mmol), bromine (5 mmol), and chlorosulfonic acid (5 mmol) was thermostated at 60 °C. The concentration of bromine was estimated by iodometry, i.e., each 5 mL of the mixture was pipetted out at appropriate intervals of time and poured into an excess amount of aqueous KI. Liberated iodine was titrated with 0.02 N $Na_2S_2O_3$. The second-order rate constants were calculated by ordinary means.

Analysis of Products. A mixture of aliphatic acid (10 mmol), bromine (10 mmol), chlorosulfonic acid (0.5 mL), and 1,2-dichloroethane (50 mL) was heated at 85 °C for 2 h.

After unreacted bromine and 20 mL of 1,2-dichloroethane were distilled off, methanol (30 mL) was added to the mixture and the solution was refluxed for 10 h. The resulting ester of the α-bromo acid was identified and estimated by means of GLC using a Yanagimoto GCG 550 gas chromatograph equipped with a copper column packed with PEG 20 M 10% on Chromosorb WAW 60–80 mesh by employing methyl caprate as an internal standard.

After removal of methanol by distillation from the ester solution the residual mixture was washed with water, dried (Na_2SO_4), and distilled in vacuo. The isolated ester of α-bromo acid was identified by NMR and IR spectroscopies. NMR and IR spectra were measured with a 60 MHz Hitachi R-24B NMR spectrometer at 35 °C and a Perkin-Elmer Model 337 spectrophotometer, respectively.

Acknowledgments. We are grateful to Mitsubishi Chemical Industry Co. and the Toa Gosei Co. for their gift of materials and also to Mr. M. Inaishi for his helpful assistance.

Registry No.—Chlorosulfonic acid, 7790-94-5.

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$$(CH_3)_2CHCO_2H \xrightarrow{P,\ Br_2} (CH_3)_2CBrCOBr \xrightarrow{Zn} (CH_3)_2C{=}C{=}O$$

$$\xrightarrow[EDC]{Cl_2} (CH_3)_2CClCOCl \xrightarrow{CH_3OH} (CH_3)_2CClCO_2CH_3$$

Resulting methyl α-chloroisobutyrate was analyzed by GLC (12%). The analogous reaction was observed with the reaction of dimethylketene with Br_2.
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Carbanion Halogenations with Carbon Tetrahalides. α-Halo Esters

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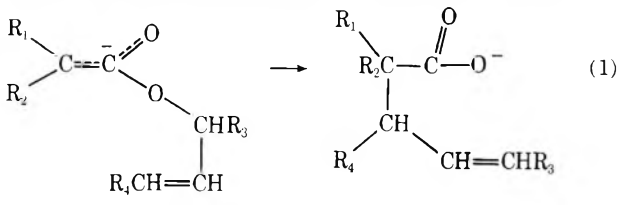
Received March 7, 1978

Carbanions generated by treatment of saturated or unsaturated esters with lithium diisopropylamide in THF at −78 °C react rapidly with carbon tetrahalides to produce α-halo esters in high yields (75–95%). Competitive bromination and chlorination of these carbanions with bromotrichloromethane are also described. These halogenations can be rationalized in terms of a radical anion–radical pair mechanism recently proposed for similar halogenations of carbanions derived from ketones or sulfones.

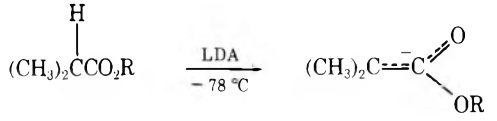
The regiospecific thermal rearrangement of enolate carbanions derived from allylic esters (eq 1), which we first described many years ago,[1] has proven to be of general synthetic usefulness. In certain cases, it is advantageous to convert the enolate anion into its *O*-trialkylsilyloxy derivative prior to rearrangement.[2]



(1)

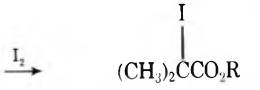
During the course of a recent study relating to this symmetry-allowed [3.3] sigmatropic rearrangement, we required a quantitative method for determining the amount of carbanion formed when allylic esters of isobutyric acid were treated with 1 equiv of lithium diisopropylamide (LDA) in THF at −78 °C.

The quantitative iodination of ester carbanions with elemental iodine, which may be used with saturated or unsatu-



1, R = CH_3
2, R = $CH_2CH{=}CH_2$

3, R = CH_3
4, R = $CH_2CH{=}CH_2$



5, R = CH_3
6, R = $CH_2CH{=}CH_2$

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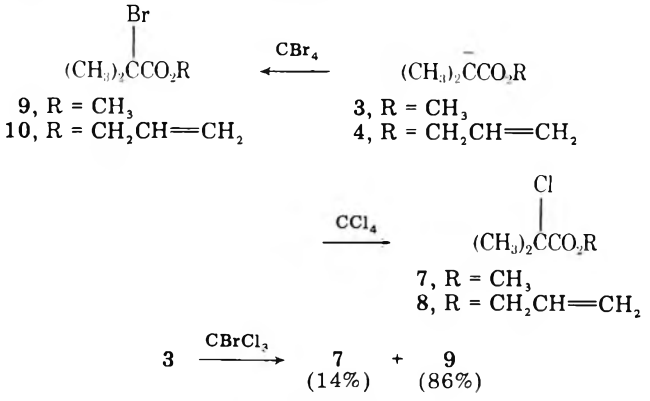
rated esters as described by Rathke et al.,[3] proved to be satisfactory in every way. In our examples, the profound change in the NMR spectra, which involves the disappearance of the methyl doublets in **1** and **2** and their replacement by a singlet in **5** and **6**, made this method very precise.

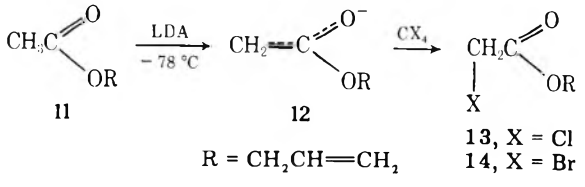
Using carbanions from saturated esters, Rathke et al.[3] also employed bromine (but not chlorine) with comparable results, but our findings are at variance with those reported with this halogen. In spite of the fact that our experience with iodination left no doubt that the transformation **1** → **3** was quantitative, treatment of **3** or **4** with exactly 1 equiv of bromine in THF produced the expected α-bromo esters contaminated by considerable amounts of the starting esters **1** or **2**.

We surmised that this strange result could be due to the reconversion of **3** into **1** (or **4** into **2**) by HBr generated from the photochemical bromination of the solvent (THF) prior to addition. In response to this proposal, a solution of bromine in carbon tetrachloride was added to **3** in THF (−78 °C). The crude product, worked up as before, contained no starting ester (**1**) but was shown (GLC and NMR) to consist of a mixture of the α-chloro and α-bromo esters **7** and **9**, respectively, with the former predominating in large excess. This result, which indicated that carbon tetrachloride is an effective chlorinating agent of ester carbanions under these conditions, has now been repeatedly demonstrated with several examples. Indeed, when the carbanions **3** or **4** are treated with carbon tetrachloride (1 equiv) at −78 °C and the mixture is allowed to warm to room temperature, the corresponding α-chloro esters (**7** or **8**) were formed in high yields (82 or 91%, respectively). Under comparable conditions, carbon tetrabromide produced the corresponding α-bromo esters (**9** or **10**, respectively). When the carbanion **3** was treated with bromotrichloromethane (1 equiv), the α-chloro and α-bromo esters (**7** and **9**) were formed in relative yields of 14 and 86%, respectively (as determined by NMR and GLC). These transformations are summarized below.



Erickson and Kornblum,[4] in a very recent study, have demonstrated that carbanions derived from primary nitroparaffins can be monohalogenated in excellent yields (82–94%) using elemental halogens. In practice, however, the metering of exactly 1 equiv of chlorine is not a simple technique.

Where applicable, we believe that the use of carbon tetrachloride has much to recommend it, especially when the carbanions undergoing chlorination contain carbon–carbon double bonds. We have now demonstrated that carbanions derived from primary esters can be selectively monohalogenated using carbon tetrahalides. Thus, when allyl acetate (**11**) was converted into its carbanion (**12**) and the latter



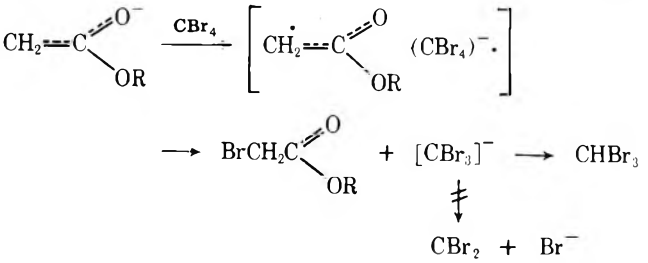
treated with carbon tetrachloride (1 equiv) at −78 °C, allyl α-chloroacetate (**13**) was formed to the extent of 74%, and no α,α-dichloroacetate could be detected. The absence of dihalogenated product indicates that the rate of halogenation of the carbanion (**12**) is much greater than the rate of proton transfer between **12** and the monochloro ester (**13**).

Similarly, **12** undergoes monobromination (ca. 75%; GLC and NMR) when treated with carbon tetrabromide. Unfortunately, in this case the pure allyl α-bromoacetate (**14**) was not easily separated by distillation, and it decomposed during attempts to separate it by column chromatography.

During the last decade, several reports have appeared describing the halogenation of carbanions with polyhaloalkanes. These include carbanions derived from diarylmethanes,[5] alkyl phosphonates,[6] ketones,[7] sulfones,[7,8] N-substituted amides and imides,[9] esters[9] (one example), and lactones[10] (one example). In other cases, carbanions derived from esters,[11] nitriles,[11] or 2-nitroalkanes[12] undergo oxidative coupling (presumably via the intermediate halogenated derivatives) to form dimeric products.

Extensive studies have been reported by Meyers et al.[7] using the system KOH (powdered)–*t*-BuOH–CCl_4, principally with ketones and sulfones. The reaction proceeds rapidly at room temperature, and the exact nature of the product(s) isolated depends on the reactivity of the first-formed halogenated ketone (or sulfone) under the conditions employed. These investigators have also studied competitive bromination vs. chlorination using bromotrichloromethane.

Our results are easily rationalized in terms of the radical anion–radical pair mechanism proposed by Meyers,[7] with the exception that the CX_3^- moiety, formed by the collapse of the radical anion–radical pair, does not decompose appreciably under the conditions which we employ to form a dihalocarbene and halide ion. For example, with all brominations of ester carbanions which we have effected with CBr_4, bromoform was always formed as a substantial product as illustrated below.



The apparent absence of dihalocarbenes in our system also explains why we were unable to detect any dihalocyclopropane derivatives in products derived from unsaturated esters.

Experimental Section

Tetrahydrofuran, carbon tetrachloride, and diisopropylamine were purified by standard methods and stored over appropriate drying agents. Carbon tetrabromide (Matheson, Coleman and Bell), bromotrichloromethane (Eastman Kodak), and *n*-BuLi (1.6 M solution in hexane) (Aldrich) were used without further purification. Allyl acetate (Matheson, Coleman and Bell) was distilled and stored over molecular sieves. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

NMR spectra were recorded on a Varian A-56/60 spectrometer, and all chemical shifts are given in ppm downfield from tetramethylsilane (δ scale). Analytical GLC analyses were recorded on a Varian 204-1B instrument fitted with flame ionization detectors using helium as a carrier gas with a flow of 40 mL/min and hydrogen with a flow rate of 40 mL/min. The column used was a 0.25 in × 10 ft stainless steel tube containing 5% QF-1 on Chromosorb W (60–80 mesh). Peaks were integrated on a Varian 477 integrator.[13]

Lithium Diisopropylamide. A 1.6 M solution of *n*-BuLi in hexane (6.875 mL, 11 mmol) was added to a solution of diisopropylamine (1.113 g, 11 mmol) in THF (2 mL) at 0 °C under argon. The mixture was stirred for 15 min at 0 °C and cooled to −78 °C before using it for the preparation of ester carbanions.

Allyl Isobutyrate (2). A solution of isobutyryl chloride (34.84 g, 327 mmol) in dry ether (30 mL) was added dropwise over a period of 1 h to a stirred solution of allyl alcohol (18.99 g, 327 mmol), pyridine (25.87 g, 327 mmol), and dry ether (50 mL) at 0 °C. The mixture was stirred for an additional 30 min and left in a refrigerator overnight. It was poured onto ice, the layers separated, and the aqueous layer was extracted with ether (2 × 30 mL). The combined organic layers were washed with cold HCl (40 mL, 2 M), saturated sodium bicarbonate solution (40 mL), and water (2 × 40 mL) and dried ($MgSO_4$). Evaporation of the solvent and distillation gave 31.43 g (75%) of **2:** bp 133–134 °C (lit.[14] bp 133 °C); NMR (CCl_4) δ 1.15 (d, 6 H), 2.52 (septet, 1 H), 4.52 (d, 2 H), 5.18 (m, 1 H), 5.38 (m, 1 H), 5.95 (m, 1 H).

Allyl α-Iodoisobutyrate. Allyl isobutyrate (1.28 g, 10 mmol) was added dropwise and with stirring to a solution of lithium diisopropylamide (11 mmol) in THF at −78 °C under argon. The reaction mixture was stirred for 30 min, and a solution of iodine (2.54 g, 10 mmol) in THF (20 mL) was added dropwise over a period of 10 min at −78 °C. The brown color of iodine disappeared immediately on addition, and a light yellow precipitate formed. The mixture was allowed to warm to room temperature and then was stirred for 1 h, during which time the color changed to dark brown. Cold HCl (20 mL, 1 M) was added, the layers separated, and the organic layer was washed with saturated sodium bicarbonate (20 mL) and water (50 mL) and dried ($MgSO_4$). The solvent was removed on a rotary evaporator to give a dark brown liquid (2.52 g, 99%) whose NMR spectrum was indistinguishable from the pure product. Distillation, with a considerable mechanical loss, gave 1.21 g (47.6%) of pure allyl α-iodoisobutyrate as a colorless liquid which becomes colored on standing: bp 28 °C (0.01 mm); NMR ($CDCl_3$) δ 2.09 (s, 6 H), 4.61 (d, 2 H), 5.24 (m, 1 H), 5.48 (m, 1 H), 5.98 (m, 1 H).

Anal. Calcd for $C_7H_{11}IO_2$: C, 33.09; H, 4.36; I, 49.95. Found: C, 32.79; H, 4.49; I, 48.30.

Methyl α-Iodoisobutyrate. Using a similar technique, methyl isobutyrate (2.04 g, 20 mmol) was converted into its anion with LDA and halogenated with iodine (5.08 g, 20 mmol) to give 4.32 g (95%) of a dark brown product whose NMR spectrum was indistinguishable from the distilled product. Distillation gave 4.02 g (88.1%) of the expected ester as a light brown liquid: bp 55–57 °C (13.4 mm) [lit.[15] bp 64 °C (12 mm)]; NMR (CCl_4) δ 2.07 (s, 6 H), 3.76 (s, 3 H).

α-Halogenation of Methyl Isobutyrate with Bromine in Carbon Tetrachloride. A. Methyl isobutyrate (2.04 g, 20 mmol) was added dropwise to a stirred solution of lithium diisopropylamide (22 mmol) in THF at −78 °C under argon. The mixture was stirred for 20 min, and a solution of bromine (3.52 g, 22 mmol) in carbon tetrachloride (10 mL, 15.94 g, 103.5 mmol) was added dropwise with stirring over a period of 10 min at −78 °C. The bromine color disappeared instantaneously. The mixture was allowed to warm to room temperature, a light yellow precipitate appeared, and stirring was continued for 1 h. Cold HCl (20 mL, 1 M) was added, the layers separated, and the carbon tetrachloride layer was washed successively with saturated sodium bicarbonate (20 mL) and water (40 mL). It was dried ($MgSO_4$) and the excess carbon tetrachloride removed on a rotary evaporator at low temperature. The brown liquid residue (2.62 g) was analyzed by GLC and consisted of a mixture of α-halo esters (95.2%) plus nonester impurities (4.8%). The ratio of methyl α-chloroisobutyrate (**7**) to methyl α-bromoisobutyrate (**9**) was 87.2:12.8.

B. The above experiment was repeated using bromine (3.2 g, 20 mmol) and carbon tetrachloride (3.08 g, 20 mmol). The brown product (3.05 g) was analyzed by GLC, which showed that it consisted of **7** and **9** in a ratio of 58.35:41.65. Only 1.5% of the crude product represented nonester impurities.

Methyl α-Chloroisobutyrate (7). Methyl isobutyrate (2.04 g, 20 mmol) was added to a stirred solution of lithium diisopropylamide (22 mmol) in THF at −78 °C under argon. The mixture was stirred for 20 min, and carbon tetrachloride (3.38 g, 22 mmol) in THF (2 mL) was added dropwise over a period of 5 min at −78 °C. The mixture was allowed to warm to room temperature and was stirred for an additional 1 h, during which time a light yellow precipitate formed. Cold HCl (20 mL, 1 M) was added, and the aqueous layer was extracted with ether (10 mL). The combined organic layers were washed with saturated bicarbonate (20 mL) and water (30 mL) and dried ($MgSO_4$). Removal of the solvent on a rotary evaporator at low temperature gave 2.24 g (83%) of the α-chloro ester (98% of **7** by GLC). Distillation, with a large mechanical loss, gave 1.01 g (37%) of pure **7:** bp 35–36 °C (16 mm) (lit.[16] bp 133–135 °C); NMR (CCl_4) δ 1.75 (s, 6 H), 3.76 (s, 3 H).

Allyl α-Chloroisobutyrate (8). In a manner similar to that described for **7**, allyl isobutyrate (2.56 g, 20 mmol) was converted to its anion with LDA and treated with carbon tetrachloride (3.38 g, 22 mmol). The crude product (3.1 g; 95% pure by GLC) was distilled with a considerable mechanical loss to give 1.52 g (46.9%) of pure **8:** bp 49–51 °C (13.5 mm); NMR (CCl_4) δ 1.75 (s, 6 H), 4.62 (d, 2 H), 5.22 (m, 1 H), 5.47 (m, 1 H), 5.97 (m, 1 H).

Anal. Calcd for $C_7H_{11}ClO_2$: C, 51.70; H, 6.82; Cl, 21.80. Found: C, 51.60; H, 6.76; Cl, 22.07.

Methyl α-Bromoisobutyrate (9). Methyl isobutyrate (1.02 g, 10 mmol) was converted to its anion as described above and treated with carbon tetrabromide (3.32 g, 10 mmol) dissolved in THF (16 mL). The crude product (1.89 g), aside from an absorption for $CHBr_3$, had an NMR spectrum identical with pure **9.** Distillation gave 1.43 g (79.4%) of pure **9:** bp 40–41 °C (16 mm) [lit.[17] bp 52.2 °C (21 mm)]; NMR (CCl_4) δ 1.90 (s, 6 H), 3.76 (s, 3 H).

Allyl α-Bromoisobutyrate (10). In a manner similar to that described above, allyl isobutyrate (1.28 g, 10 mmol) was converted to its anion and treated with carbon tetrabromide (3.32 g, 10 mmol) dissolved in THF (16 mL). The crude product (2.1 g; 95% pure by NMR) was distilled to give 1.60 g (77.3%) of pure **10:** bp 50–51 °C (12 mm); NMR (CCl_4) δ 1.92 (s, 6 H), 4.66 (d, 2 H), 5.29 (m, 1 H), 5.52 (m, 1 H), 6.01 (m, 1 H).[18]

Although this compound has been prepared[19] from α-bromoisobutyryl bromide and allyl alcohol, its physical properties have not been reported.

α-Halogenation of Methyl Isobutyrate with Bromotrichloromethane. In the usual manner, methyl isobutyrate (1.02 g, 10 mmol) was converted to its anion at −78 °C under argon and treated with bromotrichloromethane (2.18 g, 11 mmol). The crude product (1.68 g), isolated as described above, was analyzed by GLC and consisted of methyl α-chloroisobutyrate (**7**) and methyl α-bromoisobutyrate (**9**) in a ratio of 14.26:85.74, respectively. A 9% amount of the crude product represented other impurities. Within experimental error, the NMR data were in accord with those obtained by GLC.

Allyl α-Chloroacetate (13). As described above, allyl acetate (2.0 g, 20 mmol) was converted into its anion with LDA (22 mmol) at −78 °C under argon and treated with carbon tetrachloride (3.38 g, 22 mmol). The crude product (2.01 g) was analyzed by GLC and shown to contain 98% of **13.** Distillation, with a considerable mechanical loss, gave 1.32 g (49%) of allyl chloroacetate (**13**): bp 42–43 °C (13 mm) [lit.[20] bp 162–163.5 °C (766 mm)]; NMR (CCl_4) δ 4.03 (s, 2 H), 4.58 (d, 2 H), 5.19 (m, 1 H), 5.37 (m, 1 H), 5.91 (m, 1 H).

Registry No.—**1,** 547-63-7; **2,** 15727-77-2; **3,** 67194-51-8; **4,** 67194-52-9; **5,** 67194-53-0; **6,** 67194-54-1; **7,** 22421-97-2; **8,** 67194-55-2; **9,** 23426-63-3; **10,** 40630-82-8; **11,** 591-87-7; **12,** 67194-56-3; **13,** 2916-14-5; isobutyryl chloride, 79-30-1; allyl alcohol, 107-18-6; carbon tetrachloride, 56-23-5; carbon tetrabromide, 558-13-4; bromotrichloromethane, 75-62-7.

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3-Chlorophthalic Anhydride through Chlorination of Phthalic Anhydride

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Received February 17, 1978

Monochlorination of molten phthalic anhydride in the presence of ferric chloride proceeds with only a small preference (55:45) for 4-chlorophthalic anhydride over 3-chlorophthalic anhydride. Under the same conditions both monochlorophthalic anhydrides are chlorinated at rates comparable to that of phthalic anhydride itself. When 1 mol of chlorine is taken up by 1 mol of phthalic anhydride, a mixture of starting material and mono- and dichlorophthalic anhydrides is obtained together with traces of the more highly chlorinated phthalic anhydrides. Distillative separation of 3-chlorophthalic anhydride from the lower boiling 4-chlorophthalic anhydride can be readily achieved on a moderately efficient column. Convenient preparation of pure 3-chlorophthalic anhydride through distillation of chlorinated phthalic anhydride mixtures is impeded by the nearly identical boiling points of 3-chlorophthalic anhydride and 4,5-dichlorophthalic anhydride. The latter is formed to the extent of one-sixth of the dichlorophthalic anhydride fraction of the chlorinated mixtures.

Although Lewis acid catalyzed chlorination of phthalic anhydride (PAA) was reported in 1909[1] and has been extensively studied in the years since then,[2] isolation or identification of 3-chlorophthalic anhydride (3-ClPAA) as a product of the reaction has never been made. Instead, 3-ClPAA has most commonly been prepared from the corresponding nitrophthalic anhydride (3-NO_2PAA) by a high temperature (230–250 °C) ipso displacement reaction.[3] The 3-NO_2PAA, in turn, is usually prepared in modest (25–29%) overall yield by nitration of PAA, fractional crystallization of the mixed mononitrophthalic acids (formed in ~1:1 ratio), and dehydration of the separated 3-nitrophthalic acid.[4]

We were interested in obtaining quantities of 3-ClPAA for use as an intermediate in a heterocyclic synthesis and became curious as to why such a round-about method is employed for its preparation. While the literature indicates that chlorination of phthalate with sodium hypochlorite gives as much as 90% of 4-ClPAA,[5] under typical electrophilic substitution conditions the ratio of monochlorination products of PAA should be similar to that of its nitration products. Indeed, the reported[6] isolation of a fair (25%) yield of 3,6-diClPAA after more extensive chlorination of PAA in the presence of Lewis acid catalysts infers that substantial amounts of 3-ClPAA are formed since rearrangement does not occur under these conditions (vide supra).

The isomer ratio of monochlorinated products of PAA is also of theoretical interest. Electrophilic chlorinations are known to involve complexation of the aromatic substrate as the donor with the electrophile as the acceptor.[7] There are few studies of such reactions where the aromatic substrate is multiply substituted with electron-withdrawing groups making it a poorer donor. Hückel molecular orbital calculations indicate that the anhydride function will have little effect on the degenerate highest filled donor molecular orbitals of the benzene ring in PAA. Thus, little positional selectivity to electrophilic attack is anticipated. Neither the "frontier electron" method nor the "Wheland intermediate" methods of analysis of the molecular orbitals[8] of PAA suggest that its electrophilic 4 substitution should predominate over its 3 substitution. Although such conjecture is suggestive, the necessary detailed experimental product analysis for this reaction has, until now, not been available.

Results and Discussion

Product Distribution. An initial exploratory investigation indicated that molten PAA at 220–230 °C is not chlorinated either neat or in the presence of catalytic quantities of nickel acetylacetonate, cupric chloride or acetate, or aluminum chloride. In the presence of mercuric chloride, only traces of 3-ClPAA and 4-ClPAA could be detected (in about equivalent amounts by GLC) after 8 h of chlorination. With several strong Lewis acids such as $MoCl_5$, $SbCl_5$, and $FeCl_3$, PAA chlorination occurred at a substantial rate. Thus, with 1 mol of PAA and 0.1 mol of $FeCl_3$ present at 220 °C after 5 and 10 h of chlorination, 56 and 92%, respectively, of the PAA had been consumed (by GLC analysis). Based on GLC analysis calibrated with authentic samples, the reaction product after 5 h of chlorination appeared to be about 25% of 4-ClPAA, 23% of 3-ClPAA, and ~4% each of two materials with longer retention times, presumably diClPAA's.

At temperatures below about 220–230 °C, the rate of PAA chlorination slowed markedly, almost completely stopping by 200 °C. Temperatures much higher than about 240 °C, desirable for more rapid chlorination, could not be effectively employed in systems open to the atmosphere because of extensive PAA sublimation. Chlorination proceeded effectively with a ferric chloride molar concentration at 1% that of the PAA, but became very slow at 0.1%. Similar patterns of conversion of PAA to chlorinated products were found in all cases. The results consistently indicated that the catalyzed monochlorination proceeds with only a small preference (ca. 55:45) for 4-ClPAA over 3-ClPAA formation.

Monitoring the composition of the mixture through GLC analysis of samples withdrawn as the chlorination proceeded showed that both monochloro PAA's steadily increased in concentration until about one-half the PAA had been consumed. Further chlorination had the effect of increasing the proportion of compounds with longer GLC retention times, presumably polychloro PAA's, at the expense of PAA with little change occurring in the monochloro PAA concentration. As chlorination continued and the PAA became almost completely consumed, the compounds with longer GLC retention times continued to increase in relative concentration at the expense of the monochloro PAA's. These results are consistent with chlorination of both monochloro PAA's proceeding at rates comparable to chlorination of PAA under the same conditions. Thus, while a chlorine substituent is known to have a moderately deactivating effect on most electrophilic aromatic substitutions,[7] its added effect on the rate of chlorination of the highly deactivated PAA system under the relatively severe conditions required is negligible. Examination of the initial data obtained suggested that 3-ClPAA might be chlorinated less rapidly than 4-ClPAA since it appeared to be consumed more slowly during the latter stages of the reaction. Full identification of the products showed this *not* to be the case. Authentic samples of 3,6-, and 4,5-diClPAA's were obtained, and 3,4-diClPAA was identified in the mixture by its characteristic proton NMR AB quartet (cf. Experimental Section). Through GLC analysis it was established that the first of the two longer retention time materials is 3,4-diClPAA and the second 3,6-diClPAA. With the nonpolar

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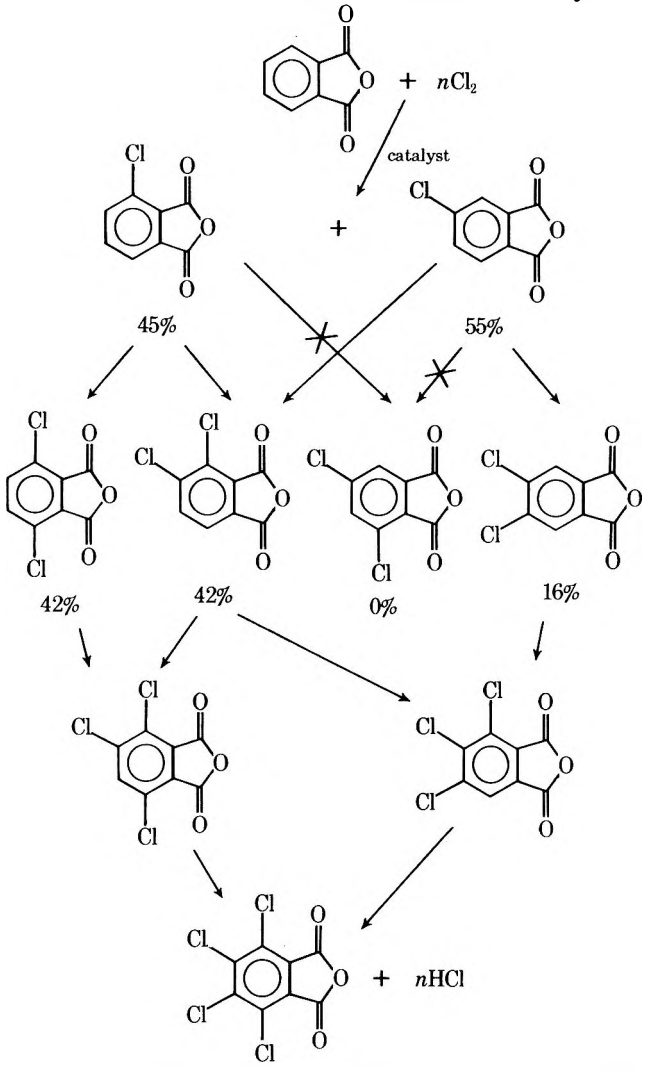
Scheme I. Products of Chlorination of Phthalic Anhydride



GLC column used (cf. Experimental section), 4,5-diClPAA proved to have precisely the same retention time as 3-ClPAA. This is consistent with the literature reports of the normal boiling points of these two compounds being identical (313 °C). With a polar GLC column (cf. Experimental Section), quantitative separation of 3-ClPAA and 4,5-diClPAA was readily achieved. No evidence for the presence of the fourth dichloro PAA isomer, 3,5-diClPAA, could be found in any of the chlorinated mixtures examined on either the polar or nonpolar GLC columns. This result is consistent with the ortho,para-directing influence of chlorine in both monochloro PAA's controlling the dichloro PAA isomer distribution. This also occurs despite the aforementioned lack of influence of the chlorine substituents on the rate of reaction. As illustrated by Scheme I, both monochloro PAA's can only yield 3,5-diClPAA through substitution meta to the chlorine already on the ring.

The data obtained from analysis of a typical PAA chlorination as it proceeded is reported in Table I, and a plot of weight percentages of the reaction mixture components as a function of the time period of chlorination is shown in Table I. The ratio of 4,5/3,4/3,6-diClPAA's remained consistently in the region of 16:42:42 before appreciable amounts of trichloro PAA's formed. An accurate quantitation of the relative rates of reactions of the dichloro PAA's was prevented by overlap of the GLC peak of 3,6-diClPAA with that of a product with a longer retention time, assigned to 3,4,5-triClPAA. The overall picture for the latter stages of the chlorination is also consistent. The presence of only two more GLC peaks with even longer retention times, the first assigned to 3,4,6-triClPAA and the last, confirmed by comparison with an authentic sample, assigned to tetrachloro PAA,[9] indicates that no significant amount of side reactions occurred.

To evaluate the possibility of isomerization among the chlorophthalic anhydrides as a possible side reaction during chlorination, experiments were conducted in which samples of 3-ClPPA, and 4-ClPAA, and chlorinated PAA mixtures were heated to 200–220 °C for periods up to 6 h in the presence of anhydrous $FeCl_3$ in the absence of chlorine. GLC analysis indicated no isomerization of any of the chloro PAA's present. Chlorinated PAA mixtures were also heated in the presence of 50 wt % of 5% palladium on carbon at 235 °C for 5 h with no change in the weight percent distribution of the original mixtures.

In an effort to alter the ratio of products, several attempts were also made to achieve free-radical chlorination of PAA through UV irradiation, but the reaction could not be induced under these conditions, even at 235 °C.

Isomer Separation. Although 4,5-diClPAA is produced to the extent of only 16% of the dichloro PAA's isomers and is thus only a minor (3–4%) component of the average monochlorinated PAA as in sample B of Table I, it represents, under such circumstance, almost 10% of the weight of 3-ClPAA. While the latter can be separated from the other components of the chlorinated mixture by fractional distillation, the presence of a 10% level of impurity makes it of unacceptable quality for most purposes. Exploratory efforts to achieve a facile nondistillative separation of 3-ClPAA from the other components of the crude monochlorinated mixture or from 4,5-diClPAA proved unsuccessful. Fractional recrystallization from *tert*-amyl alcohol, fractional melting, extraction, and sublimation were all tried without success. An alternative procedure is to chlorinate PAA to a less than average monochlorination level and thereby minimize dichlorination. This possibility was examined more closely in another chlorination

Table I. Chlorination of Phthalic Anhydride[a]

	weight %						
sample	A	B	C	D	E	F	G
reaction time, h	4	7	10	10.75	12.50	16.25	17.75
phthalic anhydride (PAA)	83.2	25.0	4.7	1.6	0.6		
4-chloro PAA	9.8	32.2	31.7	27.0	19.5	4.5	2.3
3-chloro PAA	7.0	24.9	19.0	17.6	14.0	12.3	12.8
4,5-dichloro PAA		2.5	6.0	7.0	8.2	8.5	8.5
3,4-dichloro PAA		7.7	18.4	21.9	25.1	25.9	25.6
3,6-dichloro PAA		7.7	18.4	21.9	25.2	30.4	29.9
3,4,5-trichloro PAA							
3,4,6-trichloro PAA				3.0	7.3	14.8	16.3
tetrachloro PAA						3.6	4.6

[a] Reaction conditions: reactant, 148 g of phthalic anhydride (1.00 mol); catalyst, 2.0 g of anhydrous $FeCl_3$ (0.012 mol); solvent, 5 mL of tetrachlorethane; and temperature, 235–240 °C.

Table II. Chlorination of Phthalic Anhydride[a]

	weight %								
sample	A	B	C	D	E	F	G	H	I
reaction time, h	4	5.75	10.25	15.25	18.25	20.25	22.25	25.5	28.5
phthalic anhydride (PAA)	81.6	80.1	63.7	44.0	40.6	34.9	30.8	27.2	24.2
4-chloro PAA	10.4	11.1	18.6	25.1	28.3	30.8	31.3	32.0	32.5
3-chloro PAA	8.0	8.8	15.9	21.2	21.9	21.6	23.2	22.7	23.0
4,5-dichloro PAA			0.2	1.1	1.3	1.8	2.0	2.5	2.9
3,4-dichloro PAA			0.8	3.3	4.0	5.5	6.4	7.8	8.7
3,6-dichloro PAA			0.8	3.3	4.0	5.5	6.4	7.8	8.7

[a] Reaction conditions: reactant, 1036 g of phthalic anhydride (7.00 mol); catalyst, 14 g of anhydrous $FeCl_3$ (0.086 mol); solvent, tetrachloroethane (5–10 mL); and temperature, 225–230 °C.

study, the data for which is shown in Table II. As can be seen from samples C and D of Table II, lower conversion of PAA can reduce the fraction of 4,5-diClPAA expressed as a percentage of 3-ClPAA to 5% or less. Fractional distillation can then be used to separate reasonable quality 3-ClPAA. Such a procedure requires recirculation of PAA and separation of 4-ClPAA, but it may still be more convenient than the nitration route for making 3-ClPAA in quantity.

Experimental Section

Chlorination of Phthalic Anhydride (Typical Procedure). A 2-L three-neck flask connected to a gas inlet, stirrer, and condenser–gas outlet was charged with 1036 g (7.0 mol) of commercial grade phthalic anhydride. The flask was heated in an oil bath to 200 °C, at which time 14 g (0.08 mol) of anhydrous ferric chloride and 10 mL of 1,1,2,2-tetrachloroethane were added. Refluxing tetrachloroethane returned sublimed PAA to the reaction vessel during the course of the chlorination. Chlorine from a cylinder was bubbled through the reaction mixture which was heated to and maintained at 225–230 °C. Small aliquots were removed at periodic intervals, dissolved in acetone, and analyzed by GLC.

3-Chlorophthalic Anhydride. A commercial sample of 3-chlorophthalic anhydride (mp 121–123 °C) was recrystallized from *tert*-amyl alcohol, mp 125–126 °C (reported mp 122 °C). Characteristic infrared peaks (Nujol mull) were seen at 1145, 1155, and 1360 cm^{-1}.

4-Chlorophthalic Anhydride. A 100-mL three-neck microflask fitted with a stirrer, gas inlet, and condenser was charged with 15 g of commercial (Aldrich) 4-nitrophthalic acid (0.071 mol). The solid was melted and heated for 2 h at 180 °C to allow conversion to the 4-nitrophthalic anhydride, and then it was heated to 240 °C while chlorine gas was bubbled through the melt. Aliquots were removed at periodic intervals for analysis by GLC, and the reaction was terminated after 6 h when samples showed identical spectra. The reaction mixture (consisting of about 80% of 4-chloro and 20% of 3-chloro PAA) was recrystallized twice from *tert*-amyl alcohol to yield 3.0 g of 4-chlorophthalic anhydride (mp 94–96 °C; reported mp 98 °C), which analyzed as >99% pure by GLC. Characteristic infrared peaks (Nujol mull) were seen at 1250 and 1335 cm^{-1}.

3,6-Dichlorophthalic Anhydride. A late distillation fraction of a chlorinated PAA reaction mixture consisting predominantly of dichlorophthalic anhydrides was recrystallized from *tert*-amyl alcohol (10 g/200 mL) to collect 2.3 g of 3,6-dichlorophthalic anhydride (mp 184–187 °C; reported mp 190–191 °C), which analyzed as 97.9% pure by GLC. Characteristic infrared peaks (Nujol mull) were seen at 615, 845, 1150, and 1220 cm^{-1}. The NMR spectrum showed a single peak at δ 8.00 in deuteriochloroform.

4,5-Dichlorophthalic Anhydride. A sample was prepared following a literature procedure. A chlorinated reaction mixture (10 g) containing 35.6% of 4,5-diClPAA (obtained by chlorinating 4-chloro PAA for 5.5 h) was heated in 50 mL of 97.3% concentrated H_2SO_4 for 1.5 h at 100–110 °C. The resulting mixture upon cooling was poured into 100 g of ice with stirring to precipitate a white solid which was washed with water and dried. The solid was triturated overnight with toluene. The toluene-insoluble fraction was recrystallized from water to yield 1.7 g of 96% pure (GLC) 4,5-dichlorophthalic acid (mp 190–193 °C).

The acid was heated to 210 °C for 3–4 h and cooled, and the product recrystallized from carbon tetrachloride to yield 4,5-dichlorophthalic anhydride, mp 182–185 °C (reported mp 185–187 °C).[10] Characteristic infrared peaks (Nujol mull) were seen at 612, 718, 1315, and 1385 cm^{-1}.

3,4-Dichlorophthalic Anhydride. This known compound[10] was identified in late distillation fractions through its characteristic NMR spectrum. In hexadeuterioacetone, 3,4-diClPAA exhibited a characteristic AB quartet with proper intensities: δ 8.20 (H_6), 8.03 (H_5) (J = 8 Hz). The intensity of the quartet in the NMR spectrum relative to the intensity of the protons of 3,6-diClPAA at δ 8.00 in the same distillation fractions was proportional to the GLC areas at 7.1 and 7.5 min, respectively, under the conditions described below.

GLC Conditions. Most analyses were performed on a 10 ft × ⅛ in stainless steel 20% QF-1 on 90–100 mesh Anchrom ABS column. The column temperature was programmed for 4 min at 195 °C, increasing to 250 °C at 20 °C/min. With a carrier (He) gas flow rate of approximately 20 mL/min, the approximate retention times of reaction mixture components are as follows: PAA, 4.0 min; 4-ClPAA, 5.0 min; 3-ClPAA, 6.2 min; 4,5-diClPAA, 6.2 min; 3,4-diClPAA, 7.1 min; 3,6-diClPAA, 7.5 min; 3,4,5-triClPAA, 7.6 min; 3,4,6-triClPAA, 7.9 min; and tetrachloro PAA, 8.9 min.

A 4 ft × 0.25 in stainless steel column packed with 80–100 mesh Chromosorb 101 operated at 275 °C was used for the separation of 3-ClPAA and 4,5-diClPAA by GLC. With a carrier gas (He) flow rate of >30 mL/min, the approximate retention times were found to be as follows: PAA, 13.0 min; 4-ClPAA, 19.0 min; 3-ClPAA, 26.0 min; 4,5-diClPAA, 32.0 min; 3,4-diClPAA, 43.2 min; and 3,6-diClPAA, 49.0 min.

This column appeared to deteriorate with time of operation at 275 °C, so that after ~24 h baseline drift made it unusable. Response factors were determined on both columns using weighed quantities of pure materials.

Acknowledgment. We thank Ms. G. M. Blank for some preliminary experiments and Drs. N. Colthup and J. E. Lancaster for consultation on the infrared and NMR spectra, respectively.

Registry No.—PAA, 85-44-9; 4-ClPAA, 118-45-6; 3-ClPAA, 117-21-5; 4,5-diClPAA, 942-06-3; 3,4-diClPAA, 56962-07-3; 3,6-diClPAA, 4466-59-5; 3,4,5-triClPAA, 67238-14-6; 3,4,6-triClPAA, 59317-90-7; tetrachloro PAA, 117-08-8; 4-nitrophthalic acid, 610-27-5; 4-nitrophthalic anhydride, 5466-84-2; 4,5-dichlorophthalic acid, 56962-08-4.

References and Notes

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(2) (a) U.S. Patent 1 997 226, April 9, 1935; (b) U.S. Patent 2 028 383, Jan. 21, 1936; (c) British Patent 572 160, Sept. 25, 1945; (d) U.S. Patent 2 460 565, Feb. 1, 1949.
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(5) British Patent 628 401, Aug. 29, 1949. Also cf. E. E. Ayling, *J. Chem. Soc.*, 253 (1929), and references therein.
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(8) Cf. A. Streitwieser, Jr., "Molecular Orbital Theory", Wiley, New York, N.Y., 1961, p 313 et seq.
(9) Traces of materials with retention times which we've assigned to the trichloro PAA's were also found in a commercial (Hooker Chemical Co.) sample of tetrachloro PAA.
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J. Org. Chem., Vol. 43, No. 19, 1978 3693

Brominative Cyclizations of Geranyl Derivatives

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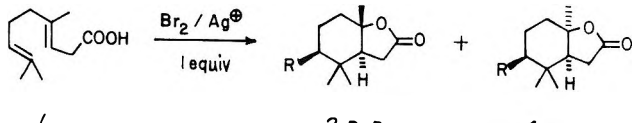
Received March 14, 1978

Homogeranic acid (1) and methyl geranylacetoacetate (18) were cyclized with bromine in the presence of silver fluoroborate to the brominated bicyclic compounds 2 and 19, respectively. Proton initiated cyclization competed with the brominative cyclization and gave trans lactone 3 and enol ether 20, respectively. Acid-catalyzed cyclization of 1 to 3 and isomerization of 3 to the cis lactone 5 were investigated. Both 3 and 5 were converted to the natural product dihydroactinidiolide (14).

The reaction of polyenes with a source of positive bromine has been demonstrated to provide a useful method for the incorporation of a bromine atom into various mono- and bicyclic carbon skeletons.[1] Although this transformation is of interest in view of the increasing number of newly discovered halogenated natural products of marine origin, the synthetic applicability is hampered by the low yields (<20%) of purified bromo compounds commonly obtained in this fashion. We would like to present observations which have arisen from some of our studies in this area.



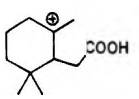
1

2, R = Br
3, R = H

4, R = Br
5, R = H

When homogeranic acid (1) was allowed to react with a nitromethane solution of 1 equiv each of bromine and silver tetrafluoroborate, the desired trans-fused bromo lactone 2 (11%), a trace of the cis-fused bromo lactone 4 (<1%), and the trans- and cis-fused norbromo lactones 3 (7%) and 5 (17%) were isolated after careful short column chromatography. The stereochemical assignments for 2 and 4 rest on comparison of appropriate spectral data with each other and with the known[2] trans- and cis-fused lactones 3 and 5. This is the first unambiguous establishment of a trans-fused bicyclic product in a bromine-induced cyclization, and compound 2 represents both the first brominated bicyclo[4.3.0] system and lactone to be generated via this route. That the presumably less stable isomer 2 is formed to the near exclusion of 4 is consistent with a concerted cyclization mechanism.

It is of interest to contrast this result with those of Kato and Kitahara,[3] who studied the acid-catalyzed ($SnCl_4$/benzene (1:10), room temperature, 4 h) cyclization of homogeranic acid and esters and reported the exclusive formation of the cis lactone 5. They claimed this result "suggests that the cyclization proceeds via a nonconcerted mechanism and cation [6] could be an intermediate."[3] This was surprising in view of the predominance of the trans-fused compounds 2 and 3 in the present cyclization. The reaction of 1 with a variety of acids was therefore examined in order to shed light on this apparent ambiguity and to determine if the unwanted norbromo products 3 and 5 were arising via a competing cyclization catalyzed by fluoroboric acid that was presumably being generated as the brominative cyclization proceeded. The results of these acid-catalyzed cyclizations of homogeranic acid (1) are shown in Table I and clearly indicate the following points.



6

(i) Proton initiated cyclization of homogeranic acid leads to the trans-fused lactone 3 as the kinetically favored product. The trans lactone 3 then isomerizes to the thermodynamically favored cis-fused lactone 5 in the presence of both Lewis and Brönsted acids (entries 1–4, 5–9, 10–12, 15–16, and 18–20). Thus, the results of Kato and Kitahara (vide supra) do not constitute evidence for a nonconcerted reaction pathway. Their reaction conditions certainly would have promoted the 3 to 5 isomerization (cf. entries 5–9).

(ii) Both cyclization of 1 to 3 and isomerization of 3 to 5 are much more facile in nitromethane solution than in a variety of less polar solvents. Furthermore, the rate of isomerization is such that the process could have occurred to a significant extent during the course of our initial brominative cyclization of 1. It was surprising, however, that *trans*-2 to *cis*-4 isomerization of the bromo lactones had occurred to such a minute extent. Indeed, when pure 2 was treated with stannic chloride or stannic bromide in deuterionitromethane, only a slow conversion to several unidentified products, none of which was the cis bromo lactone 4, ensued. A possible rationale for the dichotomous behavior of 2 and 3 under the influence of acid catalysis is available if one assumes that opening of either trans lactone 2 or 3 leads to the planar carbonium ion 6eq (see Chart I), which can only relactonize to the cis lactone 4 or 5 via perpendicular attack on the empty p orbital by the carboxyl group of an axially disposed acetic acid side chain.[4] This necessitates a conformational conversion of 6eq to 6ax, and it is this step which interferes with the overall isomerization in the brominated series (R = Br) due to the severe 1,3-diaxial interaction in 6ax (R = Br) as well as the eclipsing interaction of the bromine and methyl group which intervenes as 6eq converts into 6ax.

(iii) Aqueous fluoroboric acid (48%) *did not* cyclize 1 to 3 or isomerize 3 to 5 in nitromethane solution at a rate that was competitive with the proton incorporation and isomerization in the brominative cyclization. It therefore seemed probable that the rate of proton initiated cyclization was very susceptible to the degree of solvation of the proton itself. That is, water "buffered" the protons in the aqueous fluoroboric acid/nitromethane mixture, thus lowering their electrophili-

Chart I

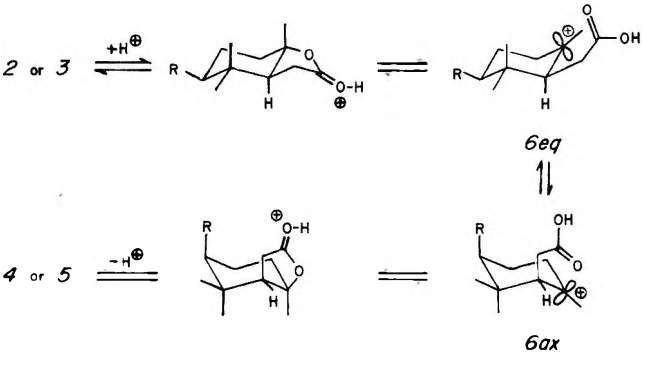


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Table I. Acid-Catalyzed Cyclizations of Homogeranic Acid (1)[a]

Entry	Acid	No. of equiv	Solvent	Time	Product ratio[b] 1(S.M.)	3(trans)	5(cis)	other[c]
1	$SnBr_4$ or $SnCl_4$	0.1	CD_3NO_2	5 min	0	2	1	0
2	$SnBr_4$ or $SnCl_4$	0.1	CD_3NO_2	11 min	0	1	2	0
3	$SnBr_4$ or $SnCl_4$	0.1	CD_3NO_2	1 h	0	1	6	0
4	$SnBr_4$ or $SnCl_4$	0.1	CD_3NO_2	2 h	0	0	1	0
5	$SnCl_4$	0.5	C_6D_6	2 min	6	1	Trace	0
6	$SnCl_4$	0.5	C_6D_6	6 min	5	5	1	0
7	$SnCl_4$	0.5	C_6D_6	22 min	7	4	1	0
8	$SnCl_4$	0.5	C_6D_6	2 h	0	1	1	0
9	$SnCl_4$	0.5	C_6D_6	16 h	0	1	4	0
10	$SnBr_4$	0.1	CD_3CN	11 min	7	2	1	0
11	$SnBr_4$	0.1	CD_3CN	40 min	Trace	4	3	0
12	$SnBr_4$	0.1	CD_3CN	3 h	0	2	3	0
13	$SnBr_4$	1.0	$CDCl_3$	2 days	1	4	1	0
14	$SnBr_4$	0.5	C_6D_6	40 h	4	3	2	1
15	HBF_4 (48%)	1.0	CH_3NO_2	1 min	4	1	Trace	1
16	HBF_4 (48%)	1.0	CH_3NO_2	10 min	Trace	6	1	1
17	HNO_3 (70%)	1.0	CD_3NO_2	2.5 h	4	1	0	1
18	BF_3·Et_2O	0.2	$CDCl_3$	1.5 h	4	1	Trace	0
19	BF_3·Et_2O	0.2	$CDCl_3$	6 h	4	4	1	0
20	BF_3·Et_2O	0.2	$CDCl_3$	24 h	1	3	1	0
21	TFA		$CDCl_3$ or CD_3NO_2			No reaction		

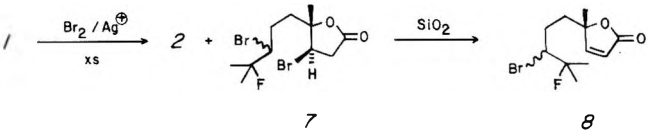
[a] All cyclizations were carried out at ambient temperatures and at concentrations of 0.1–0.2 M in 1. With the exception of entries 15 and 16, the experiments were performed directly in an NMR tube. [b] Product ratios were determined by direct comparison of the relative intensities of the three distinct methyl resonances for 1, 3, and 5 in the NMR spectra of the crude product mixtures. [c] Other unidentified products were occasionally formed as evidenced by the appearance of extraneous methyl absorptions in the crude NMR spectra.

city and ability to induce cyclization relative to the protons in the nonaqueous systems, including the bromine/silver fluoroborate/nitromethane cyclization medium.

This result led us to study the brominative cyclization under a variety of conditions (including the addition of a number of external "buffering" agents) with the hope of minimizing or eliminating the amounts of unwanted 3 and 5, thereby increasing the yield of bromo lactone 2. Table II summarizes the conditions which were varied in an attempt to accomplish this objective.

Shortening the reaction time in nitromethane at −10 °C (entry 2) resulted in less 3 to 5 isomerization but the same relative ratio of brominated (2) to nonbrominated (3 + 5) lactones. Lowering the temperature as well as shortening the reaction time (entries 3–5) finally allowed the reaction to be interrupted before completion. The dramatic rise in the ratio of 2 to 3 + 5 confirmed that the competing proton incorporation was resulting from acid that was being generated as the reaction proceeded. We thus reasoned that the undesired pathway might be swamped out by having excess brominating agent present throughout the course of the reaction. Indeed, when 2–10 equiv of bromine was used (entries 6–8), only small quantities of 3 and 5 were observed. Changing the solvent and/or brominating agent to systems that have been used previously by others[1] gave little or no cyclized bromo lactone (entries 9 and 10). Finally, the addition of external agents designed to buffer the electrophilicity of the protons present (entries 11–14) diminished the amounts of 3 and 5 that were formed; but in all cases, unidentified side products accompanied these attempts to increase the yield of bromo lactone 2.

It appeared that the most straightforward solution to obtaining the desired bromo lactone 2 on a preparative scale was to use excess brominating agent. Unfortunately, when larger quantities of homogeranic acid (1) were cyclized in this fashion, bromo lactone 2 could be isolated in only 15% yield. No trace of 3, 4, or 5 was produced, but several new products appeared. Among these were the diastereomeric dibromo fluorides 7, which underwent elimination of hydrogen bromide



7 8

upon chromatographic purification on silica gel to give 8, again as a mixture of roughly equal amounts of two diastereomers. Numerous examples of bromofluorination of olefins with bromine/silver fluoride are known.[5a] In one instance, silver fluoroborate has converted a vicinal dichloride to a monochloro monofluoride.[5b] The use of excess brominating agent thus served to provide only a modest improvement in the overall yield of the desired bromo lactone 2.[6]

Before leaving this discussion of the cyclizations of homogeranic acid, we would like to report the conversion of both the cis and trans lactones 3 and 5 to the naturally occurring dihydroactinidiolide (14),[2c,d] which has been synthesized several times.[7] One of those syntheses involved cyclization of 2-phenylsulfonylhomogeranic acid followed by thermal extrusion of benzenesulfinic acid.[8]

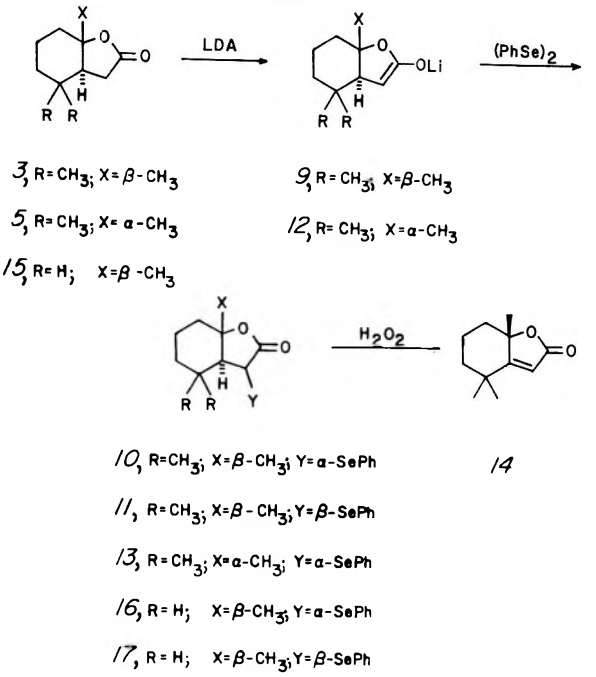
α-Phenylselenylation of the anion of trans lactone 3 with diphenyl diselenide gave a mixture of the selenides 10 and 11 in a 3:1 ratio (see Chart II). Thus, the major isomer (10) had arisen from attack of the diselenide on the less hindered α face of anion 9. Oxidation of this mixture with hydrogen peroxide was followed by thermal extrusion of benzeneselenenic acid to give dihydroactinidiolide (14) along with several other components. Presumably, the cis elimination had occurred only from the selenoxide of isomer 10. In a similar fashion, α-phenylselenylation of anion 12, generated from cis lactone 5, gave now only a single selenide, 13. Oxidation and elimination provided dihydroactinidiolide (14) as virtually the sole product due to the isomeric homogeneity of 13. It is worth noting that the conversions 3 to 10 + 11 and 5 to 13 were never efficient. It is not certain whether this was due to difficulties in generation of the hindered anion intermediates or in the subsequent reaction of these anions with diphenyl diselenide. By way of contrast, the monomethyl trans lactone 15 could be α-phenylselenylated in high yield, under the same condi-

Table II. Brominative Cyclizations of Homogeranic Acid (1)[a]

Entry	Solvent	"Br+" source	Lewis acid	No. of equiv	Temp, °C	Time	Additive (equiv)	Product ratio[b] 1(S.M.):trans Br):3(trans H):5(cis H):other[c]				
1	CH_3NO_2	Br_2	$AgBF_4$	1	−10	15 min		0	2	1	3	1
2	CH_3NO_2	Br_2	$AgBF_4$	1	−10	15 s		0	3	2	2	1
3	n-$PrNO_2$	Br_2	$AgBF_4$	1	−70	5 min		Trace	5	3	1	10
4	n-$PrNO_2$	Br_2	$AgBF_4$	1	−70	1 min		5	15	3	1	20
5	n-$PrNO_2$	Br_2	$AgBF_4$	1	−70	5 s		2	1	0	0	1
6	CH_3NO_2	Br_2	$AgBF_4$	10	−10	5 s		0	3	Trace	Trace	1
7	CH_3NO_2	Br_2	$AgBF_4$	3	−10	1 min		0	2	Trace	Trace	1
8	CH_3NO_2	Br_2	$AgBF_4$	2	−10	1 min		0	8	1	1	4
9	CH_3CN	Br_2	$AgNO_3$	1	−10	15 min		0	0	0	0	1
10	CH_2Cl_2	TBC[d]	$SnBr_4$	1	0	1 h		0	4	8	3	15
11	CD_3NO_2	Br_2	$AgBF_4$	1	−10	5 min	H_2O (5)	0	10	3	1	10
12	CD_3NO_2	Br_2	$AgBF_4$	1	−10	10 min	TMU[e] (1 or 2)	0	0	0	1	2–4
13	CH_3NO_2	Br_2	$AgBF_4$	1	−10	5 min	t-BuOH (1)	0	10	1	1	5
14	CH_3NO_2	Br_2	$AgBF_4$	1	−10	5 min	$NaHCO_3$ (10)	0	3	2	1	2

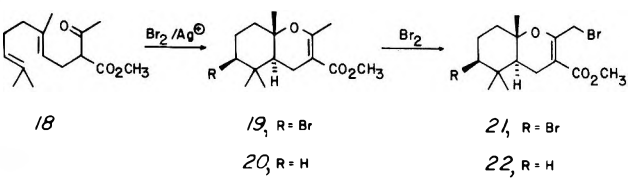
[a] Reactions were run generally on a 0.1–0.5 mmol scale. All reactions were quenched with excess sodium bicarbonate solution to halt further acid-catalyzed processes. [b] Product ratios were determined by comparison of the relative intensities of the three distinct methyl resonances for **1**, **2**, **3**, and **5** in the NMR spectra of the crude product mixtures. [c] Other unidentified products were often formed as evidenced by the appearance of extraneous methyl absorptions in the crude NMR spectra. [d] 2,4,4,6-Tetrabromocyclohexa-2,5-dienone. [e] Tetramethylurea.

Chart II

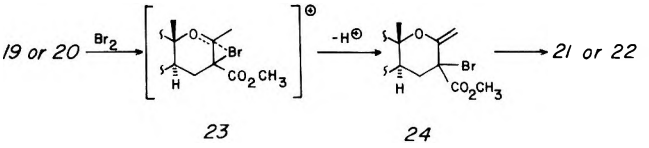


tions used for **3** and **5**, to give isomers **16** and **17** in an isomeric ratio nearly identical with that for the selenides **10** and **11**.[9]

The bromocyclization of β-keto ester **18** was also investigated. With 1 equiv of bromine/silver fluoroborate the reaction produced the brominated vinyl ether **19** (8%) and the proton cyclized enol ether **20** (22%). The latter product could be generated efficiently (83% yield) upon treatment of **18** with aqueous fluoroboric acid in nitromethane for 1 h. Use of 3 equiv of bromine/silver fluoroborate with substrate **18** eliminated the presence of **20** in the product mixture. However, the yield of **19** was not improved due to its further reaction with the excess molecular bromine to form the allylic bromide **21**. In fact, **21** or **22** could be generated from pure **19** (96%) or



20 (98%) by a rapid reaction with 1 equiv of bromine in chloroform at room temperature. These allylic brominations presumably occur via proton loss from the onium ion of partial structure **23** followed by allylic rearrangement of the allyl bromide **24**.



The conclusion to be reached from the preparative scale cyclization of both substrates **1** and **18** with excess brominating agent is that although this procedure eliminated for the most part the appearance of proton cyclized products, the excess brominating reagent provided new reaction pathways which competed with the production of the desired compounds **2** and **19**. The use of organomercurial compounds as precursors to the brominated materials is currently under investigation. Mercuric trifluoroacetate efficiently induces cationic cyclization,[10] and subsequent replacement of the carbon–mercury with a carbon–bromine bond[11] should lead to an effective solution to this problem.

Experimental Section

General Information. Melting points were determined on a Kofler hotstage and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Ariz. Column chromatography was carried out under pressure on silica gel H for TLC (EM 7736, type 60) using a modification of the short column chromatography technique.[12] Infrared spectra were recorded on Perkin-Elmer Model 237 and 257 instruments. Nuclear magnetic resonance spectra were obtained on Varian HFT-80 (proton) and XL-100 (fluorine) instruments in the Fourier transform mode. Mass spectra were determined on AEI MS-30 (electron impact, EI) and Finnigan 4000 (chemical ionization, CI) instruments.

Homogeranic Acid (1). *trans*-Geranyl bromide[13] (53.5 g, 0.25 mol) was dissolved in dry CH_3CN (200 mL). 1,4,7,10,13,16-Hexaoxacyclooctadecane (18-crown-6, 2.5 g, 9.5 mmol) was added followed by KCN (40 g, 0.615 mol). This mixture was stirred in the dark at room temperature for 6 days and filtered. Solvent removal left a residue which was triturated with 3:1 hexane/EtOAc and filtered to separate the 18-crown-6. Solvent removal left homogeranonitrile (geranyl cyanide) as a colorless oil (39 g, 0.24 mol, 96%) of sufficient purity for subsequent hydrolysis. The nitrile could be purified, if necessary, by vacuum distillation [bp 96 °C (0.5 mm) [lit.[14] bp 90–91 °C (0.2 mm)]]: NMR ($CDCl_3$) δ 1.60 (br s, 3 H), 1.68 (br s, 6 H), 2.05 (br s, 4 H), 3.03 (br d, J = 7 Hz, 2 H), 5.1 (m, 2 H); IR (neat) 2140 cm^{-1}; MS m/e (relative intensity) 163 (1), 148 (3), 69 (100).

The crude nitrile (3.5 g, 21.5 mmol) was dissolved in MeOH (27 mL), and an aqueous KOH solution [4.0 g (71 mmol) in 8 mL of H_2O] was added. The reaction mixture was refluxed for 43 h, cooled, diluted with saturated $NaHCO_3$, extracted with ether, acidified with 2 N HCl, and extracted with ether again. The final extracts were dried ($MgSO_4$), filtered, and concentrated to give crude homogeranic acid (1)[14] as a light brown oil (3.2 g, 17.6 mmol, 82%). The oil could be purified by elution through a short Florisil column with methylene chloride (>90% recovery): NMR ($CDCl_3$) δ 1.60 (br s, 3 H), 1.67 (br s, 6 H), 2.05 (br s, 4 H), 3.06 (br d, J = 7 Hz, 2 H), 5.04 (m, 1 H), 5.27 (br t, J = 7 Hz. 1 H); IR (neat) 2400–3600 and 1725 cm^{-1}; MS m/e (relative intensity) 182 (2), 167 (2), 69 (100).

Brominative Cyclization of 1. (A) With 1 Equivalent of Br_2/$AgBF_4$. The brominating reagent was prepared by adding Br_2 (210 μL, 3.8 mmol) to a solution of dry $AgBF_4$ (780 mg, 4.0 mmol) in dry CH_3NO_2 (15 mL) under a nitrogen atmosphere. This mixture was cooled to −10 °C, and homogeranic acid (1) (690 mg, 3.8 mmol) was added. The solution immediately turned yellow, and a white precipitate appeared. The reaction mixture was stirred for 20 min at −10 °C and quenched by the rapid addition of saturated $NaHCO_3$ (30 mL). This mixture was extracted with ether, and the extracts were washed (saturated NaCl), dried ($MgSO_4$), filtered, and concentrated to leave a crude brown oil (914 mg). Short column chromatography of this oil (100 g of SiO_2, 10% EtOAc/hexane elution) gave the following in order of elution: trans lactone 3[2a] (51 mg, 0.28 mmol, 7%) [NMR ($CDCl_3$) δ 0.93, 0.96, and 1.34 (s, $3CH_3$'s), 2.00–2.56 (5 line mult, C_3CH and CH_2CO); NMR (CD_3NO_2) δ 0.96 (s, $2CH_3$'s), 1.35 (s, CH_3); NMR (CD_3CN) δ 0.94 (s, $2CH_3$'s), 1.33 (s, CH_3); NMR (C_6D_6) δ 0.43, 0.52, and 0.90 (s, $3CH_3$'s); IR (neat) 1780 cm^{-1}], cis lactone 5[2d] (117 mg, 0.64 mmol, 17%) [NMR ($CDCl_3$) δ 0.91, 1.03, and 1.52 (s, $3CH_3$'s), 2.00–2.55 (6 line mult, C_3CH and CH_2CO); NMR (CD_3NO_2) δ 0.92, 1.07, and 1.51 (s, $3CH_3$'s); NMR (CD_3CN) δ 0.89, 1.03, and 1.50 (s, $3CH_3$'s); NMR (C_6D_6) δ 0.50, 0.56, and 1.14 (s, $3CH_3$'s); IR (neat) 1765 cm^{-1}], trans bromo lactone 2 (105 mg, 0.40 mmol, 11%), which was recrystallized from hexane/EtOAc to give an analytical sample [mp 112–113 °C; NMR ($CDCl_3$) δ 1.02, 1.08, and 1.38 (s, $3CH_3$'s), 2.05–2.56 (5 line mult, C_3CH and CH_2CO), 3.90 (dd, J = 5 and 11 Hz, CHBr); NMR (CD_3NO_2) δ 1.04, 1.08, and 1.38 (s, $3CH_3$'s), 4.07 (dd, J = 6 and 10 Hz, CHBr); IR (neat) 1770 cm^{-1}; MS m/e (relative intensity) 262 (1), 260 (1), 247 (13), 245 (14) (−CH_3), 219 (13), 217 (12), 181 (12) (−Br), 137 (72), 69 (100). Anal. Calcd for $C_{11}H_{17}BrO_2$: C, 50.59; H, 6.56. Found: C, 50.62; H, 6.52.], and cis bromo lactone 4 (2 mg, <1%) [NMR ($CDCl_3$) δ 1.07, 1.20, and 1.55 (s, $3CH_3$'s), 2.04–2.15 (7 line mult, C_3CH and CH_2CO), 4.1 (br mult, CHBr); IR (neat) 1760 cm^{-1}; MS m/e (relative intensity) 262 (<1), 260 (<1), 247 (28), 245 (29) (−CH_3), 219 (11), 217 (12), 181 (44) (−Br)].

(B) With Excess Br_2/$AgBF_4$. This experiment was carried out in the same manner as the above one with the following exceptions. Silver fluoroborate (500 mg, 2.5 mmol), Br_2 (132 μL, 2.5 mmol), CH_3NO_2 (7 mL), and homogeranic acid (1) (145 mg, 0.80 mmol) were used. The reaction was quenched after 1 min to give the crude product (273 mg). Short column chromatography (25 g of SiO_2, 10% EtOAc/hexane elution) gave the following in order of elution: the diastereomeric dibromo fluorides 7 (23 mg, 0.067 mmol, 8%) [NMR ($CDCl_3$) δ 1.50 (d, J = 22 Hz, CH_3CF), 1.55 (s, CH_3CO), 1.54 (d, J = 22 Hz, CH_3CF), 3.02 (two overlapping ABX systems, J_{AB} = 18 Hz, J_{BX} = J_{AX} = 8 Hz, CH_2CO_2), 3.82 (br mult, $W_{1/2}$ = 16 Hz, $CH_2CHBrCF$), 4.28 (two overlapping dd, J_{XA} = J_{XB} = 8 Hz, C_3CHBr); IR ($CHCl_3$) 1785, 750 cm^{-1}; MS m/e (relative intensity) 261 (3), 259 (3), 237 (3), 235 (3), 207 (22), 205 (21), 179 (78), 177 (63%) (−$C_6H_{11}BrF$); MS m/e (CI, NH_3 reagent gas) 380 (45), 378 (100), 376 (50) (P + NH_4^+)], bromo lactone 2 (30 mg, 0.11 mmol, 15%), and the diastereomeric bromofluorobutenolides 8 (50 mg, 0.19 mmol, 24%) [NMR ($CDCl_3$) δ 1.47 (two d, J = 21 Hz, CH_3CF), 1.49, 1.50 (two s, CH_3CO), 1.52 (two d, J = 21 Hz, CH_3CF), 3.8 (br mult, $CH_2CHBrCF$), 6.0 (two d, J = 5 Hz, $CHCO_2$), 7.3 (two d, J = 5 Hz, CH=$CHCO_2$); IR (neat) 1760 cm^{-1}; MS m/e (relative intensity) 237 (6), 235 (6), 179 (22), 123 (20), 97 (100) (−$C_6H_{11}BrF$); MS m/e (CI, NH_3 reagent gas) 298 (100), 296 (95) (P + NH_4^+); fluorine NMR ($CDCl_3$) δ (from $CFCl_3$) 137.975 (8 line m, J = 21 Hz) and 138.062 (8 line m, J = 21 Hz). A fluorine decoupling experiment confirmed the magnitude of J_{HF}'s in the proton NMR spectrum. Compound 8 was not present in the crude reaction product before SiO_2 chromatography (NMR analysis).

Dihydroactinidiolide (14) from Trans Lactone 3. Trans lactone 3 (51 mg, 0.28 mmol) was converted into the anion 9 by reaction with lithium diisopropylamide (LDA) (0.34 mmol, 1.2 equiv) at −78 °C for 30 min in dry THF (1.5 mL) under nitrogen. A THF solution (1 mL) of diphenyl diselenide (105 mg, 0.34 mmol) and HMPA (60 μL, 0.34 mmol) was added. The reaction proceeded at −78 °C for 0.5 h and then at −35 °C for 0.5 h before being quenched with 0.1 N HCl. The solution was extracted with ether, and the extracts were washed with saturated NaCl, dried ($MgSO_4$), filtered, and concentrated to give a crude oil. Purification by preparative TLC (2 × 200 × 200 mm SiO_2 plate, 20% EtOAc/hexane) gave a colorless oil (55 mg, 0.16 mmol, 59%) which proved to be a 3:1 mixture of selenides 10 and 11: NMR ($CDCl_3$) (for 10) δ 0.98, 1.25, and 1.36 (s, $3CH_3$'s), 1.95 (d, J = 14 Hz, C_3CH), 3.85 (d, J = 14 Hz, CHSe), 7.3, 7.7 (mult. ArH); NMR ($CDCl_3$) (for 11) δ 1.08, 1.29, and 1.60 (s, $3CH_3$'s), 2.29 (d, J = 8 Hz, C_3CH), 3.76 (d, J = 8 Hz, CHSe), 7.3, 7.7 (mult, ArH); IR (neat) 1770 cm^{-1}; MS m/e (relative intensity) 338 (15), 137 (66) (−CO_2–SePh); calcd for $C_{17}H_{22}O_2{}^{80}Se$, 338.0783; found, 338.0800.

This mixture (50 mg, 0.14 mmol) was dissolved in THF (5 mL), cooled to 0 °C under nitrogen, and oxidized with 30% H_2O_2 (150 μL, 1.3 mmol) in the presence of AcOH (500 μL). After 1.5 h at 0 °C, the reaction mixture was poured into saturated $NaHCO_3$ and extracted with Et_2O. The extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to leave a crude oil (27 mg, 0.15 mmol, 94%) whose major component was dihydroactinidiolide (NMR analysis). This material was purified by preparative TLC (SiO_2, 20% EtOAc/hexane) to give a colorless oil (10 mg, 37% recovery) whose spectral data were identical with those reported[2c,d] for the naturally occurring material.

Dihydroactinidiolide (14) from Cis Lactone 5. This procedure was the same as that reported above for the trans lactone 3 with the following exceptions. Cis lactone 5 (156 mg, 0.86 mmol), LDA (1.0 mmol), THF (4 mL), diphenyl diselenide (321 mg, 1.0 mmol), and HMPA (180 μL, 1.0 mmol) were the quantities used. Anion formation proceeded for 1.3 h at −78 °C. The crude product was purified by short column chromatography (5% EtOAc/hexane elution) and provided selenide 13 (92 mg, 0.27 mmol, 32%) as a white solid which was recrystallized from hexane to provide an analytical sample: mp 88–89 °C; NMR ($CDCl_3$) δ 1.02, 1.22, and 1.37 (s, $3CH_3$'s), 1.98 (d, J = 10 Hz, C_3CH), 3.63 (d, J = 10 Hz, CHSe), 7.3, 7.7 (mult, ArH); IR ($CHCl_3$) 1760 cm^{-1}; MS m/e (relative intensity) 338 (73), 137 (100) (−CO_2–SePh); calcd for $C_{17}H_{22}O_2{}^{80}Se$, 338.0628; found, 338.0676. Anal. Calcd: C, 60.53; H, 6.57. Found: C, 60.52; H, 6.65.

Oxidation of 13 (88 mg, 0.26 mmol) with 30% H_2O_2 (260 μL, 2.3 mmol) in THF (5 mL) containing AcOH (880 μL) at 0 °C for 1.5 h and at room temperature for 3 h gave, after workup as above, dihydroactinidiolide (14) (46 mg, 0.25 mmol, 98%).

Methyl Geranylacetoacetate (18). Methyl acetoacetate (2.6 g, 22 mmol) was added to LiH (190 mg, 24 mmol) in dry DMF (50 mL), and the mixture was stirred at room temperature under nitrogen for 0.5 h. Geranyl bromide (5.0 g, 24 mmol) was added, and the mixture was stirred for 3.5 h. The mixture was then diluted with pentane, washed with H_2O (3×) and brine, dried ($MgSO_4$), filtered, and concentrated to give 18 as a pale yellow oil (4.8 g, 19 mmol, 86%) which was vacuum distilled, bp 115–120 °C (0.5 mmHg). An analytical sample was obtained by preparative gas chromatography (10% Carbowax): NMR ($CDCl_3$) δ 1.6 (br s, $2CH_3C$=C's), 1.67 (br s, CH_3C=C), 2.0 (br s, $2CH_2C$=C's), 2.21 (s, CH_3CO), 2.53 (br t, J = 7 Hz, C=$CHCH_2CH_2$), 3.42 (t, J = 7 Hz, $CH(CO)_2$), 3.70 (s, CO_2CH_3), 5.0 (mult, 2HC=C's); IR (neat) 1750, 1720 cm^{-1}; MS m/e (relative intensity) 252 (1), 209 (3) (−$COCH_3$), 136 (16) (−$C_5H_8O_3$). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.53; H, 9.81.

Bromocyclization of Methyl Geranylacetoacetate (18). Keto

ester **18** (900 mg, 3.6 mmol) was added to a dry CH_3NO_2 (10 mL) solution of $AgBF_4$ (700 mg, 3.6 mmol) and Br_2 (570 mg, 3.6 mmol) at −10 °C under nitrogen. The initially orange solution quickly turned yellow, and a white precipitate appeared. After being stirred for 10 min, the reaction mixture was worked up as for the other bromocyclizations to leave a brown oil (1.15 g). Short column chromatography (125 g of SiO_2, 10% EtOAc/hexane) gave the unbrominated enol ether **20** (200 mg, 0.79 mmol, 22%), which was purified by preparative gas chromatography (10% Carbowax) to give an analytical sample [NMR ($CDCl_3$) δ 0.85, 0.97, and 1.16 (s, $3CH_3$'s), 2.17 (t, J = 1.5 Hz, $CH_3C{=}C$), 3.67 (s, CO_2CH_3); IR (neat) 1705, 1615 cm^{-1}; MS m/e (relative intensity) 252 (22). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.47; H, 9.49.], and the bromo enol ether **19** (100 mg, 0.30 mmol, 8%), which was recrystallized from CH_3OH to provide an analytical sample [mp 108–111 °C; NMR ($CDCl_3$) δ 0.98, 1.14, and 1.17 (s, $3CH_3$'s), 2.17 (t, J = 1.5 Hz, $CH_3C{=}C$), 3.67 (s, CO_2CH_3), 3.93 (dd, J = 10 and 5 Hz, CHBr); IR (KBr) 1700, 1625 cm^{-1}; MS m/e (relative intensity) 332 (4), 330 (4), 251 (13) (−Br). Anal. Calcd for $C_{15}H_{23}O_3Br$: C, 54.39; H, 7.00; Br, 24.12. Found: C, 54.39; H, 7.18; Br, 24.28.].

Acid-Catalyzed Cyclization of Methyl Geranylacetoacetate (18). Keto ester **18** (1.0 g, 4.0 mmol) was dissolved in dry CH_3NO_2 (7 mL) and treated at room temperature with 50% aqueous HBF_4 (700 μL, 4.0 mmol). After 1 h, saturated $NaHCO_3$ was added and the mixture was extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give the bicyclic ester **20** (0.83 g, 3.3 mmol, 83%) as a pale yellow oil which was greater than 95% pure by NMR analysis.

Allylic Brominations of 20 and 19. Ester **20** (24 mg, 0.096 mmol) was dissolved in $CDCl_3$ (0.5 mL), and 1 equiv of Br_2 as a 1% solution in CCl_4 was added. The solution rapidly decolorized and was then diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated to yield the allylic bromide **22** (31 mg, 0.094 mmol, 98%) as a colorless oil: NMR ($CDCl_3$) δ 0.86, 0.98, and 1.18 (s, $3CH_3$'s), 3.73 (s, CO_2CH_3), 4.00 (br d, J = 9 Hz, C**H**HBr), 4.75 (d, J = 9 Hz, CHHBr); IR (neat) 1705, 1615 cm^{-1}; MS m/e (relative intensity) 332 (2), 330 (3), 251 (28) (−Br); calcd for $C_{15}H_{23}O_3{}^{81}Br$, 332.0810; found, 332.0813.

In an entirely analogous fashion the bromo ester **19** was brominated to give the dibromide **21** in 97% yield: NMR ($CDCl_3$) δ 0.99, 1.15, and 1.21 (s, $3CH_3$'s), 3.73 (s, CO_2CH_3), 3.9 (mult, C_2CHBr), 4.00 (br d, J = 10 Hz, C**H**HBr), 4.75 (d, J = 10 Hz, CH**H**Br); IR ($CHCl_3$) 1700, 1620 cm^{-1}; MS m/e (relative intensity) 412 (4), 410 (9), 408 (5), 331 (56), 329 (57) (−Br), 249 (15) (−HBr_2); calcd for $C_{15}H_{22}O_3{}^{81}Br_2$, 411.9896; found, 411.9874.

Acknowledgment. We gratefully acknowledge the support of this research provided by Institutional Research Grant IN-13 from the American Cancer Society, by The Graduate School, University of Minnesota, and by a DuPont Young Faculty Grant. The NMR instrument was purchased through departmental NSF instrument grant number CHE 76-05167.

Registry No.—**1**, 459-85-8; **2**, 66901-56-2; **3**, 37531-07-0; **4**, 66901-57-3; **5**, 37531-06-9; 7 (isomer I), 66901-58-4; 7 (isomer II), 66901-59-5; 8 (isomer I), 66901-60-8; 8 (isomer II), 66901-61-9; **9**, 66901-62-0; **10**, 66901-63-1; **11**, 66901-64-2; **13**, 66901-65-3; **14**, 15356-74-8; **18**, 51933-45-0; **19**, 66901-67-5; **20**, 66901-68-6; **21**, 66901-69-7; **22**, 66901-70-0; *trans*-geranyl bromide, 6138-90-5; homogeranonitrile, 21677-96-3; diphenyl diselenide, 1666-13-3; methyl acetoacetate, 105-45-3.

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Direct Synthesis of Dibenzocyclooctadienes via Double Ortho Friedel–Crafts Alkylation by the Use of Aldehyde–Trimethylsilyl Iodide Adducts

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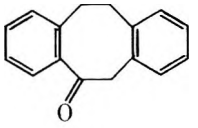
Received February 15, 1978

The development of a new, direct method for the preparation of dibenzo[*a*,*e*]cycloocta-1,5-dienes from phenylacetaldehyde by a double ortho Friedel–Crafts alkylation is described. When benzaldehyde (**2b**) is treated with trimethylsilyl iodide (**3**), α,α-diiodotoluene (**6**) is formed in high yield via the intermediacy of α-iodobenzyl trimethylsilyl ether (**4b**). Treatment of phenylacetaldehyde (**2a**) with trimethylsilyl iodide (**3**) under the same conditions gives rise to a different reaction pathway, affording initially the aldehyde iodohydrin trimethylsilyl ether (**4a**), which is transformed on standing into a mixture of three products. The major product of this mixture, isolated in slightly over 50% yield, is the interesting bicyclic ether 3,7-epoxydibenzocycloocta-1,5-diene (**8**); the minor products are 2-phenylnaphthalene (**9**) and 2-iodo-3-phenyltetralin (**10**). The bicyclic ether **8** can be easily transformed by dissolving metal reduction followed by oxidation into the ketone dibenzocycloocta-1,5-dien-3-one (**1**), which has been converted into a large variety of biologically active compounds. A possible mechanism for the reaction is discussed. The reaction of the acetaldehyde–trimethylsilyl iodide adduct (**4c**) with 2-phenylethyl trimethylsilyl ether (**21**) affords 1-methylisochroman (**25**), the expected product of the proposed mechanistic pathway. The potential utility of these α-iodoalkyl trimethylsilyl ethers (**4**) is also discussed.

Many dibenzocycloocta-1,5-diene derivatives have been shown to possess very potent biological activity ranging from antiinflammatory action to psychotropic properties.[1] Nearly all of these compounds are prepared from the aryl ketone dibenzo[*a*,*e*]cycloocta-1,5-dien-3-one (**1**), which is normally



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produced from benzalphthalide by a multistep process utilizing a Friedel–Crafts cyclization to afford the final product.[2] We now report an efficient three-step synthesis of this important intermediate **1** from phenylacetaldehyde (**2**) which involves as the key step a serendipitous double ortho Friedel–Crafts cyclization effected by trimethylsilyl iodide (**3**).[3] These results also indicate the usefulness of aldehyde iodohydrin trimethylsilyl ethers (**4**) in the Friedel–Crafts alkylation of aromatic compounds.

Results

In the course of an investigation of the reactivity of trimethylsilyl iodide (**3**) with various functional groups, it was found that aldehyde iodohydrin trimethylsilyl ethers (**4**) are readily formed from aldehydes **2** by reaction with **3** at room temperature under an inert atmosphere.[4] Although attempted isolation of the iodo silyl ethers (**4**) by distillation or silica gel

$$\underset{\mathbf{2}}{\mathrm{RCHO}} + \underset{\mathbf{3}}{\mathrm{Me_3SiI}} \underset{\Delta \text{ or } SiO_2}{\overset{25\ ^\circ C}{\rightleftharpoons}} \underset{\mathbf{4}}{\mathrm{RCH(I)OSiMe_3}}$$

chromatography causes reversion back to the aldehydes, these intermediates are stable indefinitely in solution at room temperature (see Experimental Section). During this study, it was observed that benzaldehyde [**2b** (R = Ph)] afforded α,α-diiodotoluene (**6**) and hexamethyldisiloxane (**7**) via the intermediacy of the iodo ether **4b** in over 50% isolated yield.[5] In this case, the oxygen atom of the iodo silyl ether (**4b**) must silylate a second time to yield a bis(silyl)oxonium iodide (**5**) which is transformed into the diiodide **6** and the disiloxane **7** by an S_N1 mechanism, an S_N2 mechanism, or both. The conversion of **4b** into **6** is faster than the formation of **4b** since

$$\underset{\mathbf{2b}}{\mathrm{PhCHO}} + \underset{\mathbf{3}}{\mathrm{Me_3SiI}} \xrightarrow[25\ ^\circ C,\ 30\ min]{CHCl_3} \underset{\mathbf{4b}}{\mathrm{PhCH(I)OSiMe_3}}$$

$$\mathbf{4b} \xrightarrow{\mathbf{3}} \mathrm{PhCH(I)O^+(SiMe_3)_2\ I^-} \xrightarrow[S_N2]{S_N1\ or} \underset{\mathbf{6}}{\mathrm{PhCHI_2}} + \underset{\mathbf{7}}{\mathrm{(Me_3Si)_2O}}$$

5

if one employs equimolar amounts of the aldehyde **2b** and the silyl iodide **3** a 1:1 mixture of the starting aldehyde **2b** and the diiodide **6** is produced. In all cases, the crude yield of **6** is always much higher than the isolated yield due to decomposition of this sensitive diiodide upon purification.[5]

In an attempt to extend this reaction to a general synthesis of α,α-diiodoalkanes (or the corresponding vinyl iodides) from aldehydes,[5] a solution of 1 equiv of phenylacetaldehyde (**2a**) and 2.5 equiv of trimethylsilyl iodide (**3**) in chloroform was allowed to stand at room temperature under an inert atmosphere for 15 h. Aqueous workup followed by column chromatography on silica gel afforded an approximately 1:1:1 mixture of three compounds in 90% yield. The most inter-

$$\underset{\mathbf{2a}}{\mathrm{PhCH_2CHO}} + \underset{\mathbf{3}}{\mathrm{Me_3SiI}} \xrightarrow[25\ ^\circ C,\ 10\ min]{CHCl_3} \underset{\mathbf{4a}}{\mathrm{PhCH_2CH(I)OSiMe_3}}$$

$$\mathbf{4a} \xrightarrow{25\ ^\circ C} \underset{\mathbf{8}}{\text{3,7-epoxydibenzocycloocta-1,5-diene}} + \underset{\mathbf{9}}{\text{2-phenylnaphthalene}} + \underset{\mathbf{10}}{\text{2-iodo-3-phenyltetralin}}$$

esting of these three was identified as the tetracyclic ether **8**, a white crystalline solid (mp 141.5–142.5 °C), by virtue of its spectroscopic data (see Experimental Section). The other byproducts were shown (see below) to be 2-phenylnaphthalene (**9**), a known product of acid treatment of phenylacetaldehyde,[6] and 2-iodo-3-phenyltetralin (**10**). The initial

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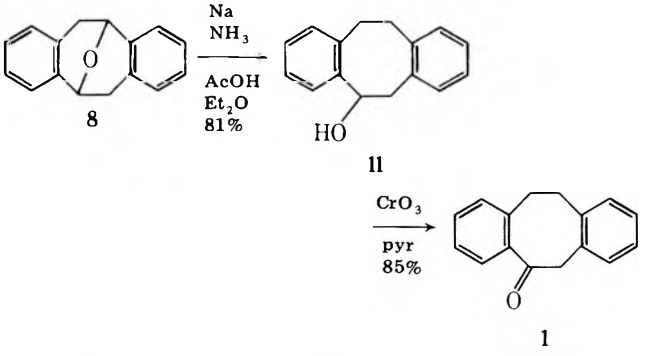
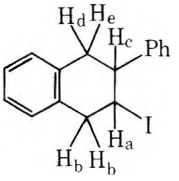
product of the reaction was the expected iodohydrin trimethylsilyl ether (**4a**) as shown by NMR measurements after a short time: ^{1}H NMR ($CDCl_3$) δ 7.29 (5 H, brd s), 6.30 (1 H, t, J = 6 Hz), 3.57 (2 H, d, J = 6 Hz), 0.1 (9 H, s). By conducting the reaction at a lower temperature for a longer period of time, one can isolate **8** in much higher yield. For example, reaction of **2a** and **3** in chloroform at 5 °C in a nitrogen atmosphere for one week afforded a 50% yield of **8**.

Since the completion of the work described in this manuscript, Kagan and Watson have reported the synthesis of this heretofore unknown ether **8** from phenylacetaldehyde (**2a**) using fluorosulfonic acid in carbon tetrachloride in just over 50% crude yield.[7] The structure of **8** was conclusively assigned by X-ray structural analysis. The remaining 50% of the reaction mixture, however, was not accounted for.

The conversion of the tetracyclic ether **8** into the desired ketone **1** was accomplished in two steps in high yield. Reduction of the benzylic ether was effected by addition of compound **8** and acetic acid in a solution of diethyl ether to a solution of sodium in liquid ammonia at −78 °C, thus affording the alcohol **11** in 81% yield. The use of acetic acid is crucial to the success of the reaction since in the absence of a proton donor no reduction is observed, and the use of other simple proton donors such as ethanol or water gives only complex mixtures in which the aromatic rings have suffered partial reduction. Furthermore, catalytic hydrogenation of the ether **8** in ethanol/acetic acid over a 10% Pd/C catalyst failed to effect any hydrogenolysis of the benzylic ether function. Oxidation of the alcohol **11** by the method of Nenitzescu[8] furnished the desired ketone **1** in 85% yield. Thus, the important ketone **1** is available from phenylacetaldehyde (**2a**) in three steps in an unoptimized, isolated yield of 34%. Its conversion into tricyclic aromatic derivatives which possess significant biological activity has already been described.[1]

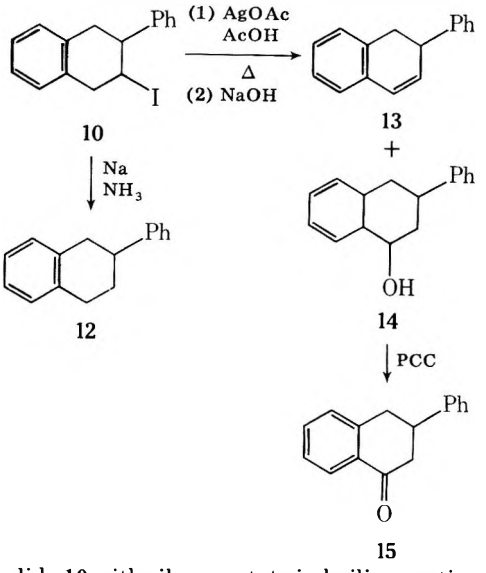


The structure of **9** was easily assigned by comparison of its spectral data (IR, NMR, and mass spectra) with those published for 2-phenylnaphthalene.[9] The assignment of structure



10

10 to the second byproduct of this reaction was made on the basis of spectroscopic and chemical evidence. The major spectroscopic evidence (in addition to consistent IR, ^{13}C NMR, and mass spectra) was the highly expanded 251 MHz ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$): δ 7.33 (9 H, m, aromatic H), 4.58 [1 H, d (J = 6.0 Hz) of t (J = 4.5 Hz), H_a], 3.61 (2 H, d, J = 4.5 Hz, H_b), 3.34 [1 H, d (J = 3.4 Hz) of t (J = 6.0 Hz), H_c], 3.21 [1 H, d (J = 10.5 Hz) of d (J = 3.4 Hz), H_d], 3.02 [1 H, d (J = 10.5 Hz) of d (J = 6.0 Hz), H_e]. The 2 protons giving rise to the signals for H_b are in fact a strongly coupled AB pattern, which, due to "deceptive simplicity",[10] affords identical splitting with H_a. The relative stereochemistry cannot be assigned at present. The chemical evidence is derived from both reductive and oxidative conversions. Reduction of **10** with sodium in ammonia afforded an 82% yield of 2-phenyltetralin (**12**), identified by comparison (^{1}H NMR, IR, MS, and gas chromatography) with an authentic sample prepared by reduction of 2-phenylnaphthalene (**9**).[11] Reaction



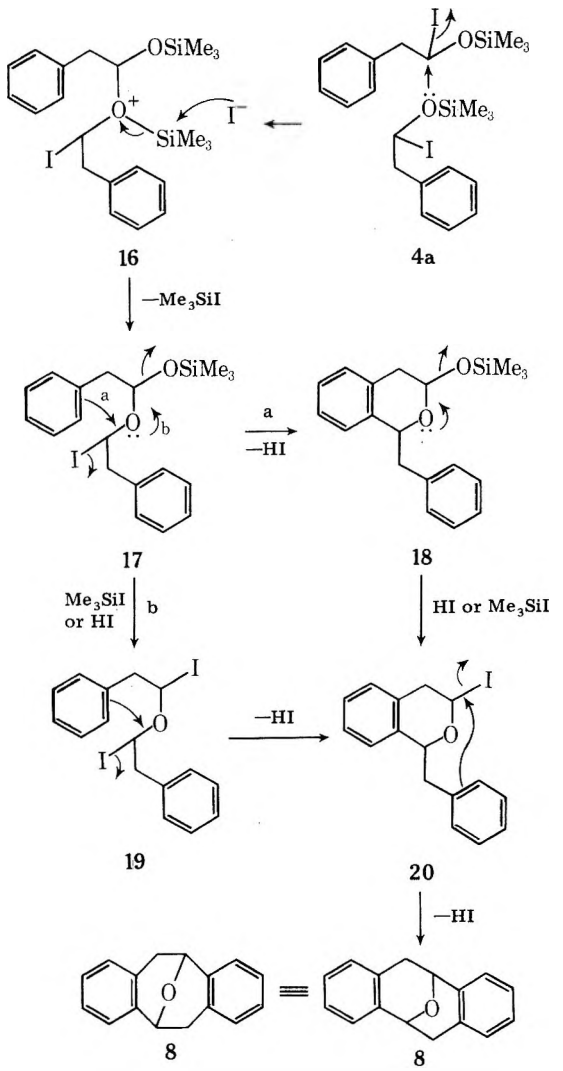
of the iodide **10** with silver acetate in boiling acetic acid followed by basic hydrolysis furnished a mixture of products which could be separated on thick-layer chromatography into an olefin and an alcohol. The olefin was assigned structure **13** on the basis of its NMR spectrum. The alcohol was assumed to have the structure **14** since on Collins oxidation it was converted into 3-phenyl-1-tetralone (**15**), identified by ^{1}H NMR, IR, and the melting point of its semicarbazone.[12]

Mechanistic Discussion

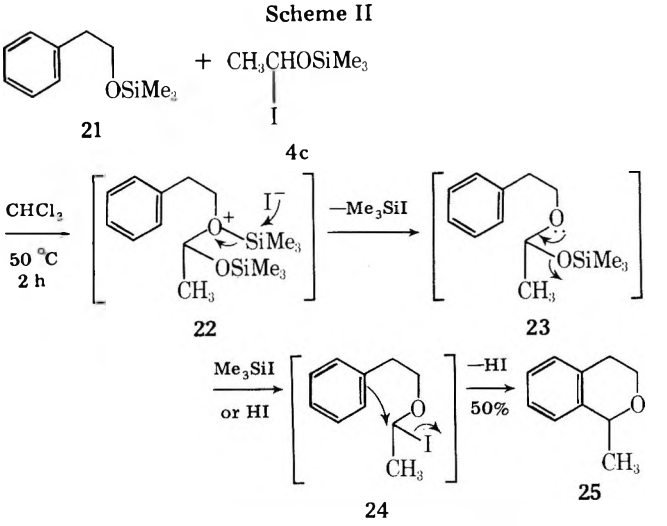
A probable mechanism for this unusual cyclization is shown in Scheme I. Displacement of iodine from one molecule of **4a** by the oxygen atom of a second molecule would lead to the silylated oxonium iodide **16**, which upon loss of trimethylsilyl iodide would afford the iodo acetal **17**. This compound would then be converted into the iodo ether **20** by either of two pathways: (a) initial Friedel–Crafts cyclization with loss of hydrogen iodide to give the acetal **18** which would then be converted into the iodo ether **20** by hydrogen iodide or trimethylsilyl iodide; or (b) initial conversion of the acetal function to the symmetrical diiodo ether **19** followed by Friedel–Crafts cyclization. The iodo ether **20** would then be transformed into **8** by a simple internal ortho Friedel–Crafts cyclization.[13] There are two major reasons for favoring this mechanism.

Most importantly, the lack of any products resulting from attack of the electrophilic aldehyde component at the normally favored para position of the second aromatic ring argues strongly for an intramolecular reaction in the initial Friedel–Crafts cyclization. For this reason, the mechanism presented by Kagan and Watson[7] for the cyclization process they observed, namely, an initial Friedel–Crafts reaction before any complexation of the aldehyde components, cannot be correct in our case since if it were one would expect a large proportion of para substitution. Therefore, there must be some complexation or association of the two aldehyde components before the initial Friedel–Crafts alkylation. We propose that this complexation involves the formation of either the iodo acetal **17** or the diiodo ether **19**. Both of these compounds would now be expected to give only ortho substitution because of the internal delivery of the electrophile to only the ortho position. Secondly, if the mechanism shown in Scheme I were correct,

Scheme I



Scheme II



one would expect that other similar systems should undergo analogous reactions. This is the case. Reaction of 2-phenylethyl trimethylsilyl ether (**21**) with the trimethylsilyl iodide adduct (**4c**) of acetaldehyde at 50 °C in chloroform for 2 h affords a 50% yield of 1-methylisochroman (**25**)[14] (Scheme II). We assume that the reaction proceeds via the intermediates **22–24**, which are analogous to those proposed in Scheme I for the formation of **8**. Again no products arising from para substitution of the aromatic ring are observed. The clean formation of **25** from **21** and **4c** offers evidence for the mechanism proposed in Scheme I. However, in both of these cases since hydrogen iodide is produced in the Friedel–Crafts alkylation or cyclization steps, this strong protic acid may complicate the detailed mechanistic picture.[15,16]

Conclusion

The α-iodo ethers **4**, which are now readily available from aldehydes, have good synthetic potential. Since they can be formed in quantitative yield even from aldehydes with very reactive α hydrogens (e.g., acetaldehyde, propanal, etc.), one might be able to use them as electrophilic aldehyde equivalents in various reactions, such as nucleophilic additions and Friedel–Crafts alkylations. Such possibilities are currently being investigated in our laboratories, as well as extensions of this double ortho Friedel–Crafts alkylation process to the preparation of other tricyclic aromatic compounds of biological interest.

Experimental Section

General. Melting points were taken on a Büchi melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 137B spectrophotometer. Proton NMR spectra were measured on a Varian T-60 spectrometer and are reported in parts per million downfield from internal tetramethylsilane, except for the spectrum of **10** which was measured at 251 MHz. Carbon NMR spectra were measured on a Varian CFT-20 spectrometer. Mass spectra were recorded on an MS-9 instrument. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Formation of Aldehyde Iodohydrin Trimethylsilyl Ethers (4). In general, to a solution of the aldehyde **2** in a chlorinated hydrocarbon solvent (CCl_4, $CHCl_3$, CH_2Cl_2, or $CDCl_3$) under a nitrogen atmosphere was added via syringe 1 equiv of trimethylsilyl iodide (**3**) at room temperature or slightly below. The solution was allowed stand for 15–30 min at room temperature. (Usually the exothermic reaction was complete after only a few minutes.) Proton NMR analysis indicated the complete disappearance of the peaks due to the aldehyde **2** and the appearance of the peaks due to the iodo ether **4**. Attempted distillation or chromatography on silica gel afforded the starting aldehyde. ^{1}H NMR for **4** [RCH(OSiMe$_3$)I]: **4a** (R = CH_2Ph) ($CDCl_3$) δ 7.29 (5 H, brd s), 6.30 (1 H, t, J = 6 Hz), 3.57 (2 H, d, J = 6 Hz), 0.02 (9 H, s); **4b** (R = Ph) (CH_2Cl_2) δ 8.00–7.60 (6 H, m); **4c** (R = CH_3) ($CDCl_3$) δ 6.08 (1 H, q, J = 7 Hz), 2.18 (3 H, d, J = 6 Hz), 0.02 (9 H, s); **4d** (R = CH_3CH_2) ($CDCl_3$) δ 6.13 (1 H, t, J = 5 Hz), 2.12 [2 H, d (J = 5 Hz) of q (J = 7 Hz)], 0.97 (3 H, t, J = 7 Hz), 0.02 (9 H, s); **4e** (R = $CH_3CH_2CH_2$) ($CDCl_3$) δ 6.23 (1 H, t, J = 6 Hz), 2.48–2.02 (2 H, m), 1.92–1.35 (2 H, m), 0.98 (3 H, t, J = 6 Hz), 0.07 (9 H, s); **4f** (R = $(CH_3)_2CH$) ($CDCl_3$) δ 6.20 (1 H, d, J = 4 Hz), 2.2–1.5 (1 H, m), 1.05 (6 H, d, J = 6 Hz), 0.07 (9 H, s); **4g** (R = $CH_3(CH_2)_4$) ($CDCl_3$) δ 6.25 (1 H, t, J = 5 Hz), 2.53–2.03 (2 H, m), 1.95–1.03 (6 H, m), 0.93 (3 H, t), 0.07 (9 H, s); **4h** (R = $CH_3(CH_2)_5$) (CH_2Cl_2) δ 6.19 (1 H, t, J = 5 Hz), 2.27 (2 H, m), 1.38 (8 H, m), 0.95 (3 H, t, J = 7 Hz), 0.1 (9 H, s).

α,α-Diiodotoluene (6). Freshly distilled benzaldehyde (**2b**) (2.1 g, 19.8 mmol) was dissolved in 10 mL of methylene chloride (dried over molecular sieves) in a 25 mL round-bottom flask. The flask was flushed with nitrogen, sealed with a rubber septum, and cooled to 0 °C in an ice bath. Trimethylsilyl iodide (**3**) (5.8 mL, 8.7 g, 43.5 mmol) was added over 3 min via syringe. The mixture was warmed to 25 °C and allowed to stand for 0.5 h. The solution was then washed with sodium thiosulfate (1 M, 10 mL) and 5 mL of saturated sodium bicarbonate and dried (sodium sulfate). The solvent was evaporated in vacuo and the residue sublimed at 55 °C and 0.02 mm of pressure, using dry ice to cool the collector, to yield 3.5 g (51.4%) of **6** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.1–7.7 (5 H, m), 6.2 (1 H, s); MS m/e 334 (M^+), 217, 204, 90. This white solid turns light brown rapidly on exposure to light and/or heat.

2,3:6,7-Dibenzo-9-oxabicyclo[3.3.1]nona-2,6-diene (8). A 50 mL Erlenmeyer flask was charged with phenylacetaldehyde (**2a**) (1.2 g, 10 mmol) and 5 mL of freshly distilled chloroform. The flask was stoppered under a nitrogen atmosphere with a serum cap and cooled in an ice bath. To this solution was added freshly distilled trimethylsilyl iodide (**3**) (1.6 mL, 2.4 g, 12 mmol), and the reaction was allowed to stand at 5 °C for 7 days. Sodium thiosulfate (1 M, 10 mL) and methylene chloride (10 mL) were added, and the mixture was stirred until the iodine color was discharged. The organic phase was separated, dried (sodium sulfate), and concentrated in vacuo. NMR analysis of this crude reaction mixture indicated the presence of 54% of the ether **8**, 25% of 2-phenylnaphthalene (**9**), and 20% of the iodide **10**. Chromatography on 35 g of silica gel eluting with either carbon tetrachloride or chloroform yielded 562 mg of the crystalline ether **8** (50%). Elution with carbon tetrachloride permits the separation of **9** and **10**.

Compound 8: mp 141.5–142.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.1 (8 H, m), 5.25 (2 H, d, J = 6 Hz), 3.55 (2 H, dd, J = 6 and 16 Hz), 2.70 (2 H, d, J = 16 Hz); ^{13}C NMR ($CDCl_3$) δ 137.78 (s), 131.58 (s), 129.08 (d), 126.83 (d), 125.96 (d), 125.14 (d), 69.56 (d), 36.12 (t); IR (liquid film) 3.25, 3.37, 6.68, 6.87. 9.22, 12.75, 12.90, 14.35, 14.65 μm; MS m/e 222 (M^+), 204, 203, 179, 178. Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.58; H, 6.24.

Compound 10: ^{1}H NMR ($CDCl_3$) δ 7.33 (9 H, m, aromatic H), 4.58 [1 H, d (J = 6.0 Hz) of t (J = 4.5 Hz), H_a], 3.61 (2 H, d, J = 4.5 Hz, H_b), 3.34 [1 H, d (J = 3.4 Hz) of t (J = 6.0 Hz), H_c], 3.21 [1 H, d (J = 10.5 Hz) of d (J = 3.4 Hz), H_d], 3.02 (1 H, d (J = 10.5 Hz) of d (J = 6.0 Hz), H_e]; IR (liquid film) 3.33, 3.48, 6.25, 6.38, 6.71, 6.90, 7.00, 8.83, 9.72, 14.32 μm; MS m/e 334 (M^+), 207.

1,2:5,6-Dibenzocycloocta-1,5-dien-3-ol (11). Ammonia (15 mL) was distilled from sodium into a 100 mL three-neck round-bottom flask equipped with a Dewar condenser under a nitrogen atmosphere. This flask was maintained at −78 °C while the ether **8** (111 mg, 0.5 mmol) and acetic acid (44 μL) in 5 mL of anhydrous diethyl ether was added. Sodium metal (61.5 mg, 2.8 mmol) was added, and the mixture was allowed to reflux for 40 min. At this time, ammonium chloride (0.5 g) was added and the ammonia was removed in a stream of nitrogen. Hydrochloric acid (1 N, 35 mL) was added, and the mixture was extracted with 2 × 20 mL of carbon tetrachloride. The organic layer was dried (sodium sulfate) and concentrated to an oil. Chromatography on silica gel, eluting with methylene chloride, yielded 91.3 mg (81.5%) of the crystalline alcohol **11** (R_f 0.3). Crystals from chloroform had mp 109–110 °C (lit.[8] mp 113–114 °C); ^{1}H NMR ($CDCl_3$) δ 7.33–7.0 (8 H, m), 5.26 (1 H, t, J = 8 Hz), 3.77–3.0 (7 H, m); MS m/e 224 (M^+), 2.06.

The conversion of **11** into **1** was carried out by a method of Nenitzescu.[8] Crystals of the ketone **1** showed mp 94.5–95.5 °C (lit.[8] mp 95 °C); 2,4-DNP, mp 195–197 °C (lit.[8] mp 198–200 °C).

2-Phenyltetralin (12). A solution of the iodide **10** (334 mg, 1 mmol) in 5 mL of diethyl ether was added to a cooled (−78 °C) flask containing 20 mL of distilled ammonia under a nitrogen atmosphere. Sodium metal (49 mg, 2 mmol) was added and the reaction stirred at −33 °C for 30 min. Ammonium chloride (0.5 g) was added, and the solvents were evaporated. Water (50 mL) was added and the aqueous mixture extracted with 2 × 30 mL of methylene chloride. The combined organic layers were dried (sodium sulfate) and concentrated in vacuo. Bulb to bulb distillation of the residue yielded 184 mg (82%) of 2-phenyltetralin (**12**): ^{1}H NMR ($CDCl_3$) δ 7.25 (5 H, s), 7.10 (4 H, s), 2.90 (4 H, m), 2.1 (2 H, m); IR (liquid film) 3.34, 3.46, 6.25, 6.33, 6.70, 6.87, 6.98, 13.16, 13.42, 14.33 μm; MS m/e 208 (M^+). This reduction product was shown to be identical with 2-phenyltetralin (**12**) by comparison (NMR, IR, MS, and gas chromatography) with an authentic sample.[11]

2-Phenyl-1,2-dihydronaphthalene (13) and 3-Phenyl-1-tetralone (15). A solution of **10** (334 mg, 1 mmol) and silver acetate (184 mg, 1.1 mmol) in 10 mL of acetic acid was refluxed for 40 min. Diethyl ether (100 mL) was added, and the solution was washed several times with saturated aqueous sodium bicarbonate, dried (sodium sulfate), and evaporated in vacuo to afford 235 mg of residue. This mixture was taken up in 15 mL of acetone to which was added 15 mL in 1 N sodium hydroxide, and the solution was allowed stand at 25 °C for 2 h. The acetone was extracted with 2 × 30 mL of ether, and the ethereal solution was dried (sodium sulfate) and concentrated in vacuo. Preparative layer chromatography of the residue on silica gel eluting with carbon tetrachloride afforded two separate bands (R_f 0.8 and 0.05). The upper band (50 mg) was assigned as 2-phenyl-1,2-dihydronaphthalene (**13**) on the basis of its NMR spectrum: ^{1}H NMR (CCl_4) δ 7.27 (5 H, s), 7.13 (4 H, s), 6.60 (1 H, dd, J = 10 and 1.5 Hz), 6.06 (1 H, dd, J = 10 and 2 Hz), 3.70 (1 H, m), 3.00 (2 H, m).

The lower band (170 mg), probably the alcohol **14**, was oxidized with pyridinium chlorochromate to afford 3-phenyl-1-tetralone (**15**) (151 mg). The structure of **15** was assigned on the basis of the compound's NMR and IR spectra and the melting point of its semicarbazone: semicarbazone, mp 209–210 °C (lit.[12] mp 208 °C); ^{1}H NMR (CCl_4) δ 7.95 (1 H, m), 7.37–7.21 (9 H, m), 3.08 (3 H, m), 2.77 (2 H, m); IR (liquid film) 5.95 μm.

1-Methylisochroman (25). A 5 mL round-bottom flask charged with freshly distilled acetaldehyde (311 mg, 7.06 mmol) and 1 mL of chloroform (dried over molecular sieves) was flushed with nitrogen and sealed with a rubber septum. To this was added via syringe trimethylsilyl iodide (**3**) (0.94 mL, 1.412 g, 7.06 mmol), the flask being cooled to keep the reaction mixture at 25 °C. (The reaction of the aldehyde and the silyl iodide is exothermic.) To this solution of **4c** in chloroform was added via syringe 2-phenylethyl trimethylsilyl ether (**21**) (2.11 mL, 9.9 mmol) (prepared by silylation of the corresponding alcohol by the usual method). The reaction mixture was warmed to 50 °C for 2 h and cooled to 25 °C, and 20 mL of diethyl ether was added. The organic solution was washed with 3 × 10 mL of 10% aqueous sodium thiosulfate and 2 × 10 mL of water, dried (sodium sulfate), and evaporated in vacuo. The residue was chromatographed on 80 g of silica gel. Elution with benzene afforded 0.553 g (50%) of the desired isochroman **25:** ^{1}H NMR ($CDCl_3$) δ 6.8–7.2 (4 H, m), 4.75 (1 H, q, J = 7 Hz), 3.5–4.3 [2 H, m (14 line pattern)], 2.4–3.2 (2 H, m), 1.57 (3 H, d, J = 7 Hz); IR (liquid film) 3.3–3.6, 8.93, 13.16, 13.60 μm; MS m/e 148 (M^+).

Acknowledgment. We wish to thank Dr. F. A. L. Anet and Dr. M. Squillacote for the 251 MHz NMR spectra and for helpful discussions. A.B.M. wishes to thank the University of California Committee on Research for a fellowship.

Registry No.—**1,** 838-15-3; **2a,** 122-78-1; **2b,** 100-52-7; **2c,** 75-07-0; **2d,** 123-38-6; **2e,** 123-72-8; **2f,** 78-84-2; **2g,** 66-25-1; **2h,** 111-71-7; **3,** 16029-98-4; **4a,** 66858-68-2; **4b,** 66858-69-3; **4c,** 66858-70-6; **4d,** 66858-71-7; **4e,** 66858-72-8; **4f,** 66858-73-9; **4g,** 66858-74-0; **4h,** 66858-75-1; **6,** 28000-59-1; **8,** 66365-45-5; **9,** 612-94-2; **10,** 66858-76-2; **11,** 888-42-6; **12,** 29422-13-7; **13,** 62019-39-0; **14,** 66858-77-3; **15,** 14944-26-4; **21,** 14629-58-4; **25,** 26164-06-7.

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(15) The suggestion that hydrogen iodide might hydrolyze the iodo silyl ethers **4a** or **4c** to the corresponding aldehydes, which would then undergo these electrophilic substitution reactions, has been made less likely by continual monitering of the reaction mixture by ^{1}H NMR spectroscopy, which indicates the absence of the aldehydes throughout the reaction. However, in the absence of the detailed reaction rates, this possibility cannot be excluded.

(16) The detailed mechanisms for the formation of **9** and **10** are not known at present. However, the fact that the aldehyde **2a** is not observed by NMR spectroscopy during the reaction leads us to suggest that both **9** and **10** may be formed from the α-iodo silyl ether **4a** by some electrophilic process.

Studies in Biomimetic Alkaloid Syntheses. 1. Alkylations of 3-Chloroindolenines

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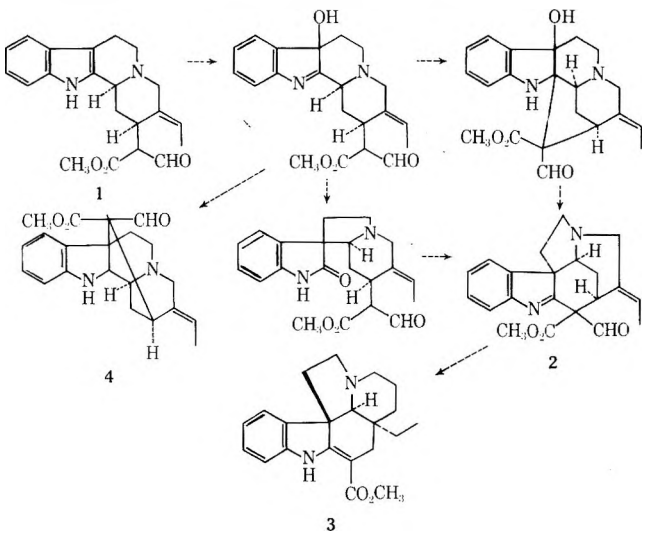
Received April 25, 1978

The chloroindolenine derivative (**6**) of tetrahydrocarbazole (**5**) reacted with thallium diethyl malonate by addition to the imine function and rearrangement to give the 3-spiro-2-alkylideneindoline (**9**). An analogous reaction was found with thallium ethoxide, leading to the imino ether **12**. However, with thallium ethyl acetoacetate the 2-spiro-3-alkylideneindoline (**15**) and the unrearranged O- and C-alkylation products **14** and **16** were formed. Substituting sodium diethyl malonate or sodium ethyl acetoacetate or the corresponding iodoindolenine in these reactions gave only tetrahydrocarbazole. The reactions are intermolecular parallels for key alkylation reactions proposed in the biosynthetic conversion of secoychimbine to strychnos and picraline alkaloids.

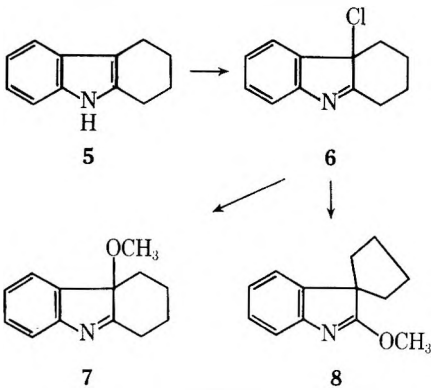
The chlorination of 2,3-disubstituted indoles readily provides 3-chloroindolenines. While reactions of the latter with hydroxide and alkoxide have been studied in the tetrahydrocarbazole[1] and in some indole alkloid[2] series and were found to lead to corresponding oxindoles, there have been no reports of the use of haloindolenines for C-alkylation reactions. Such alkylations would provide a new entry into syntheses of a variety of dihydroindole alkaloid structures and mimic key steps in the natural biosynthesis of these compounds.

Thus oxidation and intramolecular imine alkylation of secoyohimbine alkaloids (i.e., geissoschizine, **1**), followed by rearrangement, can be proposed as the natural pathway to a strychnos alkaloid skeleton (i.e., preakuammicinal, **2**) and ultimately to the aspidosperma alkaloids (i.e., vincadifformine, **3**), in accord with the result of biosynthetic plant feeding experiments with labeled precursors.[3] The proposed cyclization of an oxindole intermediate to the strychnos skeleton[3b] **2** (see Scheme I) would seem less favorable from a chemical point of view. Alternatively, direct intramolecular displacement of the (derivatized) hydroxyl group of the hydroxyindolenine leads to the picraline type alkaloids **4**. Details of the overall biosynthetic conversions of **1** to **2**, **3**, and **4** remain to be established and synthetic emulation of the biosynthetic steps leading to the strychnos skeleton has been posed as the "missing link" challenge in the formation of this major alkaloid class.[3b] The present studies provide a synthetic parallel to these hypothetical conversions. They could be extended to a total synthesis of the alkaloid vincadifformine (**3**), described in the following report.

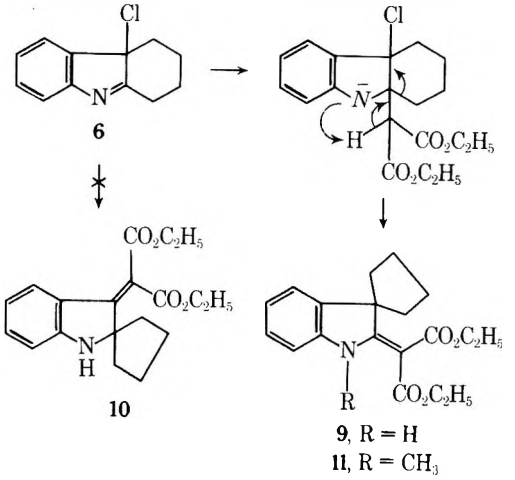
Scheme I. Biosynthetic Pathways for Generation of Strychnos, Picraline, and Aspidosperma-Type Alkaloids



The chloroindolenine **6**, prepared by chlorination of tetrahydrocarbazole **5** with *tert*-butyl hypochlorite, led on reaction with sodium methoxide in methanol at −20 °C predominantly to the methoxyindolenine **7** and to some of the rearrangement product **8**, while in methanolic sodium hydroxide the latter became the major product.[1,4]



Attempts to effect analogous halogen displacement or imine addition reactions with sodium diethyl malonate in ether, dimethylformamide, dimethyl sulfoxide, or methanol, under a variety of conditions, gave mainly recovered chloride **6** or tetrahydrocarbazole **5**. However, on refluxing thallium diethyl malonate and the chloroindolenine **6** in benzene, the unsaturated malonate **9** was formed in 47% yield, together with 10% of tetrahydrocarbazole **5**. Structure assignment as **9** for the product and exclusion of the alternative structure **10** were based on the compound's insolubility in acid, expected of a



vinylogous urethane, on a display of extended conjugation in UV (λ_{max} 299, 329 nm; ϵ 9400, 19 750) and IR (ν_{max} 1575 cm^{-1}, strong) spectra and particularly on a large difference in IR carbonyl stretching frequencies for the two ester groups. While one appears at 1710 cm^{-1}, the other is shifted to 1660 cm^{-1}

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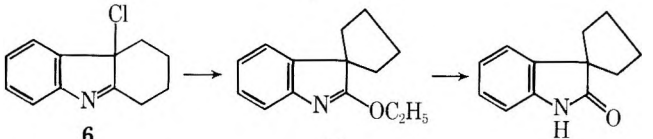
by internal hydrogen bonding. *N*-Methylation of the diester **9** gave a product **11** with a single ester carbonyl absorption band at 1695 cm^{-1}, showing about twice the extinction coefficient of those found for the two ester absorption bands in **9**.

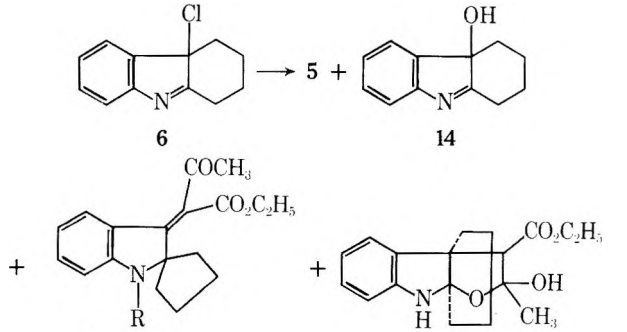
In analogy to the addition of thallium diethyl malonate to the imine function of the chloroindolenine **6** and rearrangement to the 3-spiroindoline **9**, a corresponding reaction of **6** with thallium ethoxide in benzene resulted in the formation of the imino ether **12**, which could be hydrolyzed to the oxindole **13**. No unrearranged ethoxyindolenine was formed in this reaction, in contrast to the predominant formation of the methoxyindolenine **7** obtained on reaction of the chloroindolenine **6** with sodium methoxide.



6 **12** **13**

When the chloroindolenine **6** was heated with thallium ethyl acetoacetate, tetrahydrocarbazole **5** was produced as the major product, together with the known hydroxyindolenine **14** (14%) and the ethyl acetoacetate carbon alkylation products **15** (10%) and **16** (4%). The structural assignment of **15** was based on its acid solubility and indoline UV spectrum, which excluded a structure analogous to that of the malonate product **9**. In its NMR spectrum **15** showed an NH proton singlet at δ 4.75, which could be slowly removed by hydrogen–deuterium exchange in D_2O and NaOD, or shifted to δ 9.5 in trifluoroacetic acid (broad two-proton signal for the ammonium salt). On methylation the *N*-methyl derivative **17** was obtained. These observations are not compatible with an acetoacetate adduct having a methine proton. No carbon–nitrogen double bond stretch was seen in the IR spectrum. Since only one double bond isomer was isolated, the *E,Z* orientation of ester and acyl groups in **15** relative to the aromatic ring could not be defined in the absence of the alternative isomer.[5]

Assignment of the hemiketal structure **16** to the minor alkylation product is based on its indoline UV spectrum, on a molecular ion *m/e* 317 showing incorporation of one water equivalent, on saturated ester and OH absorptions but no acyl absorption in the IR spectrum, and on an NMR methyl singlet at δ 1.7, more consistent with **16** than with a structure with an acyl group.



6 **14**

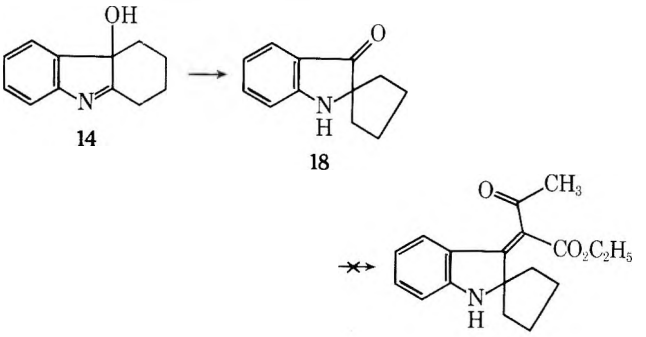
15, R = H
17, R = CH_3

16

In a search for alternatives to the thallium ethyl acetoacetate reagent it was found that detectable amounts (<3% yield) of the major alkylation product **15** were formed on reaction of the chloroindolenine **6** with ethyl acetoacetate and silver perchlorate in nitromethane[6] or with Triton B as base in a two-phase dichloromethane/water system. From a homogeneous solution of the latter reagents in an ethanol, methanol, and benzene mixture the hydroxyindolenine **14** was obtained as major acid soluble product, but no alkylation product **15** could be found.

Formation of the hydroxyindolenine **14** arises from initial O-alkylation of ethyl acetoacetate with direct displacement of chlorine in the chloroindolenine **6**. The resultant enol ether is subject to hydrolysis during acid extraction of the reaction mixture. While products **15** and **16** may be formed by an analogous direct displacement of chlorine in **6** with C-alkylation of ethyl acetoacetate, they could alternatively also be derived from O-alkylating addition of ethyl acetoacetate to the imine function of **6** and bridging of an initial enol ether product with displacement of chlorine, resulting in overall C-alkylation of ethyl acetoacetate. Preferential O- rather than C-alkylation in the ethyl acetoacetate reaction would then rationalize the lack of products analogous to **9**, derived from diethyl malonate.

In view of the facile rearrangement of the hydroxyindolenine **14** to the spiroindoxyl compound **18**,[7] these compounds were considered as possible precursors for the major alkylation product **15**. However, attempts to condense ethyl acetoacetate or its thallium salt with the ketone **18** in refluxing ethanol or benzene did not yield the keto ester **15**.



14 **18**

15

Preliminary efforts to extend this reaction to the thallium salts of acetylacetone, dimedone, ethyl benzoylacetate, ethyl cyanoacetate, malononitrile, and nitromethane, followed by an acid workup, showed that some hydroxyindolenine **14** was formed in the first three cases which can give rise to enol ethers, but not in the latter three. Tetrahydrocarbazole **5** was formed in all instances in addition to uncharacterized tarry material.

The ubiquitous formation of tetrahydrocarbazole **5** is assumed to originate from nucleophilic abstraction of halogen from the chloroindolenine **6**. Accordingly, the corresponding iodoindolenine and thallium diethyl malonate gave only tetrahydrocarbazole **5** ("$I^+ > Cl^+$").

The foregoing conversions of tetrahydrocarbazole to the alkylation and rearrangement product **9** and the alkylation product **16** provide intermolecular reaction parallels to biosynthetic conversions of the secoyohimbine (**1**) to strychnos (**2**) and pikraline (**4**) type alkaloids. In order to bring these reactions to closer analogy and to apply them to syntheses of naturally occurring alkaloids, they were extended to tetrahydrocarbolines, as described in the following report of a synthesis of vincadifformine (**3**).

Experimental Section

4a-Chloro-2,3,4,4a-tetrahydro-1*H*-carbazole (6). Tetrahydrocarbazole (1.71 g, 10 mmol) was dissolved in benzene (30 mL) containing triethylamine (1.1 mL). The mixture was cooled in ice, then *tert*-butyl hypochlorite (1.1 mL) was added slowly through a syringe needle dipping below the surface of the stirred solution. After addition was complete, stirring was maintained for 30 min, then the reaction mixture was washed three times with ice water. The benzene solution was dried by passing it through phase separating paper (Whatman No. 1 PS) and then distilling a small portion of the solvent. This solution was used directly for the subsequent reactions: IR (CCl_4) ν_{max} 3050, 2950, 2860, 1590, 1355 cm^{-1}; NMR (CCl_4) τ 2.32–2.80 (complex

m, 4 H), 7.04–7.20, 7.24, 7.41, 7.70–7.97, 8.04–8.80, 9.05 (complex m, 8 H).

2′-Ethoxyspiro(cyclopentane-1,3′-3′*H*-indole) (12). Thallium(I) ethoxide (2.5 g) was added to the above solution of **6.** The reaction mixture was stirred and refluxed for 6 h, then cooled and filtered through a short column of Florisil. Removal of the solvent furnished an oil which was absorbed on alumina (Woelm, Grade I) from light petroleum. Elution with ether–light petroleum (1:3) gave 2′-ethoxyspiro(cyclopentane-1,3′-3′*H*-indole) (**12**) (1.45 g, 67%), as a colorless oil: IR (film) ν_{max} 3010, 2960, 2880, 1580, 1460, 1400, 1380, 1340, 1270, 1025, 730 cm^{-1}; NMR (CCl_4) τ 2.6–3.1 (4 H), 5.54 (q, 2 H), 8.01 (br m, 8 H), 8.61 (t, 3 H). The structure was confirmed by acid hydrolysis[1] to spiro(cyclopentane-1,3′-3′*H*-indole)-2′(1′*H*)-one (**13**), identical with an authentic sample.

Diethyl Spiro(cyclopentane-1,3′-3′*H*-indole)-2′(1′*H*)-ylidenemalonate (9). Thallium(I) diethyl malonate (3.64 g, 10 mmol) was added to the above solution of **6.** The mixture was stirred and refluxed for 18 h and then the cooled reaction mixture was passed through a short column of Florisil. The filtrate was extracted twice with ice cold 2 N hydrochloric acid, then washed with water and dried over sodium sulfate. Removal of the solvent furnished a dark oil which partially crystallized on standing. After cooling to 0 °C, the crystals were filtered, and after recrystallization from *n*-heptane furnished diethyl spiro(cyclopentane-1,3′-3′*H*-indole)-2′(1′*H*)-ylidenemalonate (**9**): mp 102–103 °C (1.54 g, 47%); IR (CCl_4) ν_{max} 3290, 3050, 2980, 2950, 2875, 1710, 1660, 1605, 1575, 1475, 1395, 1365, 1278, 1225, 1102, 1070 cm^{-1}; NMR (CCl_4) τ 2.76–3.12 (5 H), 5.77 (quartet, 4 H), 7.4–7.6, 8.04 (complex m, 8 H), 8.68 (t, 6 H); UV (EtOH) λ_{max} (ϵ) 204 (9000), 232 (12 000), 299 (9400), 329 nm (19 750); MS *m/e* (%) 329 (M^+, 45), 288 (100), 256 (57), 170 (56), 168 (37), 182 (22). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.37; H, 7.06; N, 4.16.

Diethyl 1′-Methylspiro(cyclopentane-1,3′-3′*H*-indole)-2′-ylidenemalonate (11). A mixture of 1 g (3.3 mmol) of the malonyl adduct **9** and lithium amide (280 mg, 13.2 mmol) was refluxed in anhydrous tetrahydrofuran (20 mL) for 4 h under an atmosphere of dry nitrogen. The reaction was then cooled and a solution of methyl iodide (1.5 mL, 26.4 mmol) in dimethylformamide (5 mL) was added; the resulting mixture was stirred at 20 °C for 60 h, then poured into water and extracted three times with ether. The organic extracts were washed with water and dried over sodium sulfate and the solvent was evaporated to leave an oil which slowly crystallized. Recrystallization from *n*-heptane gave diethyl 1′-methylspiro(cyclopentane-1,3′,3′-*H*-indole)-2′-ylidenemalonate: mp 100–102 °C (600 mg, 58%); IR (CCl_4) ν_{max} 3050, 2980, 2870, 1695, 1545, 1485, 1450, 1365, 1275, 1200, 1095, 1050, 960 cm^{-1}; NMR (CCl_4) τ 3.00 (W = 46 Hz, 4 H), 5.80 (q, 4 H), 6.85 (s, 3 H), 7.3, 8.0 (br m, 8 H), 8.71 (t, 6 H); UV (EtOH) λ_{max} (ϵ) 207 (6200), 237 (8200), 302 (3700), 342 nm (10 500); MS *m/e* (%) 343 (M^+, 20), 303 (91), 184 (100), 168 (34), 167 (27), 157 (26). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.89; H, 7.44; N, 3.86.

Reaction of 4a-Chloro-2,3,4,4a-tetrahydro-1*H*-carbazole (6) with Thallium(I) Ethyl Acetoacetate Enolate. To the above solution of **6** was added thallium(I) ethyl acetoacetate enolate (3.24 g, 10 mmol). The two substances were allowed to react and the reaction mixtures worked up as in the preparation of the malonyl adduct **9.** The nonbasic product was a dark oil (1.1 g, 64%) and at least 60% of this oil was tetrahydrocarbazole (650 mg, 38%). It contained no tetrahydrocarbazole–ethyl acetoacetate adducts. The acid extracts were neutralized with ice cold potassium carbonate solution and then made strongly basic with potassium hydroxide and extracted three times with dichloromethane. The organic extracts were combined, washed with water, and dried, and the solvent was removed to give a partially crystalline material. This product was adsorbed onto a column of dry alumina, which was developed with light petroleum–ether (75:25). After development, the column was sliced into three separate bands (determined by examination under UV light) and the products were eluted from the adsorbent with dichloromethane. The most polar compound was identified as 4a-hydroxy-2,3,4,4a-tetrahydro-1*H*-carbazole (**14**) (254 mg, 14%), identical with an authentic sample.[7] The compound of middle polarity was assigned as ethyl 2-hydroxy-2-methyl-2,3,3a,8a-tetrahydro-3a,8a-butanofuro[2,3-*b*]indole-3-carboxylate (**16**) (125 mg, 4%): IR (CCl_4) ν_{max} 3385, 3000, 2945, 2860, 1730, 1615, 1480, 1465, 1450, 1423, 1375, 1347, 1315, 1305, 1280, 1250, 1185, 1128, 1047, 1005, 962, 956, 946, 905, 880 cm^{-1}; NMR ($CDCl_3$) τ 2.95 (m, 5 H), 4.3 (s, 1 H, exchanged rapidly with D_2O), 5.27 (s, 1 H, exchanged slowly with D_2O), 5.74 (q, 2 H), 6.70 (s, 1 H), 8.30 (s, 3 H), 8.65 (t, 3 H), 7.25–9.30 (complex absorption, 9 H); UV (EtOH) λ_{max} (ϵ) 212 (10 000), 240 (8700), 294 nm (2300); MS *m/e* (%) 317 (M^+, 20), 299 (41), 216 (44), 184 (100), 170 (88), 169 (79). The least polar compound was assigned as ethyl spiro(cyclopentane-1,2′-3′*H*-indole)-3′(1′*H*)-ylideneacetoacetate (**15**): mp 118–118.5 °C (300 mg, 10%); IR (CCl_4) ν_{max} 3395, 3050, 2960, 2880, 1700, 1680, 1632, 1605, 1480, 1460, 1395, 1370, 1330, 1310, 1265, 1105, 1090, 970 cm^{-1}; NMR ($CDCl_3$) τ 2.65–3.34 (7 lines, 4 H), 5.28 (s, 1 H), 5.75 (q, 2 H), 7.80 (s, 3 H), 8.68 (t, 3 H), 7.6–8.0, 8.3–8.7 (br m, 8 H); NMR (CF_3CO_2H) τ 0.5 (br s, 2 H), 2.2 (4 H), 5.61 (q, 2 H), 7.60 (s, 3 H), 8.55 (t, 3 H), 7.0–8.5 (br m, 8 H); UV (EtOH) λ_{max} (ϵ) 208 (26 000), 242 (27 500), 293 nm (5300); addition of acid gave no shifts in band positions, but all bands were weaker; addition of base increased the intensity of the 208-nm band approximately 30-fold; MS *m/e* (%) 299 (M^+, 24), 256 (100), 228 (40), 182 (48), 170 (60). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.13; H, 7.23; N, 4.45.

Ethyl 1′-Methylspiro(cyclopentane-1,2′-3′*H*-indole)-3′(1′-*H*)-ylideneacetoacetate (17). The acetoacetate adduct **15** (75 mg) was methylated with lithium amide (30 mg) in tetrahydrofuran and methyl iodide (250 μL) in DMF, as described for the malonate adduct **9**, yielding a brown oil which was taken up in light petroleum–ether (72:25) and passed through a short column of alumina to furnish ethyl 1′-methylspiro(cyclopentane-1,2′-3′*H*-indole)-3′-(1′*H*)-ylideneacetoacetate (**17**) (45 mg, 57%): IR (CCl_4) ν_{max} 3050, 2935, 2853, 1687, 1615, 1480, 1377, 1330, 1310, 1095, 977 cm^{-1}; NMR (CCl_4) τ 2.8 (2 H), 3.2–3.7 (2 H), 5.75 (q, 2 H), 7.08 (s, 3 H), 7.8 (s, 3 H), 8.66 (t, 3 H), 7.0–9.2 (complex absorption, 8 H); UV (EtOH) λ_{max} (ϵ) 211 (30 400), 247 (32 150), 317 nm (3240); MS *m/e* (%) 313 (M^+, 27), 271 (22), 270 (100), 256 (22), 242 (35), 184 (20).

Acknowledgment. This work was supported by the Cancer Institute of the National Institutes of Health with Research Grant PHS CA R01-12010.

Registry No.—**5,** 942-01-8; **6,** 42540-51-2; **9,** 66842-54-4; **11,** 66842-55-5; **12,** 66842-56-6; **13,** 41058-67-7; **14,** 42738-99-8; **15,** 66842-57-7; **16,** 66842-58-8; **17,** 66842-59-9; thallium(I) ethoxide, 20398-06-5; thallium(I) diethyl malonate, 66859-38-9; thallium(I) ethyl acetoacetate enolate, 42283-28-3.

References and Notes

(1) R. J. Owellen, *J. Org. Chem.*, **39,** 69 (1974).
(2) N. Finch and W. I. Taylor, *J. Am. Chem. Soc.*, **84,** 3871 (1962).
(3) (a) A. I. Scott, *Acc. Chem. Res.*, **3,** 151 (1970); (b) *Bioorg. Chem.*, **3,** 398 (1974).
(4) This difference has been ascribed to alternative reactions of a rearranging carbonium ion,[1] but we prefer to consider these products to be derived from respective S_N2 displacement of chloride by methoxide vs. methanol addition to the imine function and rearrangement.
(5) From other studies it is known that in 3-alkylideneoxindoles proximity of the aromatic peri proton to a *Z* (but not an *E*) oriented carbonyl group results in a downfield shift of this proton [R. I. Autrey and F. C. Tahk, *Tetrahedron*, **23,** 901 (1967)]. Comparison of NMR spectra of 3-alkylidineoxindoles bearing the required ester and acyl *Z* substituents showed the peri protons respectively shifted downfield to δ 8.45 and 8.68. (The model compounds were prepared in our group by Mr. Marvin DeTar for another synthetic project which will be described later.) However, with introduction of a tetrahedral carbon in **15** in place of the oxindole carbonyl group the aromatic proton region extends only to δ 7.4 and prevents correlation of the oxindole and indoline series and *E* vs. *Z* assignment in **15.**
(6) P. Boldt, H. Militzer, W. Thielecke, and L. Schultz, *Justus Liebigs Ann. Chem.*, **718,** 101 (1968).
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Studies in Biomimetic Alkaloid Syntheses. 2. Synthesis of Vincadifformine from Tetrahydro-β-carboline through a Secodine Intermediate

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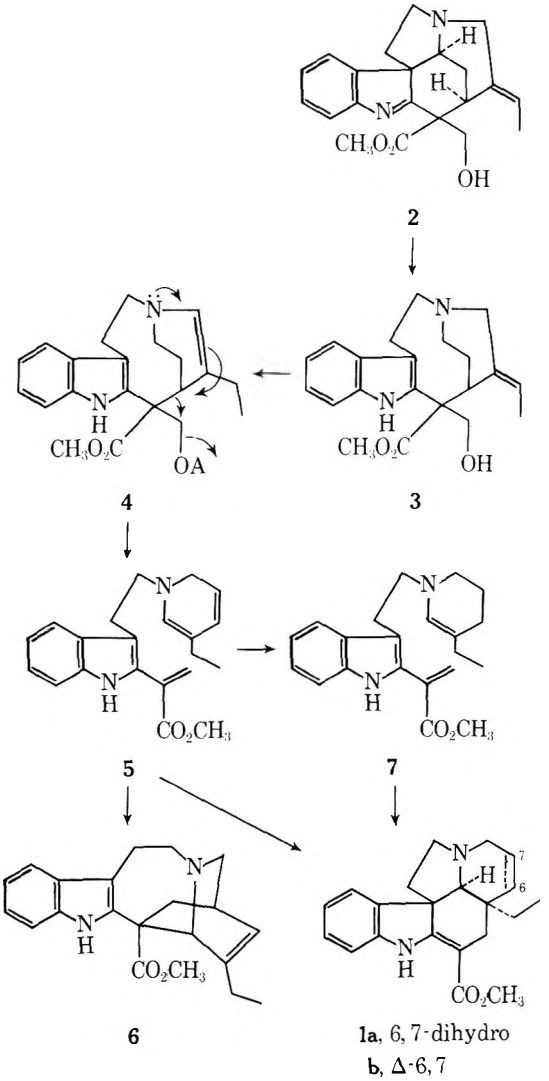
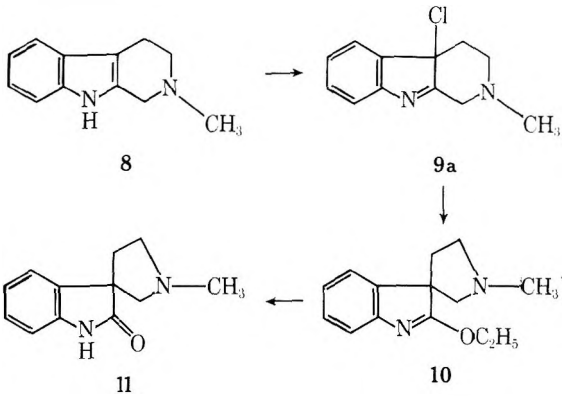
Received April 25, 1978

N-Methyl- and *N*-benzyltetrahydro-β-carbolines (**8** and **17**) on reaction with *tert*-butyl hypochlorite gave the corresponding chloroindolenines **9a,b.** The *N*-methyl compound **9a** was converted to the rearranged 2-alkoxy-3-spiropyrrolidylindolenine (**10**) and the oxindole (**11**) on treatment with thallium ethoxide, followed by hydrolysis. Reactions of the chloroindolenines **9a,b** with thallium dialkylmalonates led to the respective indoleazepines **14** and **16.** Monodecarboxylation and debenzylation of the latter provided the amino ester **20,** which was converted to vincadifformine (**1a**) by reaction with 5-bromo-2-ethylpentanal (**23**). The overall synthetic reaction sequence, which proceeded in high yields at each step, passed through the biogenetically postulated secodine **7.** This intermediate underwent a biomimetic cyclization with stereospecific generation of vincadifformine in greater than 67% yield.

Among indole and dihydroindole alkaloids, which comprise one of the largest classes of natural products with a common structural element, alkaloids with the aspidosperma skeleton, exemplified in vincadifformine (**1a**), are prominently represented. Their biosynthetic origin has been traced to tryptophan and loganin precursors with subsequent secoyohimbine (i.e., geissoschizine) and strychnos (i.e., preakuammicinal) biosynthetic stages.[1] (See corresponding structures **1, 2,** and **3** in the preceeding paper.[2]) Cleavage of ring C in preakuammicine (**2**) and reduction of the resultant immonium function leads to stemmadenine (**3**). Isomerization of the ethylidene double bond in stemmadenine (**3**) can then give rise to a tetrahydropyridine alcohol intermediate **4,** which may undergo fragmentation (as its pyrophosphate?) to a dehydrosecodine (**5**). This structure occupies a key pivotal position in alkaloid biogenesis in that it has been postulated[1,3] to serve as a precursor for generation of aspidosperma (i.e., tabersonine, **1b**) or iboga (i.e., catharanthine, **6**) alkaloid structures by alternative reactions of the acrylic ester and dienamine moieties. Furthermore, reduction to a tetrahydropyridine (perhaps by disproportionation of the dihydropyridine) will furnish a secodine intermediate **7.** The latter can undergo only one of the two fundamental cyclization pathways outlined above, thus leading to vincadifformine (**1a**). The following report describes the synthesis of vincadifformine by generation and reaction of the biogenetically proposed secodine intermediate **7.**



Chlorination of tetrahydrocarbazole and reaction of the resultant chloroindolenine with thallium diethyl malonate had resulted in a 3-spirocyclopentyl-2-alkylideneindoline.[2] Extension of this biomimetic oxidative alkylation reaction sequence to *N*-β-alkyltetrahydrocarbolines **8** and **17** could be expected to proceed in an analogous fashion to give corresponding 3-spiropyrrolidylindoline structures, which would be of potential value for indole alkaloid syntheses. Thus 4a-chloro-2-methyl-1,2,3,4-tetrahydro-4a*H*-pyrido[3,4-*b*]indolenine (**9a**) was prepared in a pilot study by reaction of the tetrahydro-β-carboline **8** with *tert*-butyl hypochlorite. In contrast to the chloroimine derived from tetrahydrocarbazole, the chloroimine **9a** is an isolable crystalline compound, stable on storage at 0 °C in the absence of acids. When treated with thallium ethoxide in refluxing benzene it gave the imido ether **10,** which in turn was hydrolyzed to the 3-spiropyrrolidyl-2-oxindole **11.**



A reaction of the chloroimine **9a** with thallium diethyl malonate, however, furnished an alkylation product which did not show the spectroscopic characteristics of the 3-spiro-2-alkylideneindoline **12,** but instead those of an indole [UV λ_{max}

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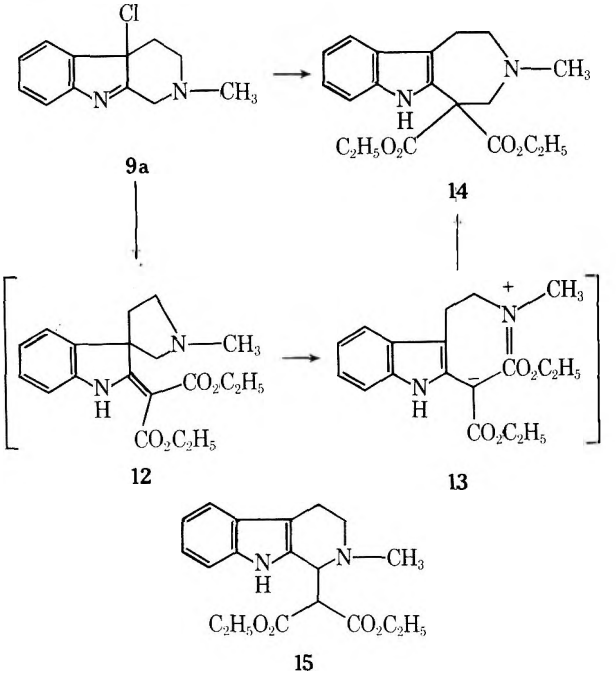
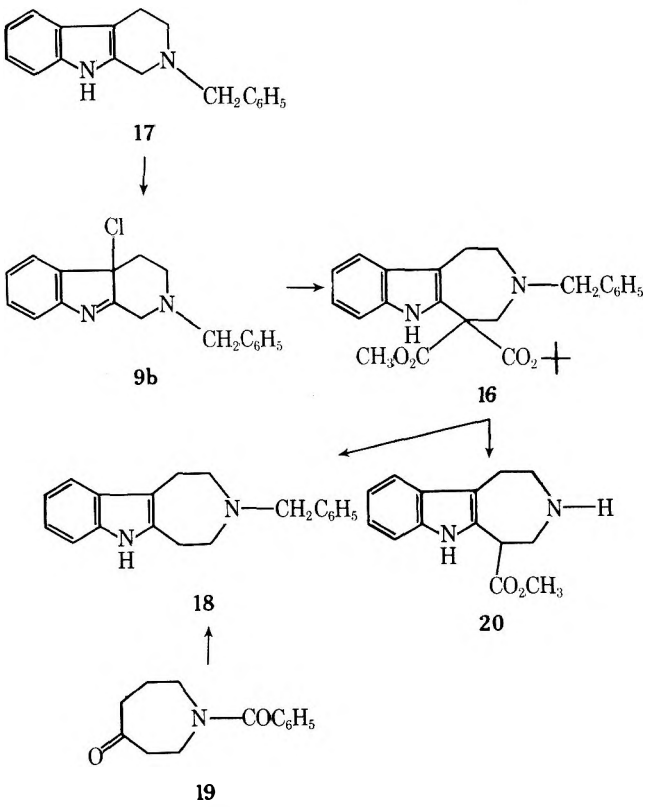
285, 293 nm; ϵ 7950, 6900; IR ν_{max} 3465 cm^{-1} (sharp NH); NMR δ 8.2 (indolic NH)]. It thus appeared that the 3-spiro-2-alkylideneindoline **12** had rearranged through a zwitterionic immonium malonate **13** to the indoloazepine **14.** An alternative malonyl tetrahydro-β-carboline structure (**15**) was considered for this product, based on an imine to enamine tautomerization in **9a** and subsequent vinylogous displacement of chloride by malonate, in analogy to such known reactions of chloroindolenines. However, the alkyl malonic ester structure **15** could be excluded by the NMR spectrum, which did not show an AB pattern for two adjacent methine protons, but instead showed a two-proton singlet at δ 3.4 for a methylene group on nitrogen.



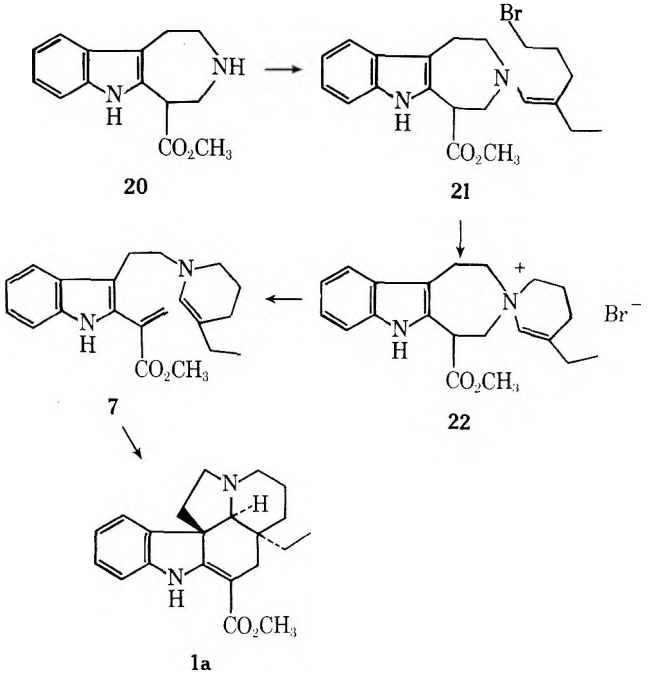
Formation of the indoloazepine **14** provided a conceptual base for syntheses of secodines and aspidosperma alkaloids. To this end it seemed advantageous to promote decarboxylation of one of the ester functions and to remove the N-b alkyl substituent. These two objectives were readily achieved through synthesis of the *tert*-butyl methyl-3-benzyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate (**16**). The starting material, *N*-benzyltetrahydro-β-carboline **17**, was most readily prepared through benzoylation of tetrahydro-β-carboline and reduction with lithium aluminum hydride, rather than through the reported Leuckart benzylation.[4,5] Conversion of this compound to the chloroindolenine **9b** with *tert*-butyl hypochlorite and triethylamine and subsequent reaction with thallium *tert*-butyl methyl malonate in refluxing benzene gave the desired azepinoindole **16** in 63–85% yield.

Vigorous acid hydrolysis resulted in double decarboxylation of the diester **16** and thus led to the azepinoindole **18.** This compound could alternatively be obtained from *N*-benzoylazepin-4-one (**19**) by a Fischer indole synthesis and reduction with lithium aluminum hydride, thus substantiating the foregoing structure assignments.[6]

While heating of the diester **16** for 1 h with aqueous methanolic hydrochloric acid resulted in double decarboxylation, only the *tert*-butyl ester function was lost in anhydrous methanol or, for optimum yield, on heating with anhydrous trifluoroacetic acid in 1,2-dichlorethane (90% yield). The benzyl group could then be quantitatively removed from the monomethylamino ester by hydrogenolysis in acetic acid over a 5% Pd/C catalyst (or analogously from the *tert*-butyl methyl diester **16**) with generation of the required azepinoindole ester **20.**

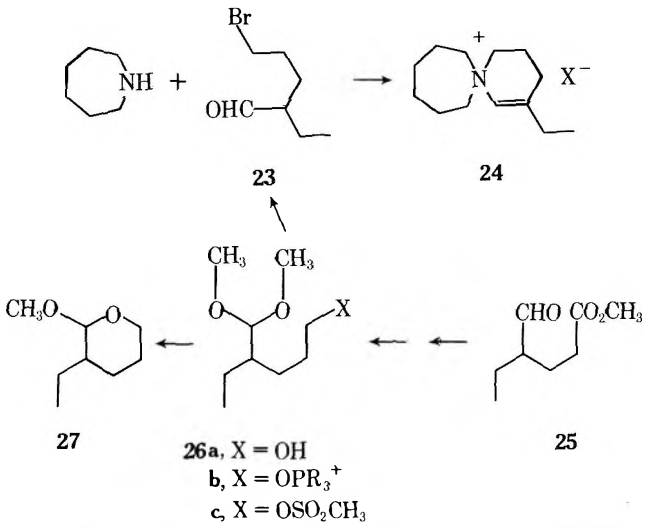


A synthesis of the key secodine intermediate **7** could now be projected through transformation of the azepine **20** into a 5-haloenamine intermediate **21,** its cyclization to a spiroenammonium salt **22,** and fragmentation of this β-ammonium ester. While spiroammonium salts have been made previously,[7,8,9] no intramolecular enamine N-alkylation reaction, needed for transformation of the indole azepine **20** to the spiroammonium salt **22,** has been reported. Thus a model reaction of hexamethyleneimine with 5-bromo-2-ethylpentanal (**23**) was studied and found to give the spiroenammonium salt **24** in 77% yield by heating the reactants in benzene.[10]



The bromo aldehyde **23** used in this reaction was made from methyl 4-formylhexanoate (**25**), which in turn is readily obtained from reaction of butyraldehyde enamines with methyl acrylate.[11] Conversion of the aldehyde **25** to its dimethyl (or

diethyl) acetal (93, 90%) and reduction with lithium aluminum hydride (90%) afforded the acetal alcohol **26a**. Initial attempts at transformation of this alcohol into a corresponding halide were complicated by the intrinsic lability of the acetal function. While trioctylphosphine and carbon tetrachloride[12] have been used with sugar hemiacetals,[13] this reagent appeared to yield primarily the tetrahydropyran **27** as a result of intramolecular methoxy O-alkylation, with displacement of trioctylphosphine oxide in intermediate **26b**. Thionyl chloride or phosphorus tribromide and pyridine also led to the tetrahydropyran **27** as major product. The reaction of the alcohol **26a** with triphenylphosphine and carbon tetrabromide was more successful (65% yield of **23**), but the most satisfactory synthesis of the bromo aldehyde **23** was obtained by quantitative transformation of the acetal alcohol **26a** to its mesylate derivative **26c** and reaction of the latter with lithium bromide in dimethylformamide. On aqueous extractive workup the bromoaldehyde was obtained in 78% yield.[14]



For continuation of the synthetic sequence the bromo aldehyde **23** was combined with the indoloazepine **20**. Under conditions which had produced the model spiroenammonium salt **24**, vincadifformine (**1a**) was generated directly. Following this reaction by high-pressure liquid chromatography it could be seen that an equimolar solution of the reactants in benzene led to formation of the intermediate bromo enamine **21** (isolated and identified by mass spectrum) with its concentration maximized after 22 h and its complete disappearance after 72 h at room temperature, or at 20 min and 3 h, respectively, at reflux. Vincadifformine was slowly generated at room temperature, but it appeared after 7 min at reflux and its concentration in refluxing benzene was maximized after 27 h. The formation of precipitates (presumably in part the spiroenammonium intermediate **22**) could be seen during the course of the reaction. Vincadifformine (**1a**) was isolated in about 23% yield from such reaction mixtures. However, when dimethylformamide at room temperature or methanol at 40 °C were used as solvent, to facilitate solution of the spiro salt **22**, and auxiliary bases such as potassium carbonate or triethylamine were added to promote the fragmentation reaction of the ammonium salt **22**, the yield of vincadifformine (**1a**) could be increased to 70%.

This last step of the synthetic sequence thus demonstrates that the previously postulated biogenetic secodine intermediate **7** can be generated and that it indeed undergoes the biogenetically proposed stereospecific cyclization to vincadifformine (**1a**) in good yield. With an overall yield of vincadifformine from the tetrahydrocarboline **17** above 50%, the synthetic reaction sequence compares quite favorably with the previously reported vincadifformine syntheses[15,16] and the biomimetically relevant synthesis of minovine.[17]

Experimental Section

4a-Chloro-2-methyl-1,2,3,4-tetrahydro-4a*H*-pyrido[3,4-*b*]indolenine (9a). *N*-Methyltetrahydro-β-carboline (2-methyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole)[18] **8** was alternatively prepared in 33% overall yield by methylation of β-carboline[19] and sodium borohydride reduction[20] of the resultant carbolinium salt. To a solution of 0.930 g (5 mmol) of **8** in 170 mL of dichloromethane containing triethylamine (550 μL), *tert*-butyl hypochlorite (550 μL) was added. The mixture was stirred at room temperature for 1 h, then it was washed with ice water, passed through phase separating paper (Whatman No. 1PS), and concentrated under reduced pressure to a volume of about 10 mL. A precipitate of unreacted starting indole separated and was filtered off (213 mg). The filtrate was evaporated to dryness to give the chloroindolenine **9a** (862 mg, 99%) as a dark oil which solidified on standing in the freezer. Further purification was not attempted: IR (CCl_4) ν 3055, 2935, 2835, 2785, 1600, 1451, 1345, 1250, 1135, 1120, 1060, 1045, 1000, 955, 870, 810 cm^{-1}. NMR ($CDCl_3$) δ 7.3–6.9 (4 H, aromatic), 3.31 (AB q, J_{AB} = 11 Hz, protons at C_1, 2 H), 7.65–7.55 (2 H), 2.26 (s, 3 H), 2.45–1.45 (2 H); UV (EtOH) λ (ε) 226 (8800), 286 (1100).

Reaction of 4a-Chloro-2-methyl-1,2,3,4-tetrahydro-4a*H*-pyrido[3,4-*b*]indolenine (9a) with Thallium(I) Ethoxide. Compound **9a** (300 mg) was dissolved in anhydrous benzene (20 mL). Thallium(I) ethoxide (340 mg, 125 μL) was added and the mixture was stirred and refluxed for 18 h. The mixture was then cooled and filtered (Whatman GF/A) to remove precipitated thallium salts. Concentration under reduced pressure gave an oil (180 mg) which was mainly 2-ethoxy-1′-methylspiro(3*H*-indole-3,3′-pyrrolidine) (**10**) together with a little **11**. This oil was dissolved in methanol (10 mL) and 2 N hydrochloric acid was added dropwise to turbidity. After adding sufficient further methanol to disperse the turbidity, the mixture was allowed to stand overnight, diluted with brine, made basic with sodium hydroxide, and extracted with chloroform. The combined extracts were washed with water, dried, and concentrated to an oil (89 mg, 32%) which crystallized on standing. Recrystallization from *n*-heptane gave 1′-methylspiro(3*H*-indole-3,3′-pyrollidine)-2(1H)-one (**11**): mp 113–115 °C; IR (CCl_4) ν 3450, 3200, 3150, 3075, 2970, 2950, 2840, 2770, 1710, 1615, 1470, 915, 790, 640 cm^{-1}; NMR ($CDCl_3$) δ 8.44 (1 H), 7.32–6.70 (aromatic, 4 H), 2.8 (br s, 2 H), 2.40 (s, methyl, 3 H), 3.0–2.0 (complex absorption, 4 H); MS *m/e* 202 (M^+). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.44; H, 7.20; N, 13.84.

Reaction of 4a-Chloro-2-methyl-1,2,3,4-tetrahydro-4a*H*-pyrido[3,4-*b*]indolenine (9a) with Thallium(I) Diethyl Malonate Salt. A solution of **9a** (220 mg, 1 mmol) in dry benzene (20 mL) was added to thallium(I) diethyl malonate salt (364 mg, 1 mmol). The mixture was stirred vigorously and heated under reflux for 20 h, cooled, and filtered (Whatman GF/A) and the solvent was removed in vacuo to leave a dark sticky gum which was adsorbed onto silica gel. Elution with ethyl acetate–dichloromethane (40:60) furnished diethyl 3-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate (**14**; 75 mg, 22%). Recrystallization from *n*-heptane gave colorless prisms: mp 84–86 °C; IR (CCl_4) ν 3465, 3450, 3050, 2985, 2935, 2850, 2803, 1740, 1650, 1525, 1455, 1235, 800 cm^{-1}; NMR ($CDCl_3$) δ 8.2 (indole NH, 1 H), 7.4–6.8 (aromatic 4 H), 4.18 (q, 4 H), 3.36 (s, protons at C_4, 2 H), 2.84 (apparent nine-line system, AA′BB′ for protons at C_1 and C_2, 4 H), 2.24 (s, 3 H) 1.25 (t, 6 H); in benzene the signal for the C_4 protons is considerably broadened, and the protons at C_1 and C_2 are a more usual AA′BB′ system; UV (EtOH) λ (ε) 235 (34 000), 285 (7950), 293 (6900), 340 nm (550); MS *m/e* (%) 344 (90), 288 (58), 227 (100), 208 (66), 184 (41), 153 (61). Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.11; H, 7.30; N, 7.96.

2-Benzoyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole. Tetrahydro-β-carboline[21] (7 g) was dissolved in dry pyridine (35 mL) and a solution of benzoyl chloride (7 mL) in dry benzene (30 mL) was added over 30 min to the stirred mixture. After heating at reflux for 30 min the reaction mixture was poured into water and extracted with chloroform. The combined chloroform extracts were washed with ice cold 2 N hydrochloric acid, water, 3 N potassium carbonate solution, and brine, and then dried over potassium carbonate. Removal of the solvent gave an oil which was triturated with toluene. Once crystallization had begun, *n*-heptane was added. Filtration gave the amide (10.55 g, 94%) as a pale yellow solid. The analytical sample was recrystallized from aqueous ethanol with the aid of charcoal: mp 155–156 °C; IR ($CHCl_3$) ν 3470, 3060, 3020, 2925, 2860, 1625, 1620, 1575, 1490, 1460, 1435, 1305, 1205, 1150, 1045, 1025, 980 cm^{-1}; NMR ($CDCl_3$) δ 8.6 (indole NH, 1 H), 7.6–6.9 (aromatic, 9 H), 4.8 (br s, C_1 protons, 2 H), 3.7 (br s, C protons, 2 H), 2.8 (br s, C_4 protons, 2 H); MS (80 eV) *m/e* 276 (8), 262 (16), 168 (15) 143 (100), 105 (15), 91 (21), 77

(16), 44 (44), 40 (71). Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.24; H, 5.92; N, 10.18.

2-Benzyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (17). 2-Benzoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-*b*]indole (10.5 g, 38.5 mmol) dissolved in tetrahydrofuran (150 mL) was added over 1 h to a stirred mixture of tetrahydrofuran (300 mL) and lithium aluminum hydride (1 M solution in ether, 42.5 mL) under a blanket of dry nitrogen. When addition was complete, the mixture was heated to reflux for 6 h. After 12 h at room temperature magnesium sulfate heptahydrate (50 g) was added, with stirring, to destroy excess hydride. After stirring for 12 h the solids were filtered off and the solvent was evaporated to give the product, mp 140–142 °C (reported[4] mp 142 °C), as a white solid (9.15 g, 91.5%).

4a-Chloro-2-benzyl-1,2,3,4-tetrahydro-1*H*-pyrido[3,4-*b*]-indolenine (9b). This compound was prepared from the tetrahydro-β-carboline **17** (1.3 g, 5 mmol) in dry benzene (100 mL) with triethylamine (550 μL) and *tert*-butyl hypochlorite (550 μL) as described above. The resultant solution of **9b** was normally used directly for the next step; however, the compound could be isolated, though it appeared to be less stable than the 2-methyl compound. Removal of the solvent from the reaction mixture in vacuo gave the chloroindolenine **9b** (1.45 g, 98%) as a dark oil: NMR (CCl_4) δ 7.5–7.0 (aromatic, 9 H), 3.58 (s, benzyl CH_2, 2 H), 3.53 (AB q, J_{AB} = 11 Hz, protons at C_1, 2 H), 2.8–2.6 (2 H), 2.55–2.48 (1 H), 2.0–1.6 (1 H).

***tert*-Butyl Methyl 3-Benzyl-1,2,3,4,5,6-hexahydroazepino-[4,5-*b*]indole-5,5-dicarboxylate (16).** The chloroindolenine **9b** was prepared by dissolving *N*-benzyltetrahydrocarboline **17** (3.522 g, 13.44 mmol) in 100 mL of dry benzene and cooling to 5 °C. To the cold stirring solution was added dry triethylamine (1.16 g, 10 mmol, 1.6 mL) followed by dropwise addition of *tert*-butyl hypochlorite (1.458 g, 13.44 mmol, 1.6 mL). The reaction was kept in an ice bath for 1.5 h, then poured into water at 0 °C (20 mL). The benzene layer was separated and dried over sodium sulfate. The solution was filtered and the volume reduce to one half by vacuum evaporation. Dry benzene was added to a total volume of ~100 mL, then thallium *tert*-butyl methyl malonate (5.28 g, 14 mmol) was added and the stirred solution refluxed for 36 h. The reaction was cooled to room temperature and filtered through glass fiber paper. The solvent was removed and the residue adsorbed onto silica gel (20 g, Woelm Activity III for dry column chromatography). The adsorbed material was placed on top of a 6 in × 1.5 in. column of the dry column silica gel and eluted with dichloromethane. The first 20 mL was discarded and the product was collected in the next 150 mL (3.69 g, 63.3%): maximum yield on a larger scale, 85%; recrystallized from aqueous methanol; mp 118–120 °C; IR ($CHCl_3$) ν 3460, 3440, 3080, 3050, 3020, 2995, 2975, 2940, 2820, 1730, 1610, 1445, 1365, 1250, 1150, 1025, 840, 695 cm^{-1}; NMR ($CDCl_3$) δ 1.44 (s, 9 H), 2.82 (br s, 4 H), 3.60 (s, 2 H), 3.66 (s, 3 H), 3.76 (s, 2 H), 6.84–7.4 (m, 9 H), 8.36 (br s, 1 H); mass spectrum (80 eV) *m/e* (rel intensity) 434 (7), 334 (30), 216 (57), 156 (57), 91 (68), 59 (78), 56 (76), 44 (81), 41 (78), 40 (100). Anal Calcd for $C_{26}H_{30}N_2O_4$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.97; H, 7.03; N, 6.16.

Methyl 3-Benzyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate. The *tert*-butyl ester **16** (1.890 g, 4.35 mmol) was dissolved in 80 mL of 1,2-dichloroethane and the system flushed with nitrogen. Anhydrous trifluoroacetic acid (1.6 mL) was added via syringe through a rubber septum. The solution was stirred at reflux for 3.5 h. The hot reaction mixture was poured into 100 mL of cold (saturated) aqueous sodium carbonate. The layers were separated and the aqueous phase was extracted with 50 mL of dichloroethane. The combined organic phases were washed with (saturated) sodium carbonate solution and filtered through phase separating paper onto anhydrous potassium carbonate. Filtration and evaporation of the solvent produced a brown oil which was triturated with ethyl acetate–heptane to induce crystallization. The off-white solid was collected in two crops to yield 1.219 g (84%) of decarboxylated amine. The compound was recrystallized twice from aqueous ethanol for analysis: mp 135–135.5 °C; IR ($CHCl_3$) ν 3480, 3075, 3045, 2940, 2840, 1740, 1600, 1500, 1460, 1435, 1350, 1275, 1230, 1220, 1200, 1163, 1026 cm^{-1}; NMR ($CDCl_3$) δ 2.94 (br s, 4 H), 3.24 (m, 2 H), 3.76 (s, 3 H), 3.88 (s, 2 H), 4.16 (m, 1 H), 6.96–7.7 (m, 9 H), 8.68 (br s, 1 H); mass spectrum (80 eV) *m/e* (rel intensity) 334 (M^+, 37), 216 (100), 156 (61), 91 (49), 42 (32). Anal Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.63; H, 6.90; N, 8.41.

Methyl *tert*-Butyl 1,2,3,4,5,6-Hexahydroazepino[4,5-*b*]indole-5,5-dicarboxylate. A solution of *N*-benzylamine **16** (202 mg, 0.465 mmol) in dry acetic acid (7.5 mL) was hydrogenated under 1 atm pressure of hydrogen with 5% Pd/C catalyst (22 mg) for 1.5 h. The catalyst was filtered and washed with hot methanol. The solvent was removed from the filtrate by evaporation, leaving a light yellow oil which was dissolved in dichloromethane (50 mL). The solution was cooled to 0 °C, 10% aqueous NaOH (25 mL) was added, and the solution was stirred vigorously for 10 min. The organic phase was separated and dried over anhydrous potassium carbonate. The solution was filtered and the solvent evaporated to a light yellow oil which resisted all attempts at crystallization, but was pure debenzylated diester amine (155 mg, 97%): IR ($CDCl_3$) ν 3445, 3435, 3035, 2975, 2915, 1730, 1615, 1455, 1430, 1365, 1250, 1140, 1020, 840, 800 cm^{-1}; NMR ($CDCl_3$) δ 1.48 (s, 9 H), 2.24 (s, 1 H), 2.96 (m, 2 H), 3.16 (m, 2 H), 3.72 (m, 2 H), 3.78 (s, 3 H), 7.04–7.60 (m, 4 H), 3.88 (br s, 1 H); mass spectrum (80 eV) *m/e* (rel intensity) 344 (M^+, 100%), 245 (82), 229 (56), 216 (96), 215 (87), 203 (87), 171 (67), 155 (74).

Methyl 1,2,3,4,5,6-Hexahydroazepino[4,5-*b*]indole-5-carboxylate (20). The monoester benzylamine (915 mg, 2.74 mmol) was dissolved in 50 mL of glacial acetic acid and 100 mg of 5% Pd/C catalyst was added. The mixture was hydrogenated under 1 atm pressure for 18 h, then filtered through glass fiber paper. The catalyst was washed with 50 mL of hot methanol and the combined filtrates were evaporated to an oily residue. The residue was dissolved in 75 mL of chloroform and 100 mL of (saturated) aqueous sodium carbonate was added. The two-phase system was stirred vigorously for 15 min and the layers were then separated. The aqueous phase was washed with chloroform and the combined chloroform phases were washed with brine, and then filtered through phase separating paper onto anhydrous potassium carbonate. The material was filtered and the solvent evaporated, leaving a thick oily residue which was solidified by trituration with ethyl acetate–heptane. The material was filtered yielding 532 mg (80%) of debenzylated amine. The mother liquor was chromatographed on silica gel with dichloromethane as eluent, producing another 87 mg of material for a combined yield of 93%. The compound can be recrystallized from ethyl acetate–heptane; mp 138–139 °C; IR ($CHCl_3$) ν 3465, 2950, 2925, 1735, 1630, 1460, 1435, 1220, 1160, 1015 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (br s, 4 H), 8.48 (br s, 1 H); mass spectrum (80 eV) *m/e* (rel intensity) 244 (M^+, 58), 215 (29), 202 (100), 170 (31), 156 (26), 142 (35), 43 (80), 42 (30).

(±)-Vincadifformine (1a). Method 1. The bromo aldehyde **23** (194.5 mg, 1 mmol) was dissolved in 6 mL of dry methanol under a nitrogen atmosphere and 123 mg (0.50 mmol) of amine **20** was added in 6 mL of methanol. The mixture was stirred at room temperature for 1 h, then dry triethylamine (0.5 mL) was added and the solution was warmed to 40 °C for 12 h. The reaction was cooled to room temperature and the solvent was evaporated. The residue was taken up in CH_2Cl_2 (40 mL) and extracted with (saturated) aqueous sodium carbonate (10 mL). The organic layer was dried over anhydrous potassium carbonate and filtered. The solvent was evaporated and the residue was spotted on a preparative TLC plate (2 mm, Merck alumina) and developed with dichloromethane. The band at R_f 0.4–0.6 was eluted, resulting in 71 mg of pure (±)-vincadifformine as a white solid.[22] The alkaloid was recrystallized from 95% ethanol: mp 124–125 °C (lit.[15] 124–125 °C); IR ($CHCl_3$) ν 3420, 3360, 2930, 2850, 2775, 1665, 1605, 1470, 1460, 1432, 1290, 1275, 1250, 1235, 1155, 1110, 1045 cm^{-1}; NMR ($CDCl_3$) δ 1.6–3.6 (complex m, 18 H), 3.76 (s, 3 H), 6.74–7.5 (m, 4 H), 8.96 (br s, 1 H); UV (EtOH) λ (log ε) 225 (4.12), 297 (3.15), 327 nm (4.06); mass spectrum (80 eV) *m/e* (rel intensity) 338 (M^+, 67), 124 (100); yield on a larger scale, 70%.

Method 2. The amine **20** (125.8 mg, 0.515 mmol) was dissolved in dry benzene (3 mL) and aldehyde **23** (97.5 mg, 0.505 mmol) was added. The mixture was stirred at 45 °C for 51 h then dissolved in ether–dichloromethane (1:4). The solution was extracted with 1.0 N HCl and the aqueous phase was washed with benzene. The aqueous layer was adjusted to pH 11–12 with 10% aqueous sodium hydroxide and extracted with chloroform. After drying and concentration, a light yellow oil remained (90 mg) which was separated by PTLC (Merck alumina, 5% methanol–95% dichloromethane). The band at R_f 0.5–0.7 was isolated and eluted, yielding (±)-vincadifformine (45 mg, 26%) as an oil which crystallized upon seeding.

High-pressure liquid chromatography analysis of vincadifformine formation is given in Table I.

Methyl 4-Dimethoxymethylhexanoate. To a solution containing anhydrous methanol (70 mL) and concentrated sulfuric acid (3 drops) was added methyl 4-formylhexanoate (**25**;[11] 10.2 g, 64.5 mmol). The solution was stirred at room temperature for 24 h and then solid potassium carbonate was added to neutralize the acid. Most of the solvent was evaporated under vacuum, water (100 mL) was added, and the solution was extracted twice with hexane (50 mL) and twice with ether. The organic phases were combined and dried over anhydrous magnesium sulfate. The solvent was evaporated under vacuum, yielding the desired acetal with no aldehyde contamination (12.27 g, 93.2%): bp 60–70 °C (Kugelrohr, 0.1 mm); IR (neat) ν 2950, 2820, 1730, 1430, 1170, 1105, 1070, 960, 885 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (t, 3 H), 1.24–1.96 (m, 5 H), 2.34 (t, 2 H), 3.32 (s, 6 H), 3.82 (s, 3 H), 4.10 (d, 1 H); mass spectrum (80 eV) *m/e* (rel intensity) 204 (M^+, 1), 203 (6), 173 (100), 141 (99), 109 (73), 99 (90), 75 (97).

Table I. High Pressure Liquid Chromatography Analysis[a] of Vincadifformine Formation

trial	reactants[b]	solvent (mL)	temp, °C	time, h	comments
1	1 equiv amine **20** 1 equiv aldehyde **23**	benzene (1)	80	24	buff ppt occurs; LC of filtrate indicates only vincadifformine; ppt used in run 5
2	1 equiv amine **20** 1 equiv aldehyde **23**	benzene (1)	room temp	36	ppt occurs; IR 1735, 1700, 1615 cm^{-1}; LC (t = 24 h) indicated two components: 1[c] (ret time 6 min), presumably uncyclized enamine, MS m/e 418, 420; 2 (ret time 8 min), identified as vincadifformine
3	1 equiv amine **20** 1 equiv aldehyde **23**	benzene (1)	room temp	48	slight ppt; peak 1 reaches max in 20–24 h, disappears within 72 h; peak 2 reaches max in 24–36 h, does not change afterwards
4	1 equiv amine **20** 1 equiv aldehyde **23**	benzene (1)	80	48	ppt occurs; LC indicates vincadifformine appears within 7 min; increases for 24–30 h; peak 1 max in 20 min then disappears in 3 h
5	ppt from run 1	benzene (1) NEt_3 (0.1)	80	24	LC indicates increase in vincadifformine concentration over 24 h; some ppt remains
6	reaction mixture from run 4	benzene (1) NEt_3 (0.1)	room temp 80	1 30	room temp does not change vincadifformine concentration; reflux does not cause any change
7	reaction mixture from run 3	benzene (1) NEt_3 (0.1) DMF (0.1)	room temp	72	LC indicates slow formation of vincadifformine, but reaction is complicated by new reaction products
8	1 equiv amine **20** 1 equiv aldehyde **23**	CH_3CN, then add NEt_3 (0.1)	room temp room temp reflux	24 3 2	LC indicates slower formation of 1 and 2 components; addition of base has no effect; peak 1 disappears with heating; workup yields mixture
9	1 equiv amine **20** 1 equiv aldehyde **23**	dioxane, then add K_2CO_3 (20 mg)	room temp room temp	1 24	reaction turns dark color; LC indicates much slower formation of components 1 and 2; workup yields mixture
10	0.5 equiv amine **20** 1 equiv aldehyde **23**	benzene (0.9) DMF (0.1) K_2CO_3 (20 mg)	room temp	24	ppt still forms; same components as run 3; workup gave 65% yield of vincadifformine as an oil
11	1 equiv amine **20** 1 equiv aldehyde **23**	benzene p-TsOH (cat)	room temp	14	LC indicates slow formation of vincadifformine; reaction complicated by additional components; workup yielded a mixture
12	1 equiv amine **20** 1 equiv aldehyde **23**	MeOH (1) add NEt_3 (0.1)	room temp room temp 40	3 2 12	no ppt; no discoloration; peak 1 (6 min) max in 3 h; addition of base (t = 3 h) causes rapid formation of vincadifformine; workup produced 67% yield of vincadifformine as an oil

[a] Column, C_{18}-Bondapack (Waters), 4 mm × 30 cm; solvent, 60% acetonitrile–40% 0.01 M aqueous ammonium carbonate; flow rate, 1.5 mL/min. [b] 1 equiv of amine *20* equals 20 mg; 1 equiv of aldehyde **23** equals 15.8 mg (12 μL). [c] While rapid volatilization of component 1 in the mass spectrometer produced the parent ion for the bromo enamine **21**, prior heating in the inlet chamber resulted in loss of this mass peak and generation of peaks corresponding to vincadifformine.

Ethyl 4-Diethoxymethylhexanoate. The ethyl acetal was prepared from the aldehyde in 84% yield in the same manner as the methyl acetal. The ester group exchanges under these conditions: bp 90–100 °C (Kugelrohr, 0.1 mm); NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.23 (t, 6 H), 1.33 (t, 3 H), 1.25–2.06 (m, 5 H), 2.43 (t, 2 H), 3.63 (q, 4 H), 4.23 (q, 2 H), 4.40 (d, 1 H).

4-Dimethoxymethyl-1-hexanol (26a). The methyl acetal ester (9.8 g, 48 mmol) was dissolved in THF (20 mL) and added dropwise at 0 °C to an ether solution of $LiAlH_4$ (50 mL of a 1 M solution). After addition was completed (~30 min) the reaction was allowed to warm to room temperature and water (1 mL) was added slowly. Enough 20% aqueous KOH was added to dissolve the solid and the solution was extracted five times with ether (25 mL). The ether extracts were washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded the desired alcohol **26a** (7.86 g, 93%) as a clear colorless liquid: IR (neat) ν 3400, 2940, 2830, 1460, 1380, 1190, 1110, 1060, 960 cm^{-1}; NMR ($CDCl_3$) δ 0.9 (t, 3 H), 1.4 (m, 7 H), 2.9 (br s, 1 H), 3.2 (s, 6 H), 3.42 (t, 2 H), 4.15 (d, 1 H).

4-Diethoxymethyl-1-hexanol. A solution of the ethyl acetal ester (9.367 g, 38 mmol) in THF (40 mL) was added at 0 °C to a solution of $LiAlH_4$ in ether (40 mL of a 1 M solution) over 0.5 h. The reaction was refluxed for 1 h and then allowed to cool to room temperature. Magnesium sulfate heptahydrate (9.86 g, 40 mmol) was added and the reaction was stirred vigorously 12 h. The solid was filtered and washed with ether several times. The combined filtrate and washings were washed with 10% aqueous KOH (10 mL) and brine (10 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by Kugelrohr distillation (bp 90–100 °C, 0.1 mm) produced the hydroxy acetal (7.0 g, 90.3%): IR (neat) ν 3400, 2985, 2940, 1880, 1460, 1380, 1115, 1065, 730 cm^{-1}; NMR ($CDCl_3$) δ 0.93 (t, 3 H), 1.23 (t, 6 H), 1.16–1.83 (m, 7 H), 2.16 (br s, 1 H), 3.66 (m, 6 H), 4.40 (d, 1 H).

1-Bromo-4-dimethoxymethylhexane. Carbon tetrabromide (1.824 g, 5.5 mmol) and triphenylphosphine (1.443 g, 5.5 mmol) in ether (15 mL) were refluxed 0.5 h, and then cooled to room temperature. Hydroxy acetal **26a** in ether (6 mL) was added dropwise, resulting in rapid decolorization of the yellow slurry and precipitation of a buff-colored solid. The mixture was filtered through Celite and the solvent was removed under vacuum. The residue was placed under high vacuum (~10^{-3} mm) to remove the excess carbon tetrabromide and the bromoform byproduct. The distillation pot was heated to 50–60 °C and the distillate was collected with the aid of a dry ice trap. The distillate was the desired bromo acetal (700 mg, 66%) contaminated with a trace of carbon tetrabromide and bromoform. This compound was used without further purification for hydrolysis.

Hydrolysis to **23** was achieved by stirring the bromo acetal in THF–1 N HCl (10:1, 6 mL) at room temperature for 24 h (94% yield).

For comparison, the bromo acetal was prepared from the bromo aldehyde **23**. The bromo aldehyde (52.4 mg, 0.27 mmol) was dissolved in dry methanol (1 mL) and one crystal of p-toluenesulfonic acid was added. The solution was stirred at room temperature for 48 h and then poured into dichloromethane (15 mL). The solution was washed with saturated aqueous sodium carbonate (5 mL) and dried over anhydrous sodium sulfate. Concentration yielded the acetal (60.4 mg, 93.2%) as a colorless oil; IR (neat) ν 2960, 1460, 1110, 1070 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (t, 3 H), 1.20–2.04 (m, 7 H), 3.38 (s, 6 H), 3.40 (t, 2 H), 4.16 (d, 1 H); mass spectrum (80 eV) m/e (rel intensity) 238, 240 (M^+, 0.01), 207, 209 (38, 37), 75 (100).

2-Methoxy-3-ethyltetrahydropyran (27). A solution of alcohol

26a (285 mg, 1.62 mmol) in ether (2 mL) was cooled to 0 °C. Phosphorous tribromide (161 mg, 0.6 mmol) was added dropwise and the mixture was stirred at 0 °C for 3 h. The reaction mixture was warmed to room temperature and stirred for another 12 h. Pentane (2 mL) was added and the liquid phase was decanted. A colorless oily residue was left after evaporation of the solvent at room temperature and 1 atm pressure. Spectral data for the product indicated the tetrahydropyran structure (**27**) as a mixture of cis and trans isomers (172 mg, 74%); IR (neat) ν 2960, 2940, 2875, 1470, 1060, 1045, 950 cm^{-1}; NMR ($CDCl_3$) δ 0.94 (m, 3 H), 1.0–2.0 (m, 7 H), 3.38, 3.46 (s, 3 H), 3.30–4.14 (m, 2 H), 4.52 (br s, 1 H); mass spectrum (80 eV) *m/e* (rel intensity) 144 (M^+, 6), 113 (25), 97 (19), 84 (27), 71 (22), 61 (56), 56 (100), 55 (39), 41 (53).

1-(Methanesulfonyl)-4-(diethoxymethyl)hexane. The mesylate of the ethyl acetal alcohol was prepared (100% yield) in the same manner as the methyl acetal mesylate **26c:** IR (neat) ν 2965, 2940, 2875, 1460, 1360, 1180, 1070, 975 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (t, 3 H), 1.20 (t, 6 H), 1.0–2.0 (m, 7 H), 3.02 (s, 3 H), 3.28–3.84 (m, 4 H), 4.16–4.26 (m, 3 H).

The product was hydrolyzed to the aldehyde by refluxing it in ether (30 mL) and 1.0 N HCl (6 mL) for 12 h. The aldehyde was converted to a DNP derivative for analysis, mp 99–100 °C. Anal Calcd for $C_{14}H_{20}N_4O_7S$: C, 43.29; H, 5.19; N, 14.43. Found: C, 43.28; H, 5.34; N, 14.48.

1-(Methanesulfonyl)-4-(dimethoxymethyl)hexane (26c). The acetal alcohol **26a** (13.55 g, 77 mmol) was dissolved in dry dichloromethane (0.2 M, 385 mL) and dry triethylamine (11.66 g, 115 mmol, 1.5 equiv) was added. The solution was cooled to −20 °C in an ice–salt bath and methanesulfonyl chloride (12.35 g, 108 mmol, 1.4 equiv) was added dropwise with stirring over 15 min. The solution was stirred an additional 0.5 h at −15 °C and then poured into a separatory funnel. The solution was washed with ice water (2 × 25 mL), cold 1.0 N HCl (2 × 25 mL), saturated sodium bicarbonate (2 × 25 mL), and finally brine (25 mL). The organic phase was dried over anhydrous magnesium sulfate and then filtered. Evaporation of the solvent yielded pure mesylate **26c** (19.43 g, 99.3%): IR (neat) ν 2970, 2945, 1465, 1360, 1180, 925, 815 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (t, 3 H), 1.20–1.92 (m, 7 H), 3.06 (s, 3 H), 3.44 (s, 6 H), 4.22–4.36 (m, 3 H).

2-Ethyl-5-bromopentanal (23). Anhydrous lithium bromide (11.39 g, 131 mmol) was dissolved in dry DMF (100 mL) and the solution was allowed to cool to room temperature. The LiBr/DMF solution was then siphoned into a flask (via double-tipped needle) containing mesylate **26c** (7.39 g, 29.1 mmol) and a magnetic stir bar. The mixture was heated to 40 °C for 6 h and cooled to room temperature. The reaction mixture was then poured into ice water (750 mL) and extracted with distilled pentane (4 × 100 mL). The pentane phase was washed with 1.0 N HCl (20 mL), water (25 mL), and saturated sodium bicarbonate (30 mL), and then dried over anhydrous sodium sulfate. Evaporation of the solvent and distillation of the residue gave bromo aldehyde **23** (4.72 g, 84%): bp 46–48 °C (0.01 nm); IR (neat) ν 2955, 2930, 2870, 2710, 1715, 1455, 1375, 1240 cm^{-1}; NMR ($CDCl_3$) δ 0.96 (t, 3 H), 1.28–2.12 (m, 7 H), 2.28 (m, 1 H), 3.46 (t, 2 H), 9.70 (d, 1 H, J = 2 Hz); mass spectrum (80 eV) *m/e* (rel intensity) 194 (M^+, 3.6), 192 (M^+, 3.9), 166 (48), 164 (57), 123 (29), 121 (32), 113 (100).

The 2,4-DNP was prepared for analysis and recrystallized from 95% ethanol, mp 105–105.5 °C. Anal. Calcd for $C_{13}H_{17}N_4O_4Br$: C, 41.84; H, 4.59; N, 15.01; Br, 21.47. Found: C, 41.91; H, 4.82; N, 15.06; Br, 21.67.

2-Ethyl-6-azoniaspiro[5.6]dodec-1-ene Bromide (24a). A solution of bromo aldehyde **23** (1.37 g, 7.1 mmol) and hexamethyleneimine (694 mg, 7 mmol) in dry benzene (30 mL) was refluxed for 12 h using a Dean–Stark trap to remove the water. A white crystalline solid precipitated and was filtered after cooling the reaction to room temperature. The solid was dried under vacuum, resulting in 1.5 g (77.3%) of spiro salt **24a:** mp 128–130 °C; NMR ($CDCl_3$) δ 1.10 (t, 3 H), 1.86–2.22 (m, 14 H), 3.82 (m, 6 H), 6.38 (br s, 1 H).

2-Ethyl-6-azoniaspiro[5.6]dodec-1-ene Tetraphenylborate (24b). To a solution of spiroamine salt **24a** (100 mg, 0.364 mmol) in 5 mL of water was added a solution of sodium tetraphenylborate (125 mg, 0.364 mmol) in 20 mL of water with vigorous stirring. The mixture was allowed to stand for 15 min, then the precipitated tetraphenylborate salt was filtered and washed with ether. The dried salt (167 mg, 89.4%) was recrystallized from acetone: mp 215–216 °C dec; NMR (acetone-d_6) δ 1.10 (t, 3 H), 1.86–2.22 (m, 14 H), 3.82 (m, 6 H), 6.38 (br s, 1 H), 6.80–7.56 (m, 20 H). Anal. Calcd for $C_{37}H_{44}NB$: C, 86.53; H, 8.63; N, 2.72. Found: C, 86.42; H, 8.57; N, 2.57.

3-Benzyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole (18). The *tert*-butyl methyl diester **16** (72.5 mg) was dissolved in methanol (1.5 mL) and 36% hydrochloric acid (1.5 mL) was added. The mixture was refluxed for 1 h, and then cooled in ice and made basic with ice cold potassium hydroxide. The product was extracted with ether and the organic extracts, after drying, were concentrated to leave a brown solid (35 mg, 73%) which was recrystallized from aqueous ethanol, mp and mmp 115—117 °C.[6] The solid was identical in all respects with authentic 3-benzyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole.[6]

Acknowledgment. This work was supported by the National Institutes of Health Research Grant RO1 CA 12010 from the National Cancer Institute.

Registry No.—(±)-**1a**, 18374-17-9; **8**, 13100-00-0; **9a**, 66859-15-2; **9b**, 66859-16-3; **10**, 66859-17-4; **11**, 66859-18-5; **14**, 66859-19-6; **16**, 66859-20-9; **16** debenzyl derivative, 66859-21-0; **7**, 47064-53-9; **17** debenzyl derivative, 16502-01-5; **18**, 7546-77-2; **20**, 66859-22-1; hexamethylenemine, 111-49-9; **20** 3-benzyl derivative, 66859-30-1; **23**, 64395-11-5; **23** DNP derivative, 66859-23-2; **24a**, 66859-24-3; **24b**, 66859-26-5; **25**, 66757-48-0; **26a**, 66859-27-6; **26c**, 66859-28-7; **27**, 66859-29-8; thallium(I) diethyl malenate salt 66859-38-9; benzoyl chloride, 98-88-4; thallium *tert*-butyl methyl malonate, 66859-39-0; methyl 4-dimethoxymethylhexanoate, 66859-31-2; ethyl 4-diethoxymethylhexanoate, 66859-32-3; 4-diethoxymethyl-1-bromo-4-(dimethoxymethyl)hexane, 66859-34-5; 1-(methanesulfonoyl)-4-(diethoxymethyl)hexane, 66859-35-6; 1-(methanesulfonyl)-4-(diethoxymethyl)hexane DNP derivative, 66859-08-3; methanesulfonyl chloride 124-63-0; 2-benzoyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole, 66859-09-4; 1-(methanesulfonyl)-4-formylhexane, 66859-10-7.

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Synthesis of L-2-Amino-4-methoxy-*trans*-but-3-enoic Acid

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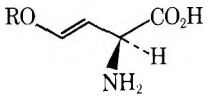
Received May 5, 1978

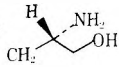
The naturally occurring amino acid, L-2-amino-4-methoxy-*trans*-but-3-enoic acid (**1a**), was synthesized starting from the aspartic semialdehyde derivative **2**. Formation of the enol ether moiety was accomplished by conversion of acetal **3a** to the hemiacetal ester **3b**, followed by pyrolysis of **3b** to yield a mixture of trans and cis enol ethers **4**. A resolution of the synthetic material was achieved by selective enzymatic hydrolysis of the *N*-acetyl group with hog kidney acylase I. This procedure provides the pure natural product **1a**, as well as partially racemized D-amino acid **8**.

In recent years, there have been found in nature a number of amino acids **1** which are unusual in that they each contain an enol ether function. The first two compounds, **1a** and **1b**,



1a, R = CH_3
b, R = $CH_2CH_2NH_2$

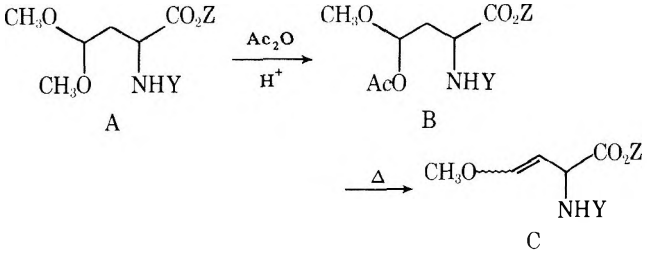
c, R =



were isolated and characterized by Scannell, Pruess, and co-workers.[1,2] The methyl enol ether **1a** was obtained from *Pseudomonas aeruginosa*,[1] while the aminoethyl enol ether **1b** was produced by an unidentified species of *Streptomyces*.[2] Rhizobitoxine (**1c**), the most complex member of this new group of amino acids, was isolated from *Rhizobium japonicum* and its structure determined by Owens and co-workers.[3,4] More recently, we have assigned the absolute configuration shown in structure **1c** to rhizobitoxine[5] and confirmed that assignment by synthesis.[6]

All three of these compounds were shown to strongly inhibit the production of ethylene by plant tissue.[2,7] Since ethylene plays a vital role in controlling certain plant life processes, this activity could be economically important.[8] In order that this area of study might be more fully explored, we have developed two potentially general methods for synthesizing members and analogues of this new class of amino acids. The first method is presented in the current paper and is illustrated by a synthesis of the methyl enol ether **1a**. The second is discussed in an accompanying paper and is illustrated by a synthesis of the racemic modification of the aminoethyl enol ether **1b**.[9]

In considering the synthesis of L-2-amino-4-methoxy-*trans*-but-3-enoic acid (**1a**), we felt that the critical steps would involve generation of the enol ether moiety in the presence of the potentially reactive amino acid portion of the molecule. We present as a solution to this problem a mild two-step sequence for the synthesis of enol ethers. The method



utilizes the conversion of an acetal A to a hemiacetal ester B, followed by pyrolysis of B under neutral conditions to yield an enol ether C. The pyrolysis of hemiacetal esters to yield enol ethers has been discussed previously in the literature.[10] Until now, however, there has not been a convenient way to make the starting esters B. In the present case, the easy and efficient production of B makes the overall sequence viable.

Aldehyde **2**, which is available by a published procedure,[11] served as our starting material (see Scheme I). Acetalization to give **3a** was accomplished in 77% yield by heating **2** at reflux temperature in methanol/trimethyl orthoformate with ammonium chloride catalyst. The dimethyl acetal **3a** seemed like a suitable precursor for the enol ether function. It was found, however, that the conditions required for the acid-catalyzed elimination of methanol from **3a** were so severe that the engendered enol ether did not survive.

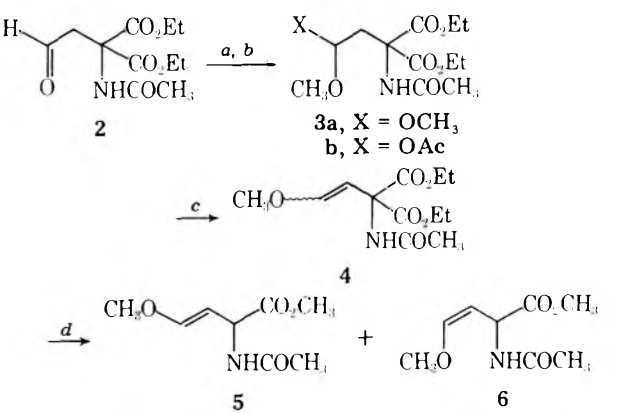
This problem was circumvented by resorting to the more labile hemiacetal ester **3b**. Thus, treatment of **3a** with acetic anhydride and dry cationic exchange resin at 65 °C cleanly effected the exchange of one methoxy group for an acetoxy group. Then, following the method of Erickson,[10] pyrolysis of the resultant hemiacetal ester **3b** at 185 °C (17 mm) gave a mixture of the trans and cis enol ethers **4** (79% from **3a**).

Dissolution of enol ethers **4** in methanolic sodium methoxide caused the removal of one ethoxycarbonyl group, resulting in a mixture of enol ethers **5** and **6**. The two compounds were separated by silica gel chromatography followed by crystallization to yield the pure trans and cis compounds **5** (39%) and **6** (12.9%).

Since the starting material **2** for the synthesis is achiral, the material in hand at this point, trans enol ether **5**, is racemic. The resolution of this substance, as well as the removal of its protecting groups, is described in the following section (see Scheme II).

Hydrolysis of the ester function in **5** with 1.05 equiv of lithium hydroxide gave the racemic lithium carboxylate salt. Incubation for 16 h at 39 °C of an aqueous solution of the salt and hog kidney acylase I effected selective hydrolysis of the L form of the *N*-acetylamino acid salt. The resultant mixture of L-amino acid **1a** and D-*N*-acetylamino acid **7** was separated by distribution between dilute hydrochloric acid (pH 2) and

Scheme I



[a] CH_3OH, $(CH_3O)_3CH$, NH_4Cl, reflux temperature. [b] Ac_2O H^+, 65 °C. [c] 185 °C (17 mm), 1.5 h. [d] $NaOCH_3$, CH_3OH.

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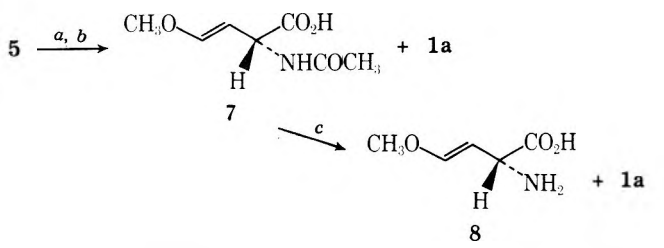
Scheme II



[a] LiOH. [b] Hog kidney acylase, 39 °C. [c] $NH_2NH_2 \cdot H_2O$ (85%), 70 °C.

ethyl acetate. The amino acid was isolated by cation exchange chromatography, followed by crystallization to give a substance (69.3% from **5**) which was shown to be identical with the naturally occurring amino acid **1a** by comparison with an authentic sample.[1,14]

The acetyl group of the D-*N*-acetylamino acid was removed by heating a solution of **7** in 85% hydrazine hydrate at 70 °C for 15 h. Removal of the hydrazine and trituration of the residue with ethanol gave an amino acid (46% yield from **5**) with the same gross structure as the methyl enol ether **1a**, as confirmed by spectral analysis. The specific rotation (see the Experimental Section) indicated that the substance consists of an 80% enantiomeric excess of the D-isomer **8**.

Experimental Section

General. Melting points were taken on a Kofler hot stage melting point apparatus (Reichert) and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 621 or a Beckman IR-9. Ultraviolet spectra were recorded on a Cary Model 16 spectrophotometer. Rotations were measured on a Perkin-Elmer 141 automatic polarimeter. Proton NMR spectra were obtained on Varian HA-100 and XL-100 instruments and are reported in parts per million downfield from internal or external tetramethylsilane. Elemental analyses and amino acid analyses were carried out under the supervision of Dr. F. Scheidl of our Microanalytical Laboratory.

Ethyl 2-Acetamido-2-ethoxycarbonyl-4,4-dimethoxybutyrate (3a). A solution consisting of 55 g (0.212 mol) of ethyl 2-acetamido-2-ethoxycarbonyl-4-oxobutyrate (**2**),[11] 134 g (1.26 mol) of trimethyl orthoformate, 1.1 g (0.02 mol) of ammonium chloride, and 880 mL of methanol was heated with magnetic stirring at reflux temperature for 48 h. The solution was allowed to cool to room temperature and diluted with ether (1500 mL). The resultant solution was washed three times with 450-mL portions of saturated sodium bicarbonate/brine (1:1) and two times with 400-mL portions of brine. The ether phase was dried over sodium sulfate and concentrated in vacuo, giving an oil which was distilled through a 4 in vacuum-jacketed Vigreux column to yield 52.6 g (77%) of **3a**: bp 138–143 °C (0.04 mm); IR ($CHCl_3$) 1738, 1683, 1598 cm^{-1}; NMR ($CDCl_3$) δ 6.86 (broad, 1 H, NH), 4.31 (t, 1 H, J = 6 Hz, $-CH_2CH(-O)_2$), 4.21 (q, 4 H, J = 8 Hz, $2CH_3CH_2O-$), 3.21 (s, 6 H, $2CH_3O-$), 2.68 (d, 2 H, J = 6 Hz, $-CH_2CH(-O)_2$), 2.03 (s, 3 H, CH_3CO-), 1.24 (t, 6 H, J = 8 Hz, $2CH_3CH_2O-$); mass spectrum, *m/e* 305 (M^+), 274, 260, 232, 217, 200, 158, 130, 75.

Anal. Calcd for $C_{13}H_{23}NO_7$: C, 51.14; H, 7.59; N, 4.59. Found: C, 51.16; H, 7.62; N, 4.54.

***dl*-Ethyl 2-Acetamido-4-acetoxy-2-ethoxycarbonyl-4-methoxybutyrate (3b).** To a solution under argon consisting of 34.8 g (0.114 mol) of **3a** and 144 mL of acetic anhydride was added 8.7 g of dry AG 50W-X4 cation exchange resin (100–200 mesh; H^+ form).[12] The resultant suspension was stirred magnetically at 65 °C for 1.5 h. The resin was removed by filtration through a sintered glass funnel, and the filtrate was concentrated in vacuo to yield **3b** as a pale yellow oil. A small sample gave the following spectral and analytical data after prolonged drying under vacuum (0.1 mm, 60 °C, 15 h): IR ($CHCl_3$) 3425, 1738, 1680, 1490 cm^{-1}; NMR ($CDCl_3$) δ 6.82 (broad, 1 H, NH), 5.73 (t, 1 H, J = 6 Hz, $-CH_2CH(-O)_2$), 4.25 (q, 4 H, J = 8 Hz, $2CH_3CH_2O-$), 3.32 (s, 3 H, CH_2O-), 2.80 (m, 2 H, $-CH_2CH(-O)_2$), 2.04 (s, 6 H, $2CH_3CO-$), 1.25 (t, 6 H, J = 8 Hz, $2CH_3CH_2O-$); mass spectrum, *m/e* 274, 260, 200, 158, 144, 116, 75.

Anal. Calcd for $C_{14}H_{23}NO_8$: C, 50.45; H, 6.96; N, 4.20. Found: C, 50.55; H, 6.87; N, 4.19.

***cis*- and *trans*-Ethyl 2-Acetamido-2-ethoxycarbonyl-4-methoxybut-3-enoate (4).** The crude hemiacetal ester **3b**, obtained from the previously described reaction, was heated under vacuum (17 mm) with magnetic stirring at 185 °C for 1.5 h. The resultant pyrolyzate was distilled through a 4 in vacuum-jacketed Vigreux column to yield 24.8 g (79% from **3a**) of a mixture consisting of the cis and trans isomers **4**: bp 138 °C (0.06 mm); NMR ($CDCl_3$) δ 6.93 (broad, NH), 6.45 (d, J = 13 Hz, trans $-OCH{=}CH-$), 5.95 (d, J = 6 Hz, cis $-OCH{=}CH-$), 5.38 (d, J = 13 Hz, trans $-OCH{=}CH-$), 5.33 (d, J = 6 Hz, cis $-OCH{=}CH-$), 4.22 (q, J = 7 Hz, CH_3CH_2O-), 3.56 (s, CH_3O-), 2.05 (s, CH_3CO-), 1.27 (t, J = 7 Hz, CH_3CH_2O-).

***dl*-Methyl 2-Acetamido-4-methoxy-*trans*-but-3-enoate (5) and *dl*-Methyl 2-Acetamido-4-methoxy-*cis*-but-3-enoate (6).** The mixture of distilled cis and trans enol ethers **4** (24.8 g, 0.091 mol) was dissolved in 350 mL of anhydrous methanol containing 2 g (0.037 mol) of sodium methoxide. The resultant basic solution (pH 10 by moist pHydrion paper)[13] was stirred under argon at ambient temperature for 24 h. The reaction mixture was neutralized with acetic acid and concentrated under reduced pressure to give an oily slurry. Addition of ether to the slurry caused the precipitation of sodium salts which were removed by filtration through a pad of diatomaceous earth. The filtrate was concentrated in vacuo to yield 17 g of an oil which was applied in ether solution (minimum volume) to a column (59 mm i.d.) containing an intimate mixture of 400 g of silica gel 60 (70–230 mesh; E. Merck Reagent catalogue #7734) and 133 g of silica gel PF-254 (E. Merck Reagent catalogue #7747). The column was developed with ether/methanol (98:2), and 20-mL size fractions were collected. The eluent was monitored by thin-layer chromatography on silica gel plates [ether/methanol (96:4); visualization with I_2]. Fractions 155–206 were combined and concentrated in vacuo, and the resultant residue was crystallized from ether/petroleum ether to yield 5.45 g (32%) of **5**: mp 47.5–49.5 °C; IR ($CHCl_3$) 3425, 1737, 1670, 1500 cm^{-1}; NMR ($CDCl_3$) δ 6.64 (d, 1 H, J = 13 Hz, $-OCH{=}CH-$), 6.15 (broad, 1 H, NH), 4.8 (m, 2 H, $-OCH{=}CHCH<$), 3.66 (s, 3 H, CH_3O-), 3.55 (s, 3 H, CH_3O-), 2.01 (s, 3 H, CH_3CO-); mass spectrum, *m/e* 187 (M^+), 155, 144, 128, 84.

Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.40; H, 7.03; N, 7.44.

The mother liquor from the above crystallization was combined with fractions 137–154 and 207–218. The solution was concentrated and the residue chromatographed on a column similar to the one just described. The appropriate fractions were concentrated, and the residue was crystallized from ether/petroleum ether to yield 1.2 g (7.0%) of **5**. A total yield of 39% was realized for **5**.

Fractions 219–336 were concentrated in vacuo, and the residue was crystallized from ether/petroleum ether to yield 2.2 g (12.9%) of **6**: mp 120–123 °C; IR ($CHCl_3$) 3440, 1735, 1675, 1515 cm^{-1}; NMR ($CDCl_3$) δ 6.32 (broad, 1 H, NH), 6.10 (d, 1 H, J = 7 Hz, $-OCH{=}CH-$), 5.28 (t, 1 H, J = 9 Hz, $-OCH{=}CHCH<$), 4.50 (dd, 1 H, J = 7 and 9 Hz, $-OCH{=}CH-$), 3.65 (s, 3 H, CH_3O-), 3.60 (s, 3 H, CH_3O-), 2.01 (s, 3 H, CH_3CO-); mass spectrum, *m/e* 187 (M^+), 155, 144, 128, 86.

Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.32; H, 6.94; N, 7.51.

L-2-Amino-4-methoxy-*trans*-but-3-enoic Acid (1a). A solution consisting of 5.0 g (0.027 mol) of **5**, 28 mL of 1 N lithium hydroxide, and 50 mL of methanol was allowed to stand at ambient temperature for 3 h. It was concentrated in vacuo, and the residue wash dissolved in 90 mL of deionized water. The pH was adjusted to 7.3 with 1 N hydrochloric acid, 18 mg of hog kidney acylase I (purchased from Sigma Chemical Co., catalogue #A-3010) was added, and the resultant solution was stirred magnetically at 39 °C for 16 h. The solution was then adjusted to pH 2 with 6 N hydrochloric acid and extracted with ethyl acetate. The aqueous phase was applied to an ion exchange column (AG 50W-X4; 100–200 mesh; pyridinium form; 250 mL of resin bed). The column was developed with water followed by 10% aqueous pyridine. The aqueous pyridine fraction was concentrated in vacuo, and the residue was crystallized from methanol to yield 1.2 g (69.3%) of **1a**: mp 225–235 °C dec; $[\alpha]^{25}_D$ +123° (c 0.7925, H_2O); NMR (D_2O) δ 7.33 (d, 1 H, J = 13 Hz, $-OCH{=}CH-$), 5.45 (dd, 1 H, J = 10 and 13 Hz, $-OCH{=}CH-$), 4.67 (d, 1 H, J = 10 Hz, $-OCH{=}CHCH<$), 4.11 (s, 3 H, CH_3O-); mass spectrum, *m/e* 86.

Anal. Calcd for $C_5H_9NO_3$: C, 45.80; H, 6.92; N, 10.68. Found: C, 45.65; H, 6.80; N, 10.89.

The synthetic material **1a** was shown by direct comparison to exhibit the same melting point behavior as the natural product,[1,14] and a mixture melting point was unchanged. The two substances have superimposable IR and NMR spectra and showed identical behavior when analyzed on an amino acid analyzer. A slight difference in the specific rotations of the natural ($[\alpha]^{25}_D$ +115°) and the synthetic ($[\alpha]^{25}_D$ +123°) materials is due to a trace impurity which is difficult to remove from the natural product.[1]

The ethyl acetate extract was concentrated in vacuo to yield 1.6 g (68.4%) of **7**: NMR (D_2O) δ 7.03 (d, 1 H, J = 12 Hz, $-OCH{=}CH-$), 5.1 (m, 2 H, $-OCH{=}CHCH$), 3.9 (s, 3 H, CH_3CO-).

D-2-Amino-4-methoxy-*trans*-but-3-enoic Acid (8). The crude

carboxylic acid 7 (2.24 g, 0.0129 mol) was dissolved in 35 mL of 85% hydrazine hydrate. The solution was heated at 70 °C for 15 h and concentrated in vacuo, and the resultant residue was dried in vacuo over concentrated H_2SO_4 to give a white solid. Trituration of the solid with ethanol gave 1.15 g (68%) of a substance which was 80% D-2-amino-4-methoxy-*trans*-but-3-enoic acid (8) and 20% racemate: mp 220 °C dec; $[\alpha]^{25}_D$ −98° (*c* 0.8370, H_2O); NMR (D_2O) δ 7.33 (d, 1 H, *J* = 13 Hz, -OCH=CH-), 5.45 (dd, 1 H, *J* = 10 and 13 Hz, -OCH-=CH-), 4.67 (d, 1 H, *J* = 10 Hz, -OCH=CHCH<), 4.11 (s, 3 H, CH_3O-); mass spectrum, *m/e* 86.

Anal. Calcd for $C_5H_9NO_3$: C, 45.80; H, 6.92; N, 10.68. Found: C, 45.90; H, 6.81; N, 10.88.

The specific rotation, $[\alpha]^{25}_D$ −98°, indicates that the D isomer is present in 80% enantiomeric excess.

Acknowledgment. We thank the staff of the Physical Chemistry Department of Hoffmann-La Roche Inc. for the determination of spectral and analytical data.

Registry No.—**1a**, 35891-72-6; **2**, 14110-03-3; **3a**, 66966-87-8; **3b**, 66966-88-9; (*E*)-**4**, 66966-89-0; (*Z*)-**4**, 66966-90-3; **5**, 66966-91-4; **6**, 66966-92-5; **7**, 66966-93-6; **8**, 67010-40-6.

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(12) The cation exchange resin AG 50W-X4 (100–200 mesh; H^+ form) was purchased from Bio Rad Laboratories, Richmond, Calif. Before use, it was washed with several portions each of water, methanol, and ether. The resin was then dried over P_2O_5 under vacuum.
(13) Some acetic acid and acetic anhydride invariably codistill with the enol ethers. Thus, a greater amount of sodium methoxide may be necessary to achieve this pH.
(14) We thank Dr. J. Scannell of the Microbiology Department at Hoffmann-La Roche Inc. for a sample of the natural amino acid **1a**.

Synthesis of DL-2-Amino-4-(2-aminoethoxy)-*trans*-but-3-enoic Acid

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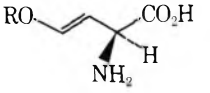
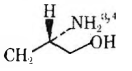
Received May 5, 1978

The racemic modification of the naturally occurring amino acid, L-2-amino-4-(2-aminoethoxy)-*trans*-but-3-enoic acid (**1b**), was synthesized starting from bis(2-chloroethyl) ether (**6**) and diethyl acetamidomalonate (**7**). The route included formation of the dehydroamino acid derivative **12**, followed by base-mediated isomerization of the double bond to form the critical enol ether linkage in **13**. Removal of the protecting groups from **13** then gave rise to the racemic amino acid **15** in an overall yield of 11%.

Recently, a new type of α-amino acid has been found in nature.[1-3] The members, **1**, of this class of compounds are

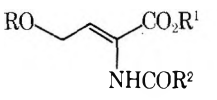


1a, R = CH_3[1]
b, R = $CH_2CH_2NH_2$[2]
c, R = 

distinguished both by having a centrally located enol ether function in the molecule and by their ability to inhibit the production of ethylene in plant tissue.[2,5] Since ethylene plays a vital role in controlling certain plant life processes, this activity is both intriguing and potentially economically important.[6]

We became interested in developing synthetic methods which would make these compounds and analogues of these compounds more readily available. One such sequence, described in the preceding paper, was used to make L-2-amino-4-methoxy-*trans*-but-3-enoic acid (**1a**).[7] The important steps of that synthesis are the generation of a hemiacetal ester followed by its pyrolysis to yield an enol ether. In this paper, we wish to describe a second route to these compounds and illustrate it with a synthesis of racemic 2-amino-4-(2-aminoethoxy)-*trans*-but-3-enoic acid (**1b**).

In our projected synthesis of **1b**, we intended to make the central enol ether function by isomerization of the double



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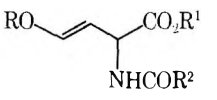

3

bond in a dehydroamino acid derivative **2** to form the enol ether **3**. The suggestion that this might be a fruitful approach comes from the studies of S. J. Rhoads and co-workers[8] and J. Hine and co-workers.[9] By studying the equilibration of methyl 4-methoxybutenoates **4**, both groups demonstrated that the double bond is stabilized more effectively by the methoxy group than by the ester. Thus, at equilibrium Hine found the mixture of olefins to be 99% **4b**, while Rhoads, under two different sets of equilibrating conditions, found the mixtures to be 92.5 and 96.9% **4b**, respectively.

$CH_3OCH_2CH{=}CHCO_2CH_3$
4a

$\rightleftarrows CH_3OCH{=}CHCH_2CO_2CH_3$
4b

In order to make the enol ether by this method, we required an appropriately substituted dehydroamino acid derivative. A recent publication by Shin and co-workers describes the synthesis of such compounds by the elimination of acetic acid from an *N,O*-diacetylhydroxyamino acid derivative.[10] This result suggested to us that dehydroamino acids could also be obtained by the elimination of HCl from a suitably disposed

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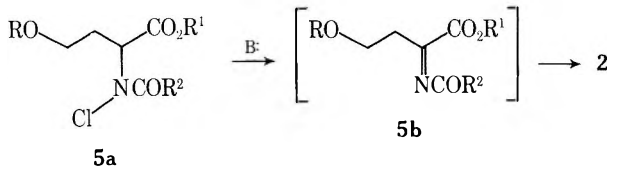


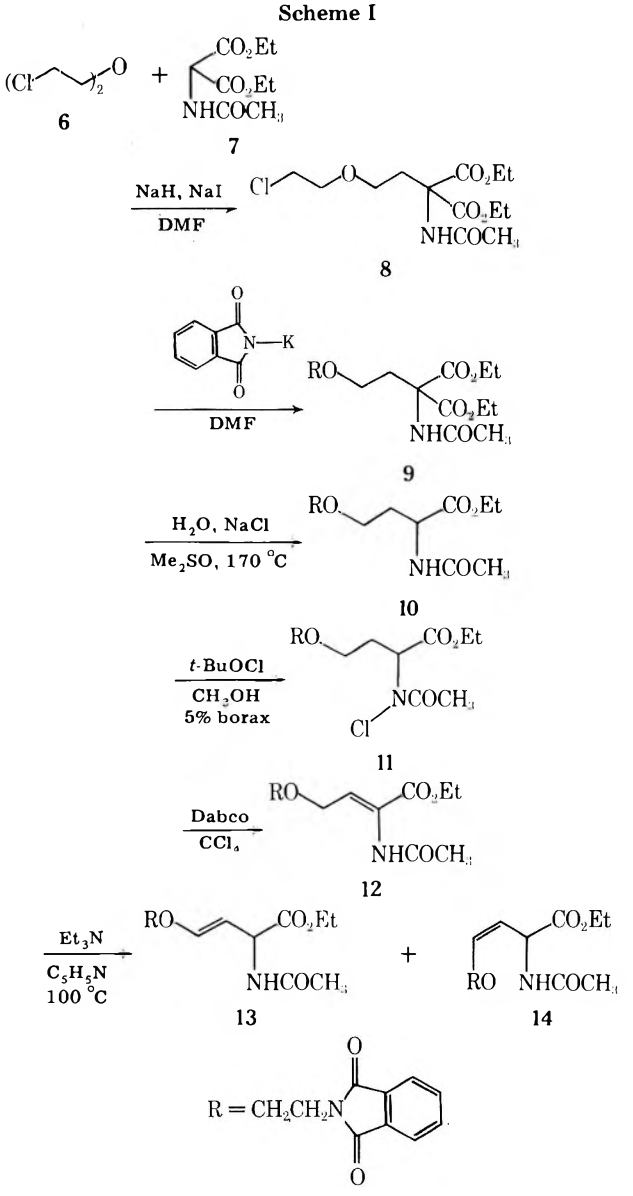
5a 5b

N-chloroamide. Thus, we hoped to convert **5a** to **2** via the acyl imine intermediate **5b.** Sometime after the completion of our work demonstrating the utility of this method, Poisel and Schmidt published essentially the same route to dehydroamino acids.[11] Following is a description of our use of this sequence to make the dehydroamino acid derivative **12.**

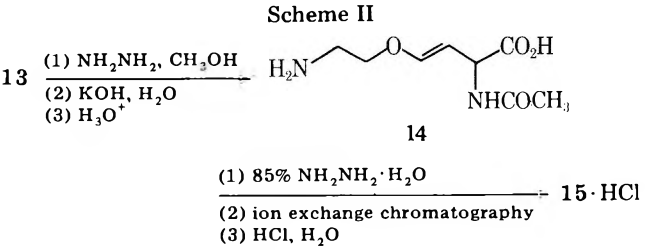
Alkylation of the sodium salt derived from diethyl acetamidomalonate (**7**) to yield the 2-chloroethyl ether **8** was accomplished in 85% yield by heating the salt at 60 °C in *N,N*-dimethylformamide solution with an excess of bis(2-chloroethyl) ether (**6**) and a catalytic amount of sodium iodide (see Scheme I). Treatment of chloroethyl ether **8** with potassium phthalimide in *N,N*-dimethylformamide solution at 100 °C gave phthalimido ether **9** (65%), which was deethoxycarbonylated by the method of Krapcho[12] to give the 2-acetamido-4-alkoxybutyrate **10** (76%). Oxidation of **10** with *tert*-butyl hypochlorite in methanol solution with borax buffer present gave an essentially quantitative yield of the *N*-chloroamide **11** as judged by TLC analysis.

The elimination of HCl from **11** followed by isomerization

Scheme I



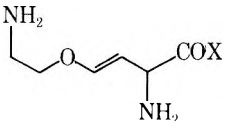
Scheme II



of the resultant acyl imine to give **12** (average yield 81%) was accomplished with 1,4-diazabicyclo[2.2.2]octane (Dabco) in carbon tetrachloride solution. In preliminary studies on a model compound, we found the choice of base to be critically important to the success of this reaction. Dabco was by far the best reagent for this conversion. The assignment of *Z* stereochemistry to **12** is based on the comparison of its NMR spectrum with a dehydroamino acid whose structure was secured by X-ray analysis.[13]

With the requisite substrate **12** in hand, we were set to attempt the deconjugation of the double bond to form the enol ether. A mixture consisting of the trans and cis enol ethers **13** and **14** and starting material **12** was obtained by heating a solution of **12** in 1:1 triethylamine/pyridine (a combination which was found empirically) at 100 °C for 37 h. The trans compound **13** was the major product from the reaction, while a moderate amount of the cis compound **14** and only a minor amount of the dehydroamino acid **12** were present in the mixture. Following the removal of solvent, the trans enol ether **13** was obtained in pure form (34%) by fractional crystallization of the reaction product. Mother liquors containing large amounts of the starting material **12** were recycled through the triethylamine/pyridine reaction conditions. Liquors containing major amounts of the cis isomer **14** were treated with iodine in glyme solution in order to effect equilibration between the trans and the cis isomers.[8] By following these procedures and then using preparative high-pressure liquid chromatography and fractional crystallization to isolate the trans isomer, yields between 50 and 65% could be realized for **13.**

Deprotection of the amino acid **13** was accomplished in the manner depicted in Scheme II. The phthalimido group was removed by treatment with anhydrous hydrazine in methanol solution. The ester was subsequently hydrolyzed by heating with 1 N potassium hydroxide solution at 90 °C for 24 h to give the *N*-acetylamino acid **14.** Lastly, the *N*-acetyl group was taken off by heating with 85% hydrazine hydrate at 80 °C for 40 h. After cation exchange chromatography, the racemic



15, X = OH
16, X = $NHNH_2$

amino acid **15** was isolated as its hydrochloride salt by crystallization from water/methanol. The synthetic material was found to have solution IR and NMR spectra which are identical with those of the natural product **1b.**[2,14] In addition, the natural and synthetic material behave identically upon analysis with an amino acid analyzer.

The mother liquors from the crystallization contained a substance shown by amino acid analysis to be more basic than the amino acid **15.** However, the NMR spectrum of this material is essentially identical with that of **15.** Most likely this new substance is the hydrazide **16,** possibly arising from hydrazinolysis of the ester during removal of the phthalimido group. In any event, treatment of the new material with 1 N KOH at 90 °C gives the amino acid **15** which can be isolated as its hydrochloride salt following cation exchange chroma-

tography. The overall yield of **15**·HCl thus obtained from **13** is 56%.

Experimental Section

General. Melting points were taken on a Kofler hot stage melting point apparatus (Reichert) and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 621 or a Beckman IR-9. Ultraviolet spectra were recorded on a Cary Model 16 spectrophotometer. Proton NMR spectra were obtained on Varian HA-100 and XL-100 instruments and are reported in parts per million downfield from internal or external tetramethylsilane.

A Waters Associates Prep LC/System 500 with a PrePAK-500 compression chamber and PrePAK-500/silica cartridges was used for preparative high-pressure liquid chromatography.

Silica gel 60 (0.063–0.200 mm) and plates precoated with silica gel 60 F-254 (both from E. Merck) were used for column and thin-layer chromatography, respectively.

Elemental analyses and amino acid analyses were carried out under the supervision of Dr. F. Scheidl of our Microanalytical Laboratories.

Ethyl 2-Acetamido-4-(2-chloroethoxy)-2-ethoxycarbonylbutyrate (8). Sodium hydride (30.9 g of a 50% oil dispersion; 0.65 mol) was placed in a dry three-neck flask equipped with a mechanical stirrer, an addition funnel, a reflux condenser, and an argon inlet. The hydride was washed with hexane and dried under a stream of argon. Dry *N,N*-dimethylformamide (500 mL) was added, and the suspension was cooled to 5 °C in an ice bath. Diethyl acetamidomalonate (**7**; 140 g, 0.65 mol) was added in portions with stirring at a rate which maintained a vigorous effervescence. After the addition was complete and the effervescence subsided, sodium iodide (9.66 g, 0.065 mol) was added in one portion and 460 g (3.2 mol) of bis(2-chloroethyl) ether (**6**) was added rapidly through the addition funnel. The reaction mixture was then heated at 60 °C with stirring for 24 h. The mixture was transferred to a one-neck flask and concentrated in vacuo on a rotary evaporator (600–800 mL removed). The residue was subjected to steam distillation until the distillate was clear (2–2.5 L). The pot residue was taken up in 500 mL of ether, and the organic solution was washed five times with 100-mL portions of brine. The ether solution was dried over anhydrous sodium sulfate and concentrated in vacuo to yield 175.7 g (84.5%) of crude **8**. This material is suitable for use in the next step.

A portion was purified by distillation to yield **8**: bp 135–140 °C (0.1 mm); IR ($CHCl_3$) 3400, 1715, 1655, 1470 cm^{-1}; NMR ($CDCl_3$) δ 6.96 (broad, 1 H, NH), 4.22 (q, 4 H, J = 6 Hz, $2CH_3CH_2O$–), 3.5 (m, 6 H, $ClCH_2CH_2OCH_2$–), 2.65 (t, 2 H, J = 6 Hz, $-CH_2CH_2C<$), 2.03 (s, 3 H, CH_3CO–), 1.25 (t, 3 H, J = 6 Hz, CH_3CH_2O–); mass spectrum, *m/e* 324 (M^+ + H), 217, 93, 63.

Anal. Calcd for $C_{13}H_{22}ClNO_6$: C, 48.23; H, 6.85; N, 4.33. Found: C, 48.06; H, 6.71; N, 4.18.

Ethyl 2-Acetamido-2-ethoxycarbonyl-4-[2-(2-phthalimido)-ethoxy]butyrate (9). A three-neck flask equipped with a mechanical stirrer, a reflux condenser, and an argon inlet was charged with 128.1 g (0.396 mol) of the chloroacetamidomalonate **8**, 109.9 g (0.59 mol) of potassium phthalimide, 6.57 g (0.04 mol) of potassium iodide, and 600 mL of dry *N,N*-dimethylformamide. The mixture was heated with stirring under argon at 100 °C for 18 h. The reaction mixture was allowed to cool and was divided into two equal portions which were processed as follows. Each was diluted with 2 L of ether, causing salts to precipitate. The solids were removed by filtration through diatomaceous earth, and the filtrates were concentrated in vacuo to remove the ether and *N,N*-dimethylformamide. The residues were each diluted with 1.5 L of ether and 100 mL of ethyl acetate. The organic phases were washed six times with water (300 mL) and once with brine (300 mL). The organic solutions were combined, dried with anhydrous sodium sulfate, and concentrated in vacuo until crystallization began. At that point, the mixture was heated on a steam bath until a clear solution was obtained. The solution was diluted with hexane until the cloud point and then set aside to crystallize. Pure **9** was collected in two crops (111.6 g, 65%): mp 101–103 °C; UV (EtOH) max 220 nm (ϵ 42 000), 240 infl (4300), 293 (920); IR ($CHCl_3$) 3410, 1775, 1738, 1712, 1678, 1495 cm^{-1}; NMR ($CDCl_3$) δ 8.0 (broad, 1 H, NH), 7.88 (s, 4 H, aromatic), 4.13 (q, 4 H, J = 7 Hz, CH_3CH_2O–), 3.5 (m, 6 H, $PhthNCH_2CH_2OCH_2$–), 2.45 (t, 2 H, J = 6 Hz, $-OCH_2CH_2C<$), 2.03 (s, 3 H, CH_3CO), 1.15 (t, 3 H, J = 7 Hz, CH_3CH_2O–); mass spectrum, *m/e* 389, 361, 319, 244, 217.

Anal. Calcd for $C_{21}H_{26}N_2O_8$: C, 58.06; H, 6.03; N, 6.45. Found: C, 58.32; H, 5.79; N, 6.40.

Ethyl 2-Acetamido-4-[2-(2-phthalimido)ethoxy]butyrate (10). A suspension consisting of 143.6 g (0.331 mol) of phthalimidoacetamidomalonate **9**, 11.9 g (0.66 mol) of water, 19.3 g (0.33 mol) of sodium chloride, and 330 mL of dimethyl sulfoxide was heated with magnetic stirring at 170 °C under argon for 8 h. The reaction mixture was allowed to cool to room temperature, diluted with 1500 mL of ethyl acetate, and washed two times with 350-mL portions of water followed by six 100-mL water washes and two 300-mL brine washes. Each aqueous layer was backwashed with a small portion of ethyl acetate which was then added to the main organic phase. The ethyl acetate solution was dried over anhydrous sodium sulfate and concentrated in vacuo to yield 91.7 g (77%) of a brown oil. This material was suitable for use in the next step.

An analytical sample was prepared by taking a portion of the oil in ether, treating the solution with charcoal, and filtering the mixture through diatomaceous earth. The filtrate was concentrated in vacuo and crystallized from ethyl acetate/petroleum ether to yield **10**: mp 90–90.5 °C; UV (EtOH) max 219 nm (ϵ 40 600), 232 infl (13 400), 240 (9400), 294 (1900), 300 infl (1800); IR ($CHCl_3$) 3300, 1775, 1730, 1720, 1640, 1555 cm^{-1}; NMR ($CDCl_3$) δ 7.8 (m, 4 H, aromatic H), 6.73 (broad, 1 H, NH), 4.64 (m, 1 H, $-CH_2CH<$), 4.08 (q, 2 H, J = 8 Hz, CH_3CH_2O–), 3.9–3.4 (m, 6 H, $PhthNCH_2CH_2OCH_2$–), 2.07 (s, 3 H, CH_3CO–), 2.02 (t, 2 H, J = 6 Hz, $-OCH_2CH_2CH<$), 1.17 (t, 3 H, J = 8 Hz, CH_3CH_2O–); mass spectrum, *m/e* 362 (M^+), 317, 289, 160.

Anal. Calcd for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.80; H, 6.32; N, 7.75.

Ethyl 2-(*N*-Chloroacetamido)-4-[2-(2-phthalimido)ethoxy]-butyrate (11). A solution consisting of 73.8 g (0.204 mol) of acetamide **10**, 8.69 g (0.023 mol) of sodium tetraborate, and 224 mL of methanol was protected from light and cooled with an ice bath to 5 °C under an atmosphere of argon. *tert*-Butyl hypochlorite (37.1 mL, 0.31 mol) was added with magnetic stirring to the solution. The ice bath was removed after addition was complete. After 45 min, an aliquot was removed and TLC analysis [silica gel plates; $CHCl_3/Et_2O$ (8:1)] showed that some starting material was still present. More *tert*-butyl hypochlorite was added in portions until TLC analysis indicated that the reaction was complete. The reaction solution was then concentrated in vacuo with protection from light to yield an oil which was taken up in carbon tetrachloride (350 mL), causing sodium salts to precipitate. The solids were removed by filtration, yielding a carbon tetrachloride solution of **11** which was used directly in the next step.

Ethyl (*Z*)-2-Acetamido-4-[2-(2-phthalimido)ethoxy]but-2-enoate (12). To the carbon tetrachloride solution of **11** obtained from the previous reaction was added 25.2 g (0.224 mol) of 1,4-diazabicyclo[2.2.2]octane (Dabco). The resultant solution was stirred magnetically for 15 h. A copious white precipitate formed after 2 h. Ethyl acetate (1 L) was added to the mixture to break up the precipitate. After allowing time for the solid to settle, the solution was decanted and the remaining precipitate washed twice with 500-mL portions of ethyl acetate. The combined organic solutions were filtered through diatomaceous earth, and the filtrate was concentrated in vacuo. The residue was taken up in chloroform and passed through a column (i.d. 47 mm) of silica gel 60 (100 g) packed in chloroform. The column was developed with 2 L of chloroform, and the chloroform solution was concentrated in vacuo to yield an oil. Crystallization from ethyl acetate/ether/hexane yielded, in two crops, 68.1 g (92.9%) of butenoate **12**, mp 113–116 °C. The average yield of **12** obtained from several large scale preparations was 81%. An analytical sample was prepared by recrystallization from the same solvent: mp 120–122.5 °C; UV (EtOH) max 220 nm (ϵ 49 200), 233 infl (21 000), 241 infl (15 700), 294 (1930), 300 (1800); IR ($CHCl_3$) 3410, 1775, 1713, 1695 infl, 1495 cm^{-1}; NMR ($CDCl_3$) δ 7.80 (m, 4 H, aromatic H), 7.53 (broad, 1 H, NH), 6.51 (t, 1 H, J = 6 Hz, $-OCH_2CH=$), 4.24 (q, 2 H, J = 8 Hz, CH_3CH_2O–), 4.18 (d, 2 H, J = 6 Hz, $-OCH_2CH=$), 3.93 and 3.74 (2 m, 2 H in each, $-NCH_2CH_2O$–), 2.13 (s, 3 H, CH_3CO–), 1.29 (t, 3 H, J = 8 Hz, CH_3CH_2O); mass spectrum, *m/e* 360 (M^+), 317, 314, 287, 174, 160.

Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 60.20; H, 5.56; N, 7.80.

Ethyl 2-Acetamido-4-[2-(2-phthalimido)ethoxy]-*trans*-but-3-enoate (13) and Ethyl 2-Acetamido-4-[2-(2-phthalimido)ethoxy]-*cis*-but-3-enoate (14). A solution consisting of 74.5 g (0.21 mol) of butenoate **12**, 487 mL of triethylamine, and 485 mL of pyridine was heated with stirring at reflux temperature under an atmosphere of argon for 37 h. The solution was allowed to cool and concentrated in vacuo. Ethyl acetate was added to the remaining oil, and the solution was concentrated again in vacuo. After repeating this process one more time, the dark brown residue was dissolved in ethyl acetate and the resultant solution was brought to the cloud point with hexane and set aside overnight to crystallize. The resultant light brown solid was collected and shown by NMR spectroscopy to consist mainly of the trans and cis enol ethers **13** and **14**. The filtrate from this crystalli-

zation was concentrated in vacuo, yielding a dark oil which was processed as described in a subsequent paragraph.

The solid was dissolved in a minimum amount of ethyl acetate, and the resultant solution was applied to a column (i.d. 47 mm) of silica gel 60 (100 g) packed in ethyl acetate. The column was developed with ethyl acetate until all UV-absorbing material was eluted. The ethyl acetate solution was concentrated in vacuo. Ether was added until the cloud point was reached, and the solution was allowed to stand undisturbed overnight while crystallization occurred (occasionally scratching or seed crystals were used to induce crystallization). The crystals which were deposited were collected by filtration (30.2 g, 41%) and shown by NMR spectroscopy to be approximately an 85:15 mixture of trans and cis enol ethers. A further crystallization from the same solvent system gave 25.5 g (34%) of **13:** mp 95–96.5 °C; UV (EtOH) max 219 nm (ϵ 49 400), 239 (11 200), 293 (2020), 300 (1860); IR ($CHCl_3$) 3435, 1778, 1717, 1678, 1504 cm^{-1}; NMR ($CDCl_3$) δ 7.8 (m, 4 H, aromatic H), 6.52 (d, 1 H, J = 12 Hz, -OC**H**=CH-), 6.25 (broad, 1 H, NH), 4.6–5.0 (m, 2 H, -OCH=C**H**CH), 4.16 (q, 2 H, J = 8 Hz, CH_3CH_2O-), 3.94 (broad s, 4 H, $>NCH_2CH_2O$-), 1.97 (s, 3 H, CH_3CO-), 1.24 (t, 3 H, J = 8 Hz, CH_3CH_2O-); mass spectrum, m/e 360 (M^+), 317, 314, 287, 174 (base), 160.

Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.96; H, 5.41; N, 7.65.

The mother liquors from the crystallizations described above contained varying amounts of the starting material **12**, trans enol ether **13**, and the cis enol ether **14**. Liquors which contained a large amount of starting material **12** were resubjected to the reaction with triethylamine and pyridine. Such material was processed as described above to yield further quantities of trans enol ether **13**.

Mixtures consisting principally of the cis enol ether were treated with iodine (20 mg of I_2/g of mixture) in dry peroxide-free glyme (10 mL/g of mixture) at 40 °C for 40 h.[8] The reaction mixture was concentrated in vacuo, leaving a residue which was dissolved in ethyl acetate. The solution was washed with 10% sodium thiosulfate solution and dried over anhydrous sodium sulfate. Concentration on a rotary evaporator yielded an oil consisting of a 3:2 mixture of trans and cis enol ethers, respectively, as determined from the NMR spectrum. This material was chromatographed in batches of 5 g each on a Waters Prep LC/System 500 with one PrePAK-500/silica cartridge using ethyl acetate/hexane/methanol (10:10:1) as the eluent. Several recycles were required for complete separation of the isomers. The α,β-unsaturated ester **12** was eluted first, followed by the trans enol ether **13** and then the cis enol ether **14**. Concentration of the appropriate fractions followed by crystallization yielded approximately 1 g of pure **13** for each 5 g of 3:2 mixture.

By diligently following these procedures, yields between 50 and 65% were realized for the trans enol ether **13**. Concentration of the fractions containing the cis isomer followed by crystallization from ethyl acetate/petroleum ether gave **14:** mp 88–90 °C; UV (EtOH) max 218 nm (ϵ 42 800), 239 infl (9800), 292 (1870), 300 infl (1750); IR ($CHCl_3$) 3435, 3410, 1775, 1735, 1715, 1670, 1513 cm^{-1}; NMR ($CDCl_3$) δ 7.8 (m, 4 H, aromatic H), 6.65 (broad, 1 H, NH), 6.07 (d, 1 H, J = 6 Hz, -OC**H**=CH-), 5.07 (t, 1 H, J = 8 Hz, -OCH=CHC**H**<), 4.61 (dd, 1 H, J = 6 and 8 Hz, -OCH=C**H**-), 4.0 (m, 6 H, CH_3CH_2O- and $>NCH_2CH_2O$-), 2.06 (s, 3 H, CH_3CO-), 1.17 (t, 3 H, J = 7 Hz, CH_3CH_2O-); mass spectrum, m/e 360 (M^+), 317, 314. 287, 174 (base), 160, 147, 130.

Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.86; H, 5.41; N, 7.65.

DL-2-Amino-4-(2-aminoethoxy)-*trans*-but-3-enoic Acid (15). The protecting groups were removed from **13** by the following multistep procedure. A solution consisting of 3.5 g (0.0097 mol) of enol ether **13**, 0.47 g (0.0146 mol) of anhydrous hydrazine, 10 mL of methanol, and 17 mL of ethanol was stirred magnetically under argon for 24 h. During this time, a copious white precipitate formed which stopped the stirring. The solid is most probably the salt which results from the reaction of the freed ϵ amine with the newly formed phthalhydrazide.

At this point, 60 mL of 1 N KOH was added directly to the reaction flask, causing the solid to dissolve. The resultant solution was heated at 90 °C under argon for 24 h. The reaction mixture was allowed to cool to ambient temperature, concentrated in vacuo to approximately half of its original volume, and acidified with 1 N HCl (3 N HCl in larger scale runs) to pH 4. This caused the precipitation of phthalhydrazide, which was removed by filtration. The pH of the filtrate, which contains the *N*-acetylamino acid **14**, was adjusted to between 6 and 7, and the filtrate was then concentrated in vacuo. The residue was dissolved in 25 mL of 85% hydrazine hydrate and the solution heated at 80 °C for 40 h. After cooling to ambient temperature, the reaction mixture was concentrated in vacuo to remove the hydrazine hydrate. The residue was dissolved in water and the pH of the solution adjusted to between 9 and 10. The solution was concentrated in vacuo, giving a yellow solid which was dried in vacuo over P_2O_5 for 4 h and then over concentrated H_2SO_4 (16 h).

The resultant yellow residue was taken up in water and applied to a cation exchange column (10-fold excess of AG 5, W-X4; 100–200 mesh; H^+ form). The column was washed with water and 10% aqueous pyridine. The amino acid **15** was eluted with 1.5 N NH_4OH. The fraction was concentrated in vacuo and the residue dried for a short time at 0.1 mm. It was then dissolved in water and the pH of the solution adjusted to 3.6 with 1 N HCl. Concentration of the solution followed by crystallization of the resultant oil from water/methanol gave 0.658 g (35%) of the monohydrochloride salt of **15**. An analytical sample was prepared by recrystallization: mp 187.5–189 °C dec; IR (KBr) 3500–2250 (broad), 1650, 1600, 1500; NMR (D_2O) δ 7.35 (d, 1 H, J = 12.4 Hz, -OC**H**=CH-), 5.53 (dd, 1 H, J = 10 and 12.4 Hz, -OCH=C**H**CH<), 4.71 (d, 1 H, J = 10 Hz, -OCH=CHC**H**<), 4.58 (m, 2 H, $-OCH_2CH_2N<$), 3.85 (m, 2 H, $-OCH_2CH_2N<$).

Anal. Calcd for $C_6H_{12}N_2O_3$·HCl: C, 36.65; H, 6.66; N, 14.25. Found: C, 36.44; H, 6.57; N, 14.08.

The synthetic amino acid was found to have solution IR and NMR spectra which are identical with those of the natural L-amino acid **1b**. Furthermore, the two materials behaved identically when they were analyzed on the Beckman Model 121M amino acid analyzer.[2,14]

The mother liquors from the crystallization of the hydrochloride salt were found by analysis on the amino acid analyzer to contain a substance which was more basic than **15**. This substance is most probably the hydrazide **16**. Upon heating the mother liquors with 15 mL of 1 N KOH at 90 °C for 40 h followed by ion exchange chromatography and crystallization, as described above, a further 0.402 g (21%) of the monohydrochloride salt **15** was obtained. Thus, the total yield of **15** from the protected amino acid was 56%.

Acknowledgment. We thank the staff of the Physical Chemistry Department of Hoffmann-La Roche Inc. for the determination of spectral and analytical data.

Registry No.—**6**, 111-44-4; **7**, 1068-90-2; **8**, 66966-94-7; **9**, 66966-95-8; **10**, 66966-96-9; **11**, 66966-97-0; **12**, 66966-98-1; **13**, 66966-99-2; **14**, 66967-00-8; **15**, 67010-41-7; **15**·HCl, 67010-42-8; potassium phthalimide, 1074-82-4.

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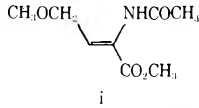
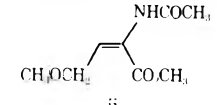
(13) During the course of our studies on these amino acids, we prepared the dehydroamino acid derivatives i and ii. The structure of i is based on an X-ray analysis carried out by Dr. J. Blount of the Physical Chemistry Department of Hoffmann-La Roche Inc. A comparison of the chemical shifts of the



i



ii

methylene protons and the adjacent olefinic proton of i, ii, and **12** is shown below. Clearly, the chemical shifts of the protons in **12** are much closer to those of i than those of ii. Thus, the stereochemistry of **12** is almost certainly the same as that present in i.

	—CH_2—	—CH=
i	δ 4.10	δ 6.70
ii	δ 4.44	δ 7.30
12	δ 4.18	δ 6.51

(14) We are grateful to Dr. J. Scannell of the Microbiology Department at Hoffmann-La Roche Inc. for a sample of the natural amino acid **1b**.

Synthesis of Two Benzofuran Neolignans

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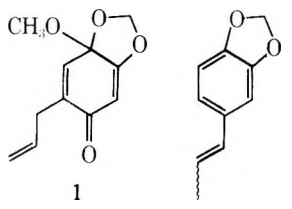
Received April 28, 1978

Condensation of 2-allyl-3,4,4-trimethoxycyclohexa-2,5-dienone (**15**) with (*E*)-isosafrole (**2**) in acetonitrile–methanol under the influence of trinitrobenzenesulfonic acid yielded a mixture of the dihydrobenzofuran **10** and the bicyclooctane **18**. Bicyclooctane **18** was unstable toward acids and isomerized rapidly to the dihydrobenzofuran **9**, the racemate of an *Aniba terminalis* constituent. Dehydrogenation with DDQ gave benzofuran **11**, another naturally occurring neolignan.

In a recent paper from this laboratory[1] the total syntheses of the neolignans guianin (**3**)[2] and burchellin (**4**),[3] from



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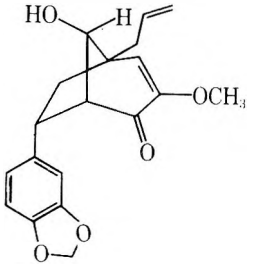

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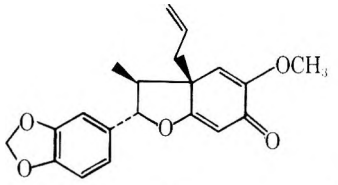

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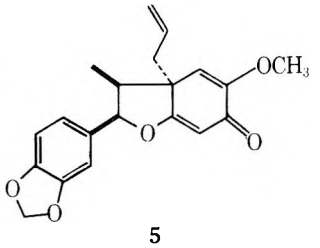

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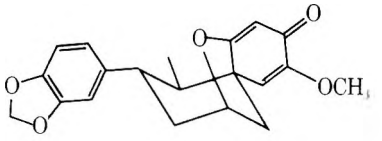
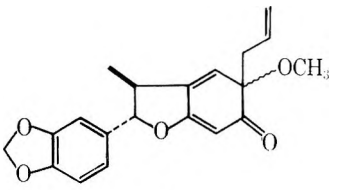


6

products formed in the acid-catalyzed condensation of the *p*-quinone ketal **1** with (*E*)-isosafrole (**2**), were described. Similarly, 2-*epi*-3a-*epi*-burchellin (**5**)[4] and futoenone (**6**)[5] were prepared starting from the same ketal **1** and (*Z*)-isosafrole (**2**). To account for the products formed in these acid-induced condensations it was postulated that bicyclo[3.2.1]-octanes with endo oriented aryl groups were the initial products resulting from concerted [2 + 4] cycloadditions. Subsequent isomerization of the kinetic adducts could have led to the more stable hydrobenzofurans with configurations corresponding to those present in the natural products **4** and **5**. Alternatively, the bicyclooctanes could have isomerized to spiro[5.5]undecanes, and the intermediate derived from (*Z*)-isosafrole (**2**) was assumed to have undergone a further cyclization to a product with a futoenone skeleton.

Certain *Aniba* species[4,6] produce the neolignans **7**, **8**, **9**, and **11**, in addition to metabolites of the guianin (**3**) and burchellin (**4** and **5**) types. The possibility that **7**, **8**, and **9** originate in vivo from the same eugenol-isoeugenol dimer by sequential Cope, retro-Claisen, and Claisen rearrangements is not unreasonable but awaits verification. It occurred to us that the dihydrobenzofuran **9** could also arise from a hitherto unknown bicyclooctane **18**, which in turn could be the outcome of a cycloaddition of *p*-quinone ketal **15** to (*E*)-isosafrole (**2**). The intermediate bicyclooctane **18** was anticipated to rearrange irreversibly to the *Aniba* constituent **9**. We have reduced this



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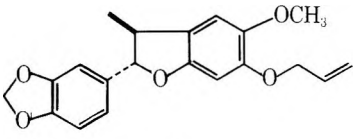

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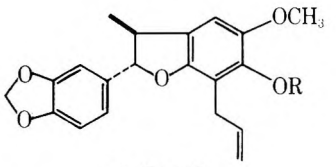
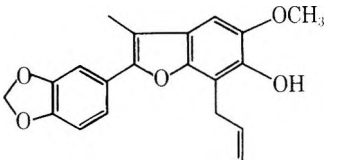


9, R = H
10, R = CH_3



11

scheme to practice, and in this paper we report the synthesis of the two neolignans **9** and **11**.

The tetrahydropyranyl ether **12** on metalation with *n*-butyllithium afforded the C_2 lithio dervative **13**. Alkylation of the corresponding cuprate with allyl bromide followed by hydrolytic removal of the protecting group furnished phenol **14**.[7] Oxidation to the *p*-benzoquinone ketal **15** was accomplished with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in methanol solution.[8] Ketal **15** was found to condense with (*E*)-isosafrole (**2**) in acetonitrile containing methanol and added 2,4,6-trinitrobenzenesulfonic acid to give an easily separable mixture of adducts consisting of the dihydrobenzofuran **10** (42% yield) and the bicyclooctane **18** (20% yield). In agreement with expectation, trifluoromethanesulfonic acid mediated isomerization of **18** gave the crystalline phenol **9**. Comparison of its ^1H nuclear magnetic resonance spectrum with that of an oily mixture of both cis and trans isomers isolated from *Aniba terminalis*[4] left no doubt that the synthesis produced the more stable trans isomer. Incidentally, this synthesis proves the relative positions of the hydroxy and methoxy groups and thus confirms the earlier conclusion based on nuclear magnetic resonance arguments.[4] The formation of the two adducts is accommodated by a scheme in

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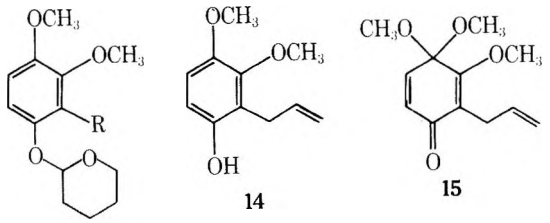
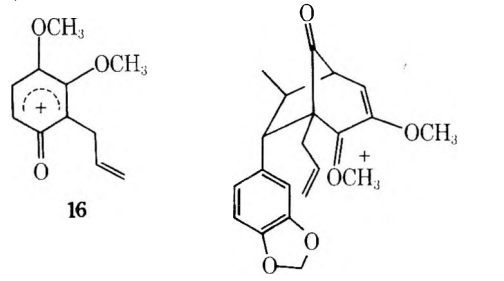
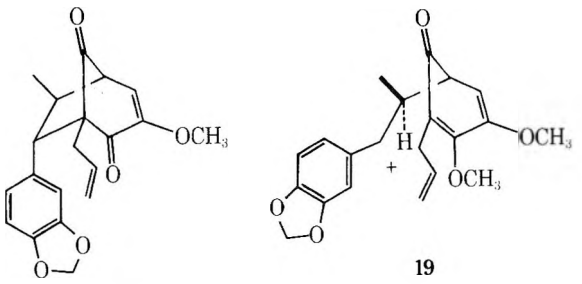


12, R = H
13, R = Li

14 15



16 17



18 19

which cation **16** and olefin **2** align themselves in a manner that favors bond formation between the most electrophilic C_6 atom of the cation **16** and the terminal carbon atom of the electron-rich olefin. A concerted [2 + 4] cycloaddition would create the oxonium ion **17**, with an endo oriented aryl group, that is captured by methanol. Hydrolysis of the hypothetical ketal during workup would give the observed bicyclooctane **18**. Alternatively, oxonium ion **17** once formed could isomerize to the benzylic cation **19**, which in turn could cyclize to the dihydrobenzofuran **10**. Ion **19** could also be the result of a process in which only one carbon–carbon bond was formed in the first step, but the stereoselective formation of a single bicyclooctane is in better agreement with a concerted rather than a stepwise process.

Finally, dehydrogenation of the dihydrobenzofuran **9** with DDQ afforded the benzofuran **11**, identical according to melting point and NMR spectrum with the natural material.[4]

Experimental Section

Melting points were determined on a Reichert hot stage microscope and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 237B or 247 grating spectrophotometer and are reported in wavenumbers (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were measured on a Varian T-60 or a Perkin-Elmer R-22 spectrometer and are given in parts per million (δ) downfield from tetramethylsilane as an internal standard; the abbreviations s, d, and m refer to singlet, doublet, and multiplet, respectively. Ultraviolet (UV) spectra were determined on a Perkin-Elmer 200 spectrophotometer, and wavelengths are reported in nanometers (nm). High-resolution mass spectra (HRMS) were measured on a DuPont CEC-110B instrument, and low-resolution mass spectra (MS) were determined on a Varian Mat 44 instrument. Elemental analyses were performed by Robertson Laboratory, Florham Park, N.J.

3,4-Dimethoxyphenol Tetrahydropyranyl Ether (12). The tetrahydropyranyl ether of 3,4-dimethoxyphenol was prepared in a standard fashion using *p*-toluenesulfonic acid monohydrate as catalyst in dichloromethane at room temperature for 2 h. Bulb-to-bulb distillation in a Büchi GKR-50 Kugelrohrapparat gave **12** as a colorless oil in 97% yield: bp 160 °C (0.02 mm); IR (CCl_4) 2943, 1511, 1230, 1155, 1122, 1100, 1031, 1017 cm^{-1}; NMR (CCl_4) δ 1.30–2.13 (m, 6), 3.73 (s, 3), 3.77 (s, 3), 3.30–4.10 (m, 2), 5.15–5.32 (m, 1), 6.17–6.77 (m, 3). Anal. Calcd for $C_{13}H_{18}O_4$: 238.12051. Found: 238.12347.

2-Allyl-3,4-dimethoxyphenol (14). To a cooled (ice bath) and stirred solution of tetrahydropyranyl ether **12** (8.32 g, 35 mmol) in anhydrous THF (80 mL) under nitrogen was added dropwise via a syringe 21 mL of *n*-BuLi (2.45 M in hexane; 52 mmol). The ice bath was removed after the addition was completed, and the resulting solution was stirred for 30 min and then left at room temperature overnight. Copper iodide (6.70 g, 35 mmol) was added in small portions to the stirred solution which was continually stirred for 1 h at room temperature. The solution was cooled (ice bath) and allyl bromide (4.5 mL, 6.3 g, 52 mmol) added via a syringe. The ice bath was removed after addition was completed, and the solution was stirred at room temperature for 1 h and then heated to reflux for 2 h. The solution was cooled and water (80 mL) added. The contents were then filtered through a pad of Celite, and ether (1 × 300 mL and 1 × 200 mL) was used to extract the filtrate. The combined ether extracts were washed with saturated aqueous ammonium chloride (1 × 100 mL) and then brine (1 × 100 mL), and the ethereal solution was concentrated in vacuo. The residue was dissolved in 135 mL of 90% aqueous methanol and 13.5 mL of 5% oxalic acid. The solution was stirred at room temperature for 1 h, followed by partitioning between water (100 mL) and ether (300 mL). The aqueous phase was separated and extracted further with ether (2 × 200 mL). The combined ether extracts were washed with water (2 × 100 mL), dried ($MgSO_4$), decolorized with charcoal, filtered, and concentrated in vacuo. The residue was then purified by column chromatography on silica gel eluting with hexane–EtOAc (4:1). Fractions judged to be identical by TLC were pooled and gave 4.18 g of **14** as a yellow oil (62% yield): IR (CCl_4) 3450, 1500, 1633, 1267, 1054, 992, 908 cm^{-1}; NMR (CCl_4) δ 3.42 (br d, 2, J = 6 Hz), 3.77 (s, 3), 3.80 (s, 3), 4.80–5.27 (m, 2), 5.68–6.30 (m, 1), 6.17 (br s, 1), 6.43 (d, 1, J = 9 Hz), 6.65 (d, 1, J = 9 Hz).

2-Allyl-3,4,4-trimethoxycyclohexa-2,5-dienone (15). To a stirred solution of DDQ (0.267 g, 1.2 mmol) in a minimum amount of methanol at room temperature was added dropwise a solution of **14** (0.190 g, 1.0 mmol) in methanol (98 mL). After addition was completed, methanol was removed in vacuo and the residue was dissolved in ether. The ethereal solution was then washed with saturated $NaHCO_3$ solution and water, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on a 20 × 20 × 0.1 cm silica gel plate using hexane–EtOAc (4:1 v/v) as solvent to give 0.165 g of **15** as a yellow oil (75% yield; about 92% pure by NMR): IR (CCl_4) 1675, 1639, 1612 cm^{-1}; NMR (CCl_4) δ 3.03 (br d, 2, J = 6 Hz), 3.35 (s, 6), 4.15 (s, 3), 4.75–5.22 (m, 2), 5.45–6.07 (m, 1), 6.25 (d, 1, J = 10 Hz), 6.47 (d, 1, J = 10 Hz); UV (95% EtOH) 227 nm (sh, ϵ 9100), 315 (3900). Anal. Calcd for $C_{12}H_{16}O_4$: 224.10486. Found: 224.10649.

***trans*-2,3-Dihydro-7-allyl-5,6-dimethoxy-3-methyl-2-(3,4-methylenedioxyphenyl)benzofuran (10) and 1-Allyl-3-methoxy-6-*exo*-methyl-7-*endo*-(3,4-methylenedioxyphenyl)bicyclo[3.2.1]oct-3-ene-2,8-dione (18).** A solution of **15** (68 mg, 0.3 mmol; about 92% pure) and isosafrole (90 μL, 101 mg, 0.6 mmol) in anhydrous acetonitrile (3 mL) containing 25 μL of methanol (18 mg, 0.6 mmol) was cooled in a dry ice–3-pentanone bath under nitrogen. A catalytic amount of trinitrobenzenesulfonic acid was then added, and the solution was stirred for 30 min. The cooling bath was removed and saturated $NaHCO_3$ solution added. The contents were transferred to a separatory funnel and extracted twice with ether. The combined ether extracts were washed with water twice, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on a 20 × 20 × 0.1 cm silica gel plate using hexane–EtOAc (3:1 v/v) as solvent to give 38 mg of **10** (42%) and 17 mg of **18** (20%).

Dihydrobenzofuran 10: mp 67–69 °C (hexane); IR (CCl_4) 1468, 1251, 1043 cm^{-1}; NMR (CCl_4) δ 1.37 (d, 3, J = 7 Hz), 3.33 (br d, 2, J = 6 Hz), 3.08–3.47 (m, 1), 3.78 (s, 6), 4.87–5.20 (m, 2), 4.97 (d, 1, J = 9 Hz), 5.96 (s, 2), 5.76–6.20 (m, 1), 6.52 (br s, 1), 6.74–6.93 (m, 3); MS *m/e* (relative intensity, %) 354 (M^+, 100). Anal. ($C_{21}H_{22}O_5$) C, H.

Bicyclooctane 18: mp 117–119 °C (methanol); IR (CCl_4) 1766, 1695, 1612 cm^{-1}; NMR ($CDCl_3$) δ 1.14 (d, 3, J = 7 Hz), 2.18–2.69 (m, 3), 2.80–3.07 (m, 2), 3.66 (s, 3), 5.04–5.36 (m, 2), 5.86 (s, 2), 5.56–6.13 (m, 1), 6.29–6.73 (m, 4); MS *m/e* (relative intensity, %) 340 (M^+, 5), 178 (69), 162 (100). Anal. ($C_{20}H_{20}O_5$) C, H.

***trans*-2,3-Dihydro-7-allyl-6-hydroxy-5-methoxy-3-methyl-2-(3,4-methylenedioxyphenyl)benzofuran (9).** A solution of **18** (32.5 mg) in dry acetonitrile (1 mL) was cooled in an ice bath. One drop of trifluoromethanesulfonic acid was added, and the solution was stirred for 30 min. Saturated $NaHCO_3$ solution was added, and the contents were extracted with ether. The ether solution was dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on a 20 × 20 × 0.05 cm silica gel plate using hexane–EtOAc (4:1 v/v) as solvent to give 17.3 mg (53%) of **9**: mp 79–80 °C (hexane);

IR ($CHCl_3$) 3546, 1466, 1334, 1243, 1031 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (d, 3, J = 7 Hz), 3.40 (br d, 2, J = 6 Hz), 2.90–3.53 (m, 1), 3.85 (s, 3), 4.83–5.30 (m, 2), 5.01 (d, 1, J = 9 Hz), 5.68 (s, 1), 5.95 (s, 2), 5.47–6.40 (m, 1), 6.53 (br s, 1), 6.72–7.00 (m, 3); MS m/e (relative intensity, %) 340 (M^+, 100).

7-Allyl-6-hydroxy-5-methoxy-3-methyl-2-(3,4-methylenedioxyphenyl)benzofuran (11). Starting with 107 mg (0.3 mmol) of **18**, 98 mg of crude dihydrobenzofuran **9** was obtained using the conditions described above. The crude dihydrobenzofuran **9** was then dissolved in THF (1 mL) and cooled in an ice bath while a solution of DDQ (65 mg, 0.3 mmol) in THF (1 mL) was added dropwise to it. After 10 min, the contents were diluted with ether and then washed with water. The aqueous washing was back extracted with ether, and the combined ether extracts were washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on a 20 × 20 × 0.1 cm silica gel plate using hexane–EtOAc (6:1 v/v) as solvent to give 45 mg (42%) of **11**: mp 123–124 °C (hexane–diethyl ether); IR ($CHCl_3$) 3567, 1475, 1350, 1258, 1046 cm^{-1}; NMR ($CDCl_3$) δ 2.38 (s, 3), 3.72 (br d, 2, J = 7 Hz), 3.94 (s, 3), 4.98–5.33 (m, 2), 5.83 (s, 1), 6.01 (s, 2), 5.89–6.40 (m, 1), 6.80 (s, 1), 6.91 (d, 1, J = 8 Hz), 7.18–7.36 (m, 2); UV (95% EtOH) 254 nm(log ϵ 3.92), 290(sh, 4.16), 328 (4.51);[9] MS m/e (relative intensity, %) 338 (M^+, 100).

Acknowledgment. We are indebted to the National Institutes of Health (GM 09686) and the Hoffmann-La Roche Foundation for financial support. High-resolution mass spectra were measured in the National Institutes of Health supported facility at the Massachusetts Institute of Technology (Grant FR 00317) under the direction of Professor K. Biemann.

Registry No.—**2,** 4043-71-4; **9,** 67010-45-1; **10,** 66967-24-6; **11,** 57467-91-1; **12,** 66967-25-7; **14,** 66967-26-8; **15,** 66967-27-9; **18,** 66967-28-0; allyl bromide, 106-95-6.

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A Useful Synthesis of 3-Oxodihydroisoindoles

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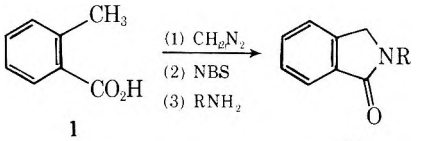
Received April 20, 1978

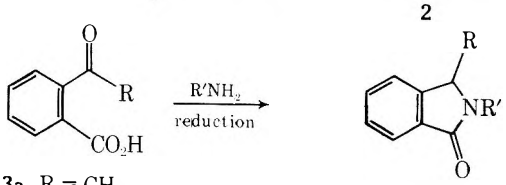
A useful one-step conversion of o-acylbenzoic acids (**3**) to 3-oxodihydroisoindoles (**4**) has been developed. Thus, reductive amination of **3** with a primary amine, the amine hydrochloride, and sodium cyanoborohydride or sodium borohydride in acetonitrile effected the conversion of **3** to **4**. The success of this method is dependent on the initial formation in acetonitrile of a 1-alkyl-1-(alkylamino)dihydroisobenzofuran-3-one, a "ring tautomer" such as **7**, which on protonation is reduced rapidly to **4** by these metal hydrides. Other nucleophiles (CH_3NH_2 and CN^-) were substituted for the metal hydrides to synthesize 1-substituted analogues of **4** such as 1,2-dimethyl-1-cyano-3-oxodihydroisoindole (**6**).

In the preparation of isoindoles[1] as well as the elaboration of certain natural products,[2,3] 3-oxodihydroisoindoles have served as important synthetic intermediates. Routes of limited utility to these lactams have been described.[4,5] In addition, Danishefsky has reported a useful two-step method to convert methyl o-toluate to *N*-methyl-3-oxodihydroisoindole (eq 1).[2] What we believe to be an equally attractive route to 3-oxodihydroisoindoles in general and a better route from o-acylbenzoic acids to 1,2-disubstituted analogues specifically is set forth below (eq 2).



(1)

1 2



(2)

3a, R = CH_3
b, R = C_2H_5
c, R = n-C_3H_7
d, R = H
e, R = C_6H_5

4a, R = R' = CH_3
b, R = CH_3; R' = C_2H_5
c, R = CH_3, R' = n-C_3H_7
d, R = CH_3; R' = 
e, R = CH_3; R' = $C_6H_5CH_2$
f, R = C_2H_5; R' = CH_3
g, R = n-C_3H_7; R' = CH_3
h, R = H; R' = CH_3
i, R = CH_3; R' = $CH(CH_3)_2$

These lactams (**4**) were required as intermediates for the synthesis of 1,2,3-trisubstituted isoindoles, a class of compounds which has received very limited attention in the literature.[6] Initially, commercially available o-acetylbenzoic acid (**3a**) was hydrogenated to o-ethylbenzoic acid, and this acid was carried through the three-step process of eq 1 with methylamine as the base to provide **4a**. Although this approach was successful with several other primary amines, it was apparent that an alternate direct route (eq 2) from o-acylbenzoic acids **3** to the desired lactams **4** offered certain advantages. Thus, the acids **3** are more readily available either commercially[7] or by synthesis[8] than the corresponding o-alkylbenzoic acids which, in fact, frequently are prepared from **3**. Furthermore, this synthesis in comparison with that of eq 1 involved fewer operational steps and avoided the handling of the intermediate bromo esters which are potent lachrymators.

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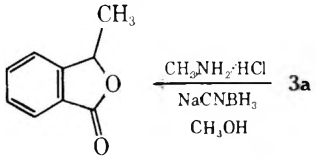
Table I. ^{13}C NMR Chemical Shifts[a] (ppm) in $CDCl_3$

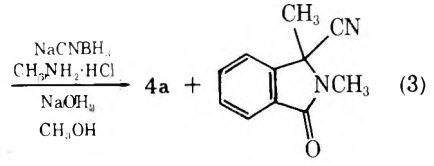
Assignment	Compound no. 5	3a	7	7 HCl	4a	12	13	13 HCl
C-CH_3	20.4	26.7	27.0	25.1	17.9	23.0	22.8	21.8
N-CH_3 (exo)			28.8	32.3			28.3	25.0[b]
N-CH_3 (ring)					26.9	23.4	25.2	25.6[b]
Benzylic	77.7	*d*	107	*d*	57.6	88.3	78.8	78.2
Aromatic	121.7	122.7	122.5	125.1	121.8	121.6	121.7	123.3
Aromatic	125.6	126.3	125.6	127.5	123.4	122.9	123.2	124.0
Aromatic	125.8	126.3	128.4	129.8	128.0	129.1	128.8	131.2
Aromatic	129.1	130.4	130.0	131.7	132.0	130.2	132.0	131.4
Aromatic	134.1	134.5	134.0	134.4	133.3	132.1	132.5	133.6
Aromatic	151.3[c]	148.9	148.6	137.3	146.8	148.4	147.4	140.6
Carbonyl	170.4	168.9	169.2	166.5	168.0	166.9	167.2	167.3

[a] Relative to internal $(CH_3)_4Si$. [b] These assignments may be reversed. [c] Chemical shifts in this row are for the aromatic carbon adjacent to the benzylic carbon of the "ring tautomers". [d] This carbon atom was not observed due to broadening caused by interconversion of "ring and chain tautomers".

Reductive amination with a primary amine and sodium cyanoborohydride[9] ($NaCNBH_3$), a reagent with high selectivity for carbon–nitrogen double bonds, was assumed to be the ideal method for a one-step conversion of **3** to **4** since the concentration of intermediate imine would be expected to be low with an aromatic ketone. In practice, however, addition of $NaCNBH_3$ to a methanol solution of *o*-acetylbenzoic acid (**3a**) and methylamine hydrochloride gave only the lactone **5** (eq 3). The desired lactam **4a** was obtained on treatment of



5



(3)

6

3a or the sodium salt of **3a** with methylamine, methylamine hydrochloride, and $NaCNBH_3$; however, it was contaminated with 15–20% of a byproduct **6**.

The probability that cyanide (derived hydrolytically from the $NaCNBH_3$ in this reaction medium) was adding to the imine intermediate to form **6** prompted a solvent change to acetonitrile. Thus, a solution of **3a** in acetonitrile was treated with anhydrous methylamine followed by addition of methylamine hydrochloride and $NaCNBH_3$. These conditions effected the conversion of **3a** to **4a** in high yield with no detectable contamination by either **5** or **6**. Surprisingly, substitution of sodium borohydride ($NaBH_4$) for $NaCNBH_3$ gave the same result in this case.

The generality of this method was tested using **3a** with $NaCNBH_3$ and the following primary amines: ethyl-, *n*-propyl-, 2-propyl-, cyclopropyl-, benzyl-, and *tert*-butylamines. High yield conversions to the corresponding lactams **4** were observed except with 2-propyl-[10] and *tert*-butylamines. In these cases, the only product isolated was the lactone **5**. This method was further tested using methylamine and either $NaBH_4$ or $NaCNBH_3$ with the following o-acylbenzoic acids: *o*-propionyl- (**3b**), o-butyryl- (**3c**), *o*-formyl- (**3d**), and *o*-benzoylbenzoic acids (**3e**). Good yields of the lactams were obtained with the exception of **3e**, which gave only a lactone product.

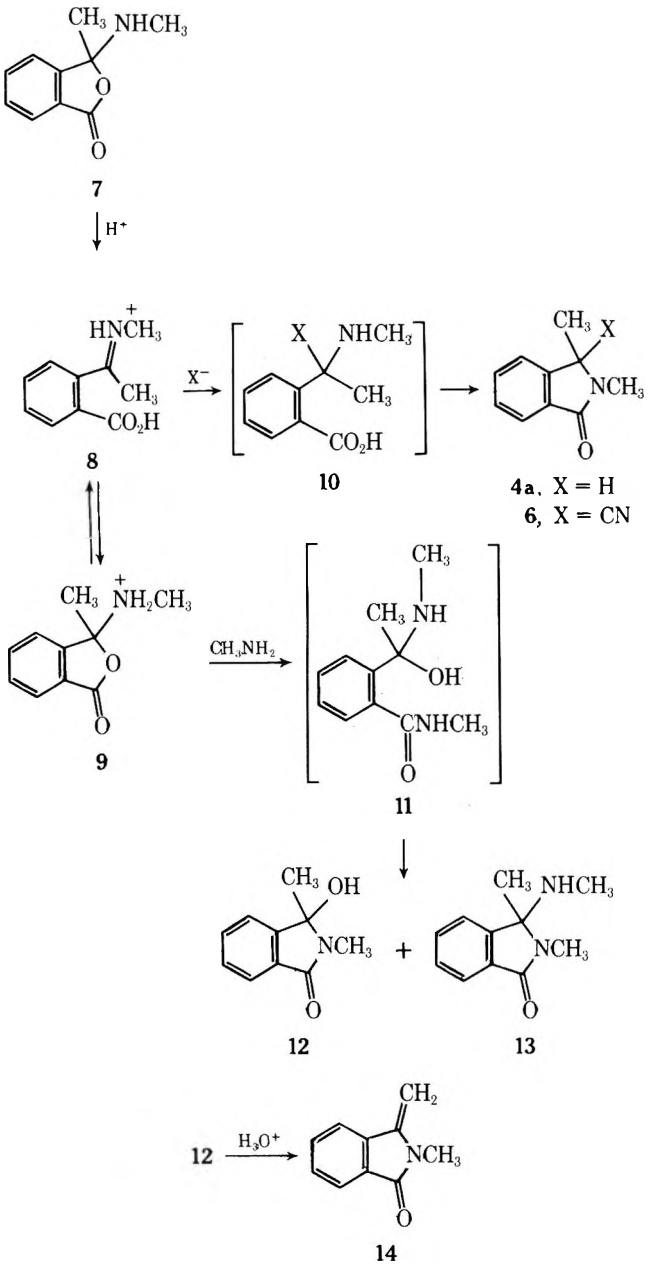
In order to examine this reaction in more detail, a solution of **3a** in acetonitrile was saturated with anhydrous methylamine and then evaporated. The resulting crystalline white solid exhibited spectral properties (see Experimental Section and Table I) totally consistent with the ring tautomer **7**. The ^1H NMR chemical shifts for the C-CH_3 and N-CH_3 groups of **7** remain constant in Me_2SO-d_6, $CDCl_3$, and CD_3CN, while the NMR spectra of systems such as **3a**, which may exist as ring and chain tautomers, are solvent dependent.[11] When the reaction of **3a** with methylamine was monitored by ^1H NMR spectroscopy, the conversion of **3a** to **7** was so rapid that the intermediate carbinolamine and imine were not observed.

The ring tautomer **7** was hydrolyzed readily to **3a** on exposure to dilute aqueous acid. Solutions of **7** in aprotic solvents, however, were remarkably stable. Thus, recrystallization of **7** from hot hexane could be carried out with minimal loss, and **7** could be recovered from acetonitrile solution to which either methylamine, methylamine hydrochloride, or $NaCNBH_3$ had been added. The conversion of **7** to **4a** occurred only when the latter two reagents (methylamine hydrochloride and $NaCNBH_3$) were both present in the reaction medium. However, **7** underwent reduction to a mixture of products including **5** and **4a** when $NaBH_4$ alone was added. Again, the combination of $NaBH_4$ and methylamine hydrochloride was required for smooth conversion of **7** to **4a** in acetonitrile.

These results suggested that protonation of **7** was instrumental in the reduction process. Thus, addition of methylamine hydrochloride could effect conversion of **7** to the protonated ring chain tautomers **8** and **9**, which should exhibit enhanced reactivity toward metal hydride reducing agents and other added nucleophiles. To test this concept, sodium cyanide (NaCN) was added to an acetonitrile solution of **7**. After 3 h, conversion of **7** to the cyanide adduct **6** could not be detected (TLC). The subsequent addition of methylamine hydrochloride to this solution, however, resulted in the rapid efficient conversion of **7** to **6**. That the amine hydrochloride was serving solely as a proton source was supported by the observation that substitution of ethylamine hydrochloride for methylamine hydrochloride did not change the product composition in either this reaction or the hydride reduction of **7** to **4a**. Furthermore, while **7** was recovered after standing for 24 h in acetonitrile containing methylamine, the addition of methylamine hydrochloride to this solution slowly (24 h) transformed **7** to a mixture of **12** and **13**. These results are illustrated in Scheme I.

That **12** and **13** have the ring tautomer structure was clearly evident both from their ^{13}C NMR spectra and from the fact that they could be recovered from acetonitrile solution after treatment with $NaBH_4$ and methylamine hydrochloride. The lactam **13** also was stable in aqueous hydrochloric acid and could be isolated as a hydrochloride. The lactam **12** on similar

Scheme I



treatment gave the unstable dehydration product **14**.

Thus, **7** on protonation is transformed to the ring and chain tautomers **8** and **9**, which are converted to products by added nucleophiles. Although this process was not observable directly by ^{1}H NMR spectroscopy due to the low concentration (~1%) of **8** and **9** under the reaction conditions, a comparison of the ^{13}C NMR spectra (Table I) of **7** and **7** HCl supported this concept. Thus, the resonance (107 ppm) for the benzylic carbon atom in **7** disappears in the spectrum of **7** HCl due to line broadening as a consequence of the equilibrium **8** ⇄ **9**. The benzylic carbon atom also is not observed in **3a**, which is a mixture of ring and chain tautomers. Furthermore, the chemical shift for the comparable carbon atom in **13** is not changed appreciably by protonation of the nitrogen consistent with the view that both species are ring tautomers. In addition, the aromatic ring carbon adjacent to this center exhibits a much larger (11.3 ppm) upfield shift on protonation of the nitrogen in **7** than is observed for protonation of **13** (6.8 ppm).[12] Lastly, the product compositions outlined in Scheme I are best understood in terms of the equilibrium **8** ⇄ **9**.

In conclusion, a useful one-step method for converting o-acylbenzoic acids to 1,2-disubstituted 3-oxodihydroisoindoles has been described. This transformation passes through a 1-alkyl-1-(alkylamino)isobenzofuran-3-one intermediate which is subsequently protonated and reduced by metal hydrides. The only limitations to this method are its failure with highly hindered amines (*tert*-butylamine) and aromatic ketones (*o*-benzoylbenzoic acid).

Experimental Section

Melting points (Thomas-Hoover melting point apparatus) and boiling points are uncorrected. Spectra were obtained as follows: IR spectra on a Perkin-Elmer 237; mass spectra on an AEI MS 902 by direct insertion; ^{1}H NMR spectra on a Varian T-60 or EM 390 spectrometer using $(CH_3)_4Si$ as an internal standard; and ^{13}C NMR spectra on a Varian CFT-20. GLC was performed on a Hewlett-Packard Model 5700A/3370B GLC using a glass column (6 ft × 2 mm) packed with 1% OV-17 on 100 *N* 120 mesh Gas-Chrom Q with a helium flow rate of 32 mL/min.

1,2-Dimethyl-3-oxodihydroisoindole (4a). To a solution of methylamine (1.8 g, 0.06 mol) in acetonitrile (150 mL) was added **3a** (4.1 g, 0.025 mol) followed after 15 min by methylamine hydrochloride (3.4 g, 0.05 mol) and $NaCNBH_3$ (2.0 g, 0.03 mol). The reaction mixture was stirred for 3 h. The solvent was removed under reduced pressure and the residue slurried with H_2O. The pH was adjusted to 4 with concentrated HCl, and the resulting solution was extracted with chloroform (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. Distillation of the concentrate gave 3.5 g (87%) of **4a:** bp 95–97 °C (0.3 Torr); ^{1}H NMR ($CDCl_3$) δ 1.5 (d, 3 H, CCH_3, J = 7 Hz), 3.1 (s, 3 H, NCH_3), 4.4 (q, 1 H, benzylic, J = 7 Hz), 7.4–7.9 (m, 4 H, aromatic); IR (neat) 1685 (C=O) cm^{-1}; MS *m/e* (%) 161 (33, M^+), 146 (100, $M^+ - CH_3$); GLC (99%), retention time 2.8 min (130 °C).

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.53; H, 6.83; N, 8.69. Found: C, 74.91; H, 6.95; N, 8.41.

1-Methyl-2-ethyl-3-oxodihydroisoindole (4b). Compound **4b** was prepared from **3a** (3.3 g, 0.02 mol), ethylamine (4.5 g, 0.1 mol), ethylamine hydrochloride (4.05 g, 0.05 mol), and $NaCNBH_3$ (2.0 g, 0.03 mol) in acetonitrile (150 mL) as described for the synthesis of **4a.** Distillation gave 2.8 g (86%) of **4b:** bp 98–102 °C (0.1 Torr); ^{1}H NMR ($CDCl_3$) δ 1.0 (t, 3 H, NCH_2CH_3, J = 7 Hz), 1.2 (d, 3 H, CCH_3, J = 7 Hz), 3.3 (m, 1 H, NCH_2), 3.7 (m, 1 H, NCH_2), 4.8 (q, 1 H, benzylic, J = 7 Hz), 7.4–8.0 (m, 4 H, aromatic); IR (neat) 1690 (C=O) cm^{-1}; MS *m/e* (%) 177 (11, M^+), 162 (100, $M^+ - CH_3$); GLC (99%), retention time 7.5 min (130 °C).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.43; H, 7.43; N, 8.00. Found: C, 75.15; H, 7.09; N, 7.91.

1-Methyl-2-*n*-propyl-3-oxodihydroisoindole (4c). Compound **4c** was prepared from **3a** (3.3 g, 0.02 mol), *n*-propylamine (5.9 g, 0.1 mol), *n*-propylamine hydrochloride (4.8 g, 0.05 mol), and $NaCNBH_3$ (2.0 g, 0.03 mol) as described for **4a.** Distillation gave 3.3 g (88%) of **4c:** bp 98–102 °C (0.1 Torr); ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3 H, $N(CH_2)_2CH_3$, J = 7 Hz), 1.4 (d, 3 H, CCH_3, J = 7 Hz), 1.6–2.0 (m, 2 H, NCH_2CH_2), 3.2 (m, 1 H, NCH_2), 3.9 (m, 1 H, NCH_2), 4.5 (q, 1 H, benzylic, J = 7 Hz), 7.4–8.0 (m, 4 H, aromatic); IR (neat) 1690 (C=O), cm^{-1}; MS *m/e* (%) 189 (6, M^+), 174 (100, $M^+ - CH_3$), 160 (30, $M^+ - C_3H_7$); GLC (99.3%), retention time 7.7 min (130 °C).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.19; H, 7.93; N, 7.40. Found: C, 75.90; H, 8.19; N, 7.12.

1-Methyl-2-cyclopropyl-3-oxodihydroisoindole (4d). A solution of **3a** (3.3 g, 0.02 mol) and cyclopropylamine (5.7 g, 0.1 mol) was stirred overnight. To this solution was added cyclopropylamine hydrochloride (4.7 g, 0.05 mol) followed by the portionwise addition (six equal portions over 60 min) of $NaBH_4$ (1.2 g, 0.03 mol). The solvent was removed under reduced pressure, the residue slurried with H_2O (75 mL), the pH adjusted to 4 with concentrated HCl, and the resulting solution extracted with chloroform (4 × 75 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Distillation of the concentrate gave 3.0 g (80%) of **4d:** bp 131–133 °C (0.1 Torr); ^{1}H NMR ($CDCl_3$) δ 0.6–1.2 (m, 4 H, methylene), 1.6 (d, 3 H, CH_3, J = 7 Hz), 2.7 (m, 1 H, NCH), 4.5 (q, 1 H, benzylic, J = 7 Hz), 7.2–8.0 (m, 4 H, aromatic); IR (neat) 1675 (C=O) cm^{-1}; MS *m/e* (%) 187 (77, M^+), 172 (100, $M^+ - CH_3$); GLC (92%), retention time 6.0 min (130 °C). An analytical sample was obtained from a center cut of the distillate.

Anal. Calcd for $C_{12}H_{13}NO$: C, 77.00; H, 6.95; N, 7.49. Found: C, 77.41; H, 6.91; N, 7.30.

1-Methyl-2-benzyl-3-oxodihydroisoindole (4e). Compound **4e** was prepared from **3a** (32.8 g, 0.2 mol), benzylamine (64.3 g, 0.6 mol), benzylamine hydrochloride (57 g, 0.4 mol), and $NaBH_4$ (5.3 g, 0.14

mol) in acetonitrile (1000 mL) as described for **4d.** Distillation gave 29 g (61%) of **4e:** bp 158–162 °C (0.1 Torr); ^{1}H NMR ($CDCl_3$) δ 1.4 (d, 3 H, CCH_3, J = 7 Hz), 4.2 (d, 1 H, $C_6H_5CH_2$, J = 15 Hz), 4.3 (q, 1 H, benzylic, J = 7 Hz), 5.3 (d, 1 H, $C_6H_5CH_2$, J = 15 Hz), 7.2–8.0 (m, 4 H, aromatic); IR (neat) 1670 (C=O) cm^{-1}; MS *m/e* 237 (M^+), 222 ($M^+ - CH_3$), 147 ($M^+ - C_7H_7$) GLC (98.8%), retention time 10.6 min (160 °C).

Anal. Calcd for $C_{16}H_{15}NO$: C, 81.01; H, 6.33; N, 5.90. Found: C, 80.71; H, 6.17; N, 6.11.

1-Ethyl-2-methyl-3-oxodihydroisoindole (4f). Compound **4f** was synthesized from **3b** (3.5 g, 0.02 mol), methylamine (3.1 g, 0.1 mol), methylamine hydrochloride (6.75 g, 0.1 mol), and $NaCNBH_3$ (2.0 g, 0.03 mol) in acetonitrile as described for **4a.** Distillation gave 3.0 g (86%) of **4f:** bp 100–103 °C (0.3 Torr); ^{1}H NMR ($CDCl_3$) δ 0.6 (t, 3 H, CCH_3, J = 6 Hz), 2.0 (m, 2 H, CCH_2), 3.1 (s, 3 H, NCH_3), 4.5 (t, 1 H, CH, J = 4 Hz), 7.4–8.0 (m, 4 H, aromatic); IR (neat) 1690 (C=O) cm^{-1}; MS *m/e* (%) 175 (7, M^+), 146 (100, $M^+ - C_2H_5$); GLC (98.8%), retention time 4.9 min (130 °C).

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.43; H, 7.43; N, 8.00. Found: C, 75.08; H, 7.19; N, 8.13.

1-Propyl-2-methyl-3-oxodihydroisoindole (4g). Compound **4g** was prepared from **3c** (3.8 g, 0.02 mol), methylamine (3.1 g, 0.1 mol), methylamine hydrochloride (6.75 g, 0.1 mol), and $NaBH_4$ (1.2 g, 0.03 mol) in acetonitrile (150 mL) as described for **4d.** Distillation gave 2.8 g (80%) of **4g:** bp 102–106 °C (0.4 Torr); ^{1}H NMR ($CDCl_3$) δ 0.8–2.0 (m, 7 H, $CH_2CH_2CH_3$), 3.0 (s, 3 H, NCH_3), 4.4 (t, 1 H, benzylic, J = 4 Hz), 7.2–7.9 (m, 4 H, aromatic); IR (neat) 1690 (C=O) cm^{-1}; MS *m/e* (%) 189 (5, M^+), 146 (100, $M^+ - C_3H_7$); GLC (96%), retention time 5.1 min (130 °C). A center cut of the distillate was used as an analytical sample.

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.19; H, 7.94; N, 7.41. Found: C, 76.41; H, 8.11; N, 7.13.

2-Methyl-3-oxodihydroisoindole (4h). Compound **4h** was prepared from **3d** (3.0 g, 0.02 mol) as described for **4g.** Distillation gave 2.0 g of **4h,** bp 135–140 °C (2 Torr), which crystallized. Recrystallization from cyclohexane gave 1.4 g (46%) of **4h:** mp 116–118 °C (lit.[13] mp 116.5 °C); ^{1}H NMR ($CDCl_3$) δ 3.1 (s, 3 H, NCH_3), 4.2 (s, 2 H, NCH_2), 7.3–7.9 (m, 4 H, aromatic); IR (Nujol) 1675 (C=O) cm^{-1}.

Anal. Calcd for C_9H_9NO: C, 73.32; H, 6.11; N, 9.50. Found: C, 73.41; H, 5.94; N, 9.89.

1-Methyl-2-(2-propyl)-3-oxodihydroisoindole (4i). A solution of **3a** (3.3 g, 0.02 mol) and 2-propylamine (5.9 g, 0.1 mol) in acetonitrile (200 mL) was heated under reflux for 18 h. The solvent was evaporated and the residue extracted into hot hexane. Cooling gave 3.3 g of crystalline 1-methyl-1-(2-propylamino)isobenzofuran-3-one: mp 80–82 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (d, 6 H, CCH_3, J = 6 Hz), 1.9 (s, 3 H, CCH_3), 2.8 (m, 2 H, CH and NH), 7.4–8.0 (m, 4 H, aromatic); IR (Nujol) 1740 cm^{-1}.

This compound was dissolved in acetonitrile (100 mL) to which was added anhydrous HCl (0.7 g) and $NaBH_4$ (0.76 g, 0.02 mol). After stirring overnight, the solvent was evaporated and the residue slurried with 0.1 M aqueous HCl. The pH was adjusted to 8 with concentrated aqueous NH_3 and the mixture extracted with chloroform (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Distillation of the concentrate gave 2.6 g (70%) of **4i:** bp 88–91 °C (0.1 Torr); ^{1}H NMR ($CDCl_3$) δ 1.0 and 1.09 (dd, 6 H, $CH(CH_3)_2$, J = 6 Hz), 1.25 (d, 3 H, CCH_3, J = 6 Hz), 4.0 (p, 1 H, $CH(CH_3)_2$, J = 6 Hz), 4.25 (q, 1 H, benzylic, J = 6 Hz), 7–7.8 (m, 4 H, aromatic); IR (neat) 1685, 1230, 760, 720, 690 cm^{-1}; MS *m/e* (%) 189 (18, M^+), 174 (100, $M^+ - CH_3$), 132 (32), 131 (28), 103 (13).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.19; H, 7.93; N, 7.40. Found: C, 76.11; H, 7.98; N, 7.31.

1-Methyl-1-(methylamino)isobenzofuran-3-one (7). Anhydrous methylamine (1.6 g, 0.05 mol) was introduced through a gas inlet tube into a solution of **3a** (1.64 g, 0.01 mol) in acetonitrile (100 mL). After stirring for 15 min, the solution was concentrated to dryness under reduced pressure and the residue was recrystallized from hexane to yield 1.5 g (85%) of **7:** mp 110–113 °C; ^{1}H NMR ($CDCl_3$) δ 1.8 (s, 3 H, CCH_3), 2.2 (s, 3 H, NCH_3), 2.5 (s, 1 H, NH), 7.3–7.9 (m, 4 H, aromatic); MS *m/e* (%) 177 (6, M^+), 162 (77), 147 (100), 132 (78); IR (Nujol) 3340 (NH), 1740 (C=O), 1030, 860, 730, 710 cm^{-1}; $pK_a(H_2O)$ = 8.5.

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.77; H, 6.26; N, 7.90. Found: C, 67.84; H, 6.26; N, 8.06.

Conversion of 7 to 7 Hydrochloride. A solution of **7** in $CHCl_3$ was treated with anhydrous HCl and then filtered and concentrated to dryness under reduced pressure. Recrystallization of the residue from $CHCl_3$–hexane gave **7** hydrochloride: mp 135–137 °C; ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3 H) and 2.78 (s, 3 H) (CCH_3 and NCH_3), 7.4–8.2 (m, 6 H, aromatic and 2 H exchanged by D_2O); IR (Nujol) 2700, 2580, 2460, 1695 (C=O) cm^{-1}.

Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.23; H, 5.66; N, 6.55. Found: C, 55.91; H, 5.72; N, 6.61.

Reaction of 7 with Methylamine Hydrochloride and NaCN. A solution of **3a** (2.5 g, 0.015 mol) and methylamine (2.3 g, 0.075 mol) in acetonitrile (100 mL) was slurried with methylamine hydrochloride (5.1 g, 0.075 mol) for 20 min and then treated with NaCN (1.8 g). After stirring for 18 h, the solvent was evaporated, water added, the pH adjusted to 3 with concentrated HCl, and the reaction mixture extracted with $HCCl_3$ (3 × 100 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated. Recrystallization of the solid residue from cyclohexane gave 2.0 g (71%) of **6,** mp 101–103 °C. The spectral properties of this sample were identical with those of the sample prepared below.

1,2-Dimethyl-3-oxodihydroisoindol-1-ol (12) and 1,2-Dimethyl-1-methylamino-3-oxodihydroisoindole (13). A solution of **3a** (3.28 g, 0.02 mol), anhydrous methylamine (3.1 g, 0.1 mol), and methylamine hydrochloride (1.35 g, 0.02 mol) in acetonitrile (300 mL) was stirred for 48 h and filtered, and the filtrate was evaporated under reduced pressure. The residue was extracted with chloroform (100 mL) and filtered, and the filtrate was concentrated to dryness under reduced pressure. The residue was chromatographed on silica gel with ethyl acetate containing 2% methanol as eluent. Eluted first was **12:** mp 127–129 °C (lit.[14] mp 128–130 °C); ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 3 H, CCH_3), 2.65 (s, 3 H, NCH_3), 4.8 (br s, 1 H, OH), 7.2–7.6 (m, 4 H, aromatic); IR (Nujol) 3240, 1675 cm^{-1}.

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.25; N, 7.90. Found: C, 67.61; H, 6.36; N, 7.68.

Eluted second was **13:** mp 104–107 °C; ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 3 H, CCH_3), 1.77 (s, 3 H, $NHCH_3$), 2.53 (s, 1 H, NH), 2.93 (s, 3 H, NCH_3), 7.3–7.8 (m, 4 H, aromatic); MS *m/e* (%) 190 (1, M^+), 175 (2, $M^+ - CH_3$), 160 (100, $M^+ - NHCH_3$); IR (Nujol) 3300, 1670 (C=O), 1170, 790, 700 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}N_2O$; C, 69.47; H, 7.36; N, 14.74. Found: C, 69.67; H, 7.66; N, 14.87.

Conversion of 13 to 13 Hydrochloride. A solution of **13** in chloroform was treated with anhydrous HCl and filtered, and the filtrate was evaporated to dryness. The residue was recrystallized from hexane–chloroform to yield **13** hydrochloride: mp 150–152 °C; ^{1}H NMR ($CDCl_3$) δ 2.1 (s, 3 H) and 2.2 (s, 3 H) ($NHCH_3$ and CCH_3), 3.27 (s, 3 H, NCH_3), 7.3–8.2 (m, 5 H, aromatic and NH_2); IR (Nujol) 2660, 2520, 2500, 2480, 1715 (C=O), 1585, 1080,1110, 700, 770 cm^{-1}.

Anal. Calcd for $C_{11}H_{15}ClN_2O$: C, 58.27; H, 6.67; N, 12.35. Found: C, 58.20; H, 6.56; N, 12.30.

Reaction of 3a with Methylamine Hydrochloride and $NaCNBH_3$ in Methanol. A solution of **3a** (16.4 g, 0.1 mol), methylamine hydrochloride (13.5 g, 0.2 mol), and $NaCNBH_3$ (6.5 g, 0.1 mol) in methanol (200 mL) was stirred for 24 h. The solvent was removed under reduced pressure, and the residue was slurried with 1.5 N aqueous HCl (300 mL) and extracted with chloroform (4 × 75 mL). The combined extracts were dried over Na_2SO_4 and filtered, and the filtrate was evaporated to yield 13.6 g (92%) of **5:** ^{1}H NMR ($CDCl_3$) δ 1.6 (d, 3 H, CCH_3, J = 7.5 Hz), 5.55 (q, 1 H, benzylic, J = 7.5 Hz), 7.2–7.9 (m, 4 H, aromatic); MS *m/e* 148 (M^+), 133 ($M^+ - CH_3$) 105 ($C_6H_5CO^+$); GLC 99%. These spectral properties were identical with those of **5** from independent synthesis.[5,15]

Reaction of 3a with Methylamine Hydrochloride, NaOH, and $NaCNBH_3$ in Methanol. To a solution of **3a** (24.6 g, 0.15 mol) in methanol (300 mL) was added NaOH (6 g, 0.15 mol) followed by methylamine hydrochloride (68 g, 1.0 mol) and $NaCNBH_3$ (9.75 g, 0.15 mol). After stirring for 24 h, the solvent was removed under reduced pressure and the residue slurried with 3 N aqueous HCl (500 mL). The pH was adjusted to 8.5 (aqueous NH_3) and the solution extracted with chloroform (4 × 100 mL). The combined extracts were dried over Na_2SO_4 and filtered, and the filtrate was evaporated to yield a liquid (28.9 g). GLC analysis indicated two components (**4a** and **6**) in a 70:30 ratio. Fractional distillation (0.25 Torr) separated 10 g of **4a** (bp 100–103 °C) and gave a fraction (10 g) containing a mixture of **4a** and **6.** The pot residue (5.35 g) crystallized and was recrystallized from cyclohexane to yield 3.7 g of **6:** mp 101–104 °C; ^{1}H NMR ($CDCl_3$) δ 1.8 (s, 3 H, CCH_3), 3.2 (s, 3 H, NCH_3), 8.0 (m, 4 H, aromatic); MS *m/e* 186 (M^+); IR (KBr) 2200 (C≡N), 1690 (C=O) cm^{-1}.

Anal. Calcd for $C_{11}H_{10}N_2O$; C, 70.67; H, 5.78; N, 14.99. Found: C, 71.00 H, 5.55; N, 14.96.

Hydrolysis of 12. A solution of **12** (0.88 g, 0.005 mol) in 6 N aqueous HCl (20 mL) was warmed to 80 °C for 45 min, cooled, and extracted with chloroform (4 × 20 mL). The combined extracts were dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. TLC (silica gel; benzene–dioxane–acetic acid, 25:5:1) demonstrated this to be a six component mixture containing **12, 3a,** and **14.** Column chromatography on silica gel eluting with ethyl ace-

tate gave 0.18 g of **14**: ^{1}H NMR ($CDCl_3$) δ 3.23 (s, 3 H, NCH_3), 4.81 (d, 1 H, vinyl, J = 3 Hz), 5.17 (d, 1 H, vinyl, J = 3 Hz), 7.4–7.9 (m, 4 H, aromatic); MS m/e 161 (M^+), 104, 78, 66; IR (neat) 1700 (C=O), 770, 700 cm^{-1}.

Hydrolysis of 7. A solution of 7 (1.77 g, 0.01 mol) in 0.1 N aqueous HCl (15 mL) on standing overnight deposited crystalline **3a** (1.5 g). A solution of 7 (0.88 g, 0.005 mol) in 6 N aqueous HCl (20 mL) was warmed to 80 °C, cooled, and extracted with chloroform (4 × 20 mL). The combined extracts were dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The ^{1}H NMR and TLC characteristics of the concentrate (0.7 g) were qualitatively identical with those of the crude reaction mixture obtained on hydrolysis of **12**: Chromatography on silica gel eluting with ethyl acetate gave 0.15 g of **14**.

Acknowledgment. The authors wish to thank Dr. David Cochran for ^{13}C NMR spectra, Mr. Robert Rhodes for mass spectra, Mr. A. Augenblick for GLC analyses, Mr. K. B. Streeter and Mrs. Jan Stranick for the microanalyses, and Professor Gordon Gribble for many valuable discussions.

Registry No.—**3a,** 577-56-0; **3b,** 2360-45-4; **3c,** 19666-03-6; **3d,** 119-67-5; **4a,** 58083-35-5; **4b,** 58083-36-6; **4c,** 58083-39-9; **4d,** 58083-37-7; **4e,** 1726-16-5; **4f,** 66967-33-7; **4g,** 66967-34-8; **4h,** 5342-91-6; **4i,** 66967-35-9; **5,** 3453-64-3; **6,** 66967-36-0; **7,** 66967-29-1; **7** HCl, 66967-30-4; **12,** 29879-71-8; **13,** 66967-31-5; **13** HCl, 66967-32-6; **14,** 32360-90-0; methylamine, 74-89-5; sodium cyanoborohydride, 25895-60-7; ethylamine, 75-04-7; *n*-propylamine, 107-10-8; cyclopropylamine, 765-30-0; benzylamine, 100-46-9; 2-propylamine, 75-31-0.

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Fries Rearrangement of Trimethylhydroquinone Diacetate. A Novel Hydroquinone to Resorcinol Transformation

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Received April 5, 1978

Fries rearrangement of trimethylhydroquinone diacetate (**1b**) ($AlCl_3$, 220 °C) leads to 1-(2,6-dihydroxy-3,4,5-trimethylphenyl)ethanone (4) and not the expected (and previously reported) 1-(2,5-dihydroxy-3,4,6-trimethylphenyl)ethanone (**2a**). Resorcinol 4 arises via secondary rearrangements of the normal products 2a and **2b**. A mechanistic rationale is proposed.

While pursuing synthetic studies aimed at (2*R*,4′*R*,8′*R*)-α-tocopherol (vitamin E),[1] we recently required dihydroxytrimethylacetophenone **2a** as a starting material. A search of the literature revealed two apparent preparations of this substance; however, the reported melting points were not in agreement. In 1938, von Werder and Jung[2] described **2a** as a yellow solid, mp 152 °C, prepared by Fries rearrangement of trimethylhydroquinone diacetate (**1b**) using aluminum chloride at 220 °C. On the other hand, Manecke and Bourwieg, in 1962, claimed that treatment of trimethylhydroquinone (**1a**) with boron trifluoride–acetic acid complex at 100 °C produced the monoacetate **2b** which, upon saponification, yielded **2a** obtained as a yellow solid, mp 111 °C. We have reinvestigated these transformations and now wish to report that while the latter material is, in fact, **2a**, the dihydroxyacetophenone isolated from high temperature aluminum chloride treatment of **1b** is the resorcinol **4**.

Results

Repetition of the boron trifluoride–acetic acid treatment of **1a**[3] smoothly gave **2b** which, in turn, yielded the acetyl hydroquinone **2a**, mp 107–108 °C, after exposure to methanolic sodium hydroxide. The spectral properties of this acetophenone as well as the derived diacetate **3** were in accord with the proposed structural arrangement (see below and Experimental Section).

In contrast, treatment of **1b** with aluminum chloride at 220 °C[2] led to a mixture of products which, although complex, was amenable to analysis by GC and GC–MS. While the major component was, in fact, a dihydroxytrimethylacetophenone (mol wt 194), its retention time was clearly different from that of **2a**, of which substance only trace amounts were detectable. In addition, two chromones were produced whose structures were subsequently proven to be **5a** and **5b** as proposed originally by von Werder and Jung.[2]

On a preparative scale, these three components could be isolated in quite pure form by column chromatography. The dihydroxyacetophenone so obtained was recrystallized several times yielding a yellow solid, mp 136–145 °C, which despite the broad melting range appeared homogeneous on GC analysis. For reasons that are not apparent, we were unable to obtain a sharp melting point for this substance through further recrystallization; nonetheless, we assume it is identical with the product for which von Werder and Jung reported mp 152 °C.

The ^{1}H NMR spectrum of this acetophenone was revealing in its relative simplicity (four singlets in a ratio of 2:3:3:6) which, in contrast to that of **2a** (six singlets in a ratio of 1:1:

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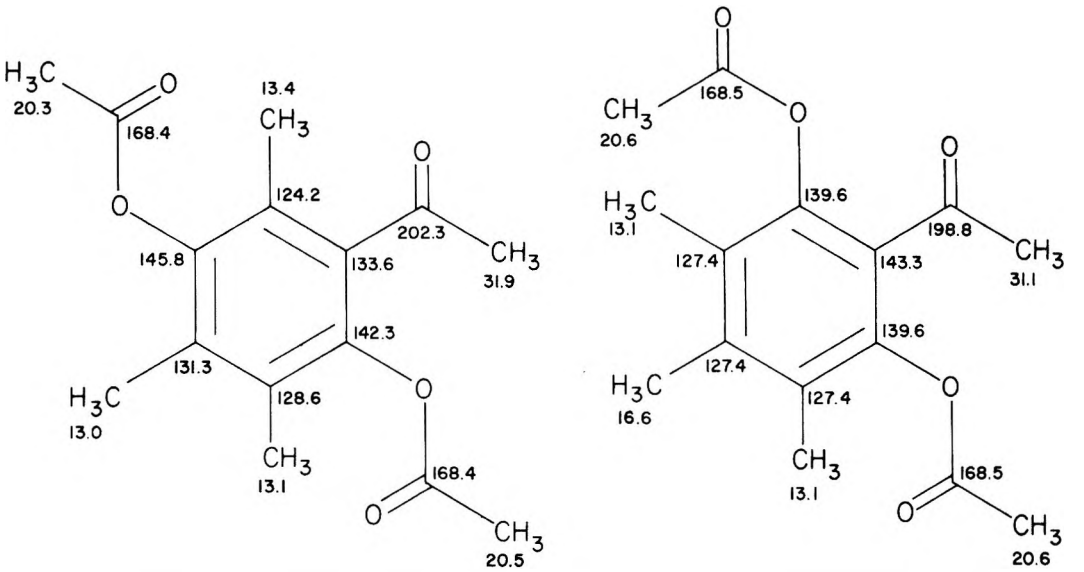
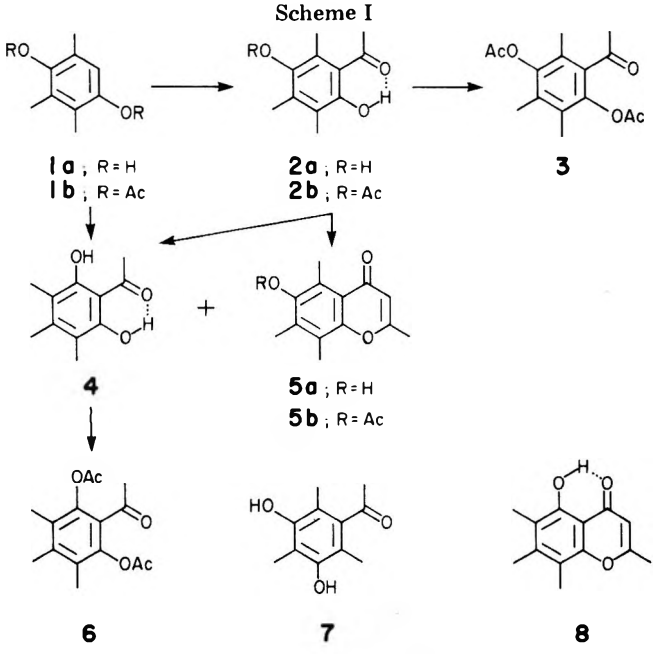


Figure 1. ^{13}C NMR of **3** and **6** taken from the wide-band ^{1}H-decoupled spectra measured in $CDCl_3$. Chemical shifts are in ppm relative to Me_4Si as an internal standard.

Scheme I



3:3:3:3), suggested the presence of a highly symmetrical structural arrangement. Of the six isomeric dihydroxytrimethylacetophenones, only two are symmetrical, namely **4** and **7**. However, the latter possibility was eliminated when it was noted that the observed product exhibited a carbonyl absorbtion at 1625 cm^{-1} compatible only with an H-bonded acetophenone. Furthermore, the ^{1}H NMR band due to the phenolic protons occurred at relatively low field (δ 10.45 ppm) again indicating the presence of intramolecular H bonding possible in **4**, but not in **7**. Final confirmation of structure **4** for the acetophenone derived from $AlCl_3$ rearrangement of **1b** was achieved by ^{13}C NMR spectroscopy. The proton decoupled ^{13}C NMR spectra of the derived diacetate **6** and the isomer **3** are summarized in Figure 1. Whereas **3** exhibits 14 distinct resonances, **6**, possessing mirror plane symmetry, gives rise to only nine, in agreement with the proposed structure.

Chromones **5a** and **5b** were prepared by independent synthesis for comparison purposes. Thus **2a** was treated with sodium hydride–ethyl acetate producing a β-diketone which was directly cyclized with HCl in acetic acid.[4,5] This gave **5b** (44%) which upon mild alkaline hydrolysis furnished the hydroxy chromone **5a**. These materials were identical with those produced in the $AlCl_3$ rearrangement of **1b**. Spectral examination (IR, NMR) of **5a** indicated the absence of intramolecular H bonding. In this manner it was established that the chromones derived from the Fries rearrangement originated from **2a** or **2b** and not from **4** in which case a 5-hydroxychromone (**8**) would have resulted.[6]

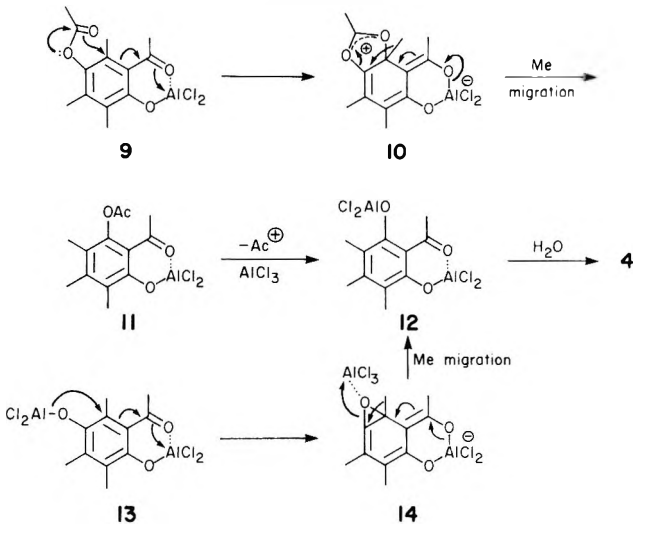
Further scrutiny of the Fries rearrangement ($AlCl_3$) of **1b** revealed that at temperatures below 220 °C (120–160 °C), mixtures containing both **2a** and **4** were obtained; the more vigorous the conditions, the more **4** was produced. In fact, we were unable to effect conversion of **1b** to **2a** or **2b** without the concomitant formation of substantial amounts of **4** using aluminum chloride. Since it appeared that **4** had arisen by further rearrangement of either **2a** or **2b**, we subjected both of the latter compounds to the reaction conditions. The results of these experiments as well as those involving **1b** are presented in Table I and clearly show that **4** is, in fact, derived from rearrangement of both **2a** and **2b**. The mixture obtained starting from **1b** and that from **2b** were similar in that **4**, **5a**, and **5b** comprised 88% of the crude product. On the other hand, the mixture arising from **2a** was much more complex and contained a substantial amount (28%) of trimethylhydroquinone (**1a**) in addition to **4**, **5a**, and **5b**. It should be noted that in all three experiments, several unidentified minor products were observed. One of these exhibited a molecular weight of 194 and is, therefore, assumed to be a third isomeric dihydroxytrimethylacetophenone. Because this substance was usually produced in very small quantities, its structure elucidation was not pursued.

Discussion

The migration of alkyl groups during the Fries rearrangement of phenolic esters with aluminum chloride is a well-known phenomenon.[7] In general, if the newly introduced acyl moiety encounters an ortho alkyl substituent, the alkyl group migrates to a meta position in order to relieve steric strain.[7b] The transformations of **2a** and **2b** to **4** represent additional examples of this type of rearrangement; however, the simultaneous 1,2 migration of an hydroxyl (or acetoxyl) group appears to be unprecedented and constitutes the rather remarkable conversion of a hydroquinone to a resorcinol.

A possible mechanistic rationale for this secondary rearrangement is delineated in Scheme II. Thus one might envi-

Scheme II



sion complex **9** (derived from **1b** via the initially formed **2b**) undergoing an intramolecular conjugate addition as shown, promoted by chelation with aluminum and leading to the zwitterionic enolate species **10**. Regeneration of the ketone moiety can then occur *with methyl migration* producing **11** in which the original *o*-methyl and *m*-acetoxyl substituents have been transposed. Deacetylation then yields complex **12** which on hydrolysis provides the observed resorcinol **4**. Alternatively, **12** could be derived from hydroquinone **2a** via intermediates **13** and **14** which are analogous to **9** and **10**, respectively. It should be noted, however, that the ring strain associated with epoxide **14** would render such an intermediate far less favorable than **10**. This may explain why the yield of **4** is substantially higher starting from **1b** or **2b** than from **2a** since, in the latter case, the relatively slow rate of formation of **14** could lead to the intervention of competitive reaction pathways such as the observed deacylation to give **1a**.

Two factors appear responsible for the propensity of hydroquinones **2a,b** to rearrange into resorcinol **4**. The first, and probably most significant, involves steric considerations. In complexes **9** and **13**, a severe steric interaction results from the proximity of the methyl substituent attached to the ketone moiety and that protruding from the ortho position of the aromatic ring (C-6). This unfavorable compression is relieved by the rearrangement to **12**. Secondly, the formation of **12** gives rise to a species having enhanced chelation ability by virtue of the 2,6-dihydroxy substitution pattern. With regard to the chromones **5a,b**, it should be recognized that the formation of these heterocycles like the deacetylation process (**2a** → **1a**) represents an alternative pathway by which the unfavorable steric interactions present in **9** and **13** can be alleviated.[8]

The failure to observe compounds **4**, **5a**, or **5b** in the product derived from the boron trifluoride–acetic acid procedure[3] is probably due to the relatively mild conditions employed which, although sufficient to bring about the Fries rearrangement, are not capable of promoting the further rearrangements noted with neat aluminum chloride.

As a synthetic method for preparing resorcinols such as **4**, the aluminum chloride treatment of hydroquinone diacetates elucidated herein would appear to be severely limited in scope by the steric requirements mentioned above and, therefore, we have not pursued this line of investigation. However, we have encountered other examples of rather unusual chemistry associated with the congested nature of acetophenones **2a,b** and related compounds.[9] These studies will be reported in due course.

Table I. $AlCl_3$ Isomerizations[a]

starting material	registry no.	product distribution, %[b] 4[c,j]	5a[d,k]	5b[e,l]
1b	7479-28-9	62.9 (61.0[i])	8.4	16.8[f]
2a	64794-45-2	33.9 (28.9[i])	4.1	2.6[g]
2b	66901-79-9	54.6 (52.7[i])	14.1	19.2[h]

[a] 220 °C, 30 min. [b] Percentage of crude reaction product determined by GC analysis, Hewlett-Packard 5710A; 3 m × 4 mm (i.d.) column, 10% OV-101 on GCQ 100/120; temperature program for 80–260 °C, 2 °C/min; He carrier gas flow rate 30 mL/min. [c] Retention time 73 min; observed mol wt 194 (GC–MS). [d] Retention time 88 min; observed mol wt 218 (GC–MS). [e] Retention time 93 min; observed mol wt 260 (GC–MS). [f] Eight unidentified minor components present; **2a** (retention time 71 min) absent. [g] 27.6% **1a** present (retention time 56 min, observed mol wt 152 (GC–MS)) and 11 unidentified minor components; **2a** absent. [h] Six unidentified minor components present; **2a** absent. [i] Yield based on weight of crude product and percentage composition. [j] Registry no. 66842-24-8. [k] Registry no. 66842-25-9. [l] Registry no. 66842-26-0.

Experimental Section

All reactions were carried out under an atmosphere of argon. Melting points were determined in open capillaries and are uncorrected. The "usual work-up" involves dilution with water or saturated brine followed by three extractions with the specified solvent. The organic extracts were then combined, washed with saturated brine, dried over anhydrous magnesium sulfate, filtered, and concentrated at 40–50 °C under water aspirator pressure using a rotary evaporator. The residue was dried to constant weight under high vacuum. Column chromatography was performed using EM Silica Gel 60, 0.063–0.2 mm. Thin-layer chromatography was performed using EM 60F-254 precoated silica gel plates developed with either 1:1 hexane–ether or 1:1 toluene–ethyl acetate. Spots were detected with UV light and phosphomolybdic acid spray followed by heating. Infrared spectra were measured in chloroform solution and ultraviolet spectra in 95% ethanol. A Varian XL-100 instrument was used to obtain the NMR spectra. Chemical shifts are reported relative to tetramethylsilane as an internal standard. Low resolution mass spectral and GC–MS determinations were carried out using an electron energy of 70 V. Conditions for the GC separations are described in Table I.

1-(2,5-Dihydroxy-3,4,6-trimethylphenyl)ethanone (2a). Trimethylhydroquinone (**1a**) was converted into the monoacetate **2b** in 90% yield, using boron trifluoride–acetic acid complex as described previously.[3] Saponification of this material with methanolic sodium hydroxide gave **2a** in 71% yield, as a yellow solid, mp 107–108 °C (lit.[3] mp 111 °C), after recrystallization from carbon tetrachloride. In another experiment, a sample, mp 107–108.5 °C (from chloroform–hexane), exhibited: IR 3620 (OH), 1623 cm^{-1} (H-bonded C=O); UV_{max} 277 (ε 6650), 365 (2000), 215 (12 600) (sh), 240 nm (4600) (sh); NMR ($CDCl_3$) δ 11.59 (s, 1, bonded OH), 4.54 (s, 1, OH), 2.57 (s, 3, CH_3C=O), 2.39, 2.20, 2.15 (3s, 9, $ArCH_3$); NMR (Me_2SO-d_6) δ 8.53 (s, 1, bonded OH), 7.57 (s, 1, OH), 2.35 (s, 3, CH_3C=O), 2.04, 1.99, 1.96 (3s, 9, $ArCH_3$); MS, *m/e* 194 (M^+); TLC, R_f 0.26 (1:1 hexane–ether).

1-(2,5-Dihydroxy-3,4,6-trimethylphenyl)ethanone Diacetate (3). A solution of 0.2 g (1.03 mmol) of **2a** in 4 mL of pyridine and 3 mL of acetic anhydride was stirred at room temperature for 17 h then evaporated in vacuo. The residue was dissolved in dichloromethane and the solution was washed with saturated aqueous sodium bicarbonate then processed in the usual manner giving 0.28 g (96.1%) of **3** as a yellow solid. Recrystallization from ethanol afforded a tan solid: mp 116–118.5 °C (lit.[3] mp 123 °C); IR 1763 (ester C=O) 1698 cm^{-1} (ketone C=O); NMR ($CDCl_3$) δ 2.41 (s, 3, CH_3COAr), 2.32 (s, 3, CH_3CO_2Ar), 2.24 (s, 3, CH_3CO_2Ar), 2.07, 2.02 (2s, 9, $ArCH_3$); UV 210 (ε 16 700) (sh), 243 (3500) (sh), 280 nm (800) (sh); MS, *m/e* 278 (M^+).

Aluminum Chloride Rearrangements. a. Trimethylhydroquinone Diacetate (1b). An intimately ground mixture of 1.18 g (5 mmol) of trimethylhydroquinone diacetate (**1b**) and 1.76 g (13.1 mmol) of anhydrous aluminum chloride was heated at 220 °C for 30 min.[2] After cooling, the dark reaction mixture was treated with dilute aqueous hydrochloric acid and dichloromethane and the resulting mixture was stirred for 30 min at room temperature. Work-up with dichloromethane in the usual manner gave 0.94 g of a yellow-green solid (see Table I for GC analysis). This material was chromato-

graphed on 100 g of silica gel. Elution with 4:1 and 2:1 hexane–ether afforded 0.563 g of 1-(2,6-dihydroxy-3,4,5-trimethylphenyl)ethanone (4) (TLC, R_f 0.34, 1:1 hexane–ether) as a yellow solid, mp 124–140 °C, which was 86.6% pure by GC analysis (see Table I for conditions). Three crystallizations from ligroin (bp 60–90 °C) gave a yellow solid, mp 136–145 °C (lit.[2] mp 152 °C), which was 100% pure as determined by GC analysis: IR 3605 (OH), 1625 cm^{-1} (H-bonded C=O); UV_{max} 280 (14 900), 360 (2800), 210 (16 900) (sh), 224 nm (10 960) (sh) (lit.[2] UV_{max} 279, 360 nm); NMR (Me_2SO-d_6) δ 10.45 (s, 2, bonded **OH**), 2.70 (s, 3, CH_3C=O), 2.17 (s, 3, C-4 ArCH_3), 2.07 (s, 6, C-3, C-5 ArCH_3); MS, *m/e* 194 (M^+).

Further elution with pure ether gave 98 mg of acetoxy chromone **5b** as a tan solid (TLC, R_f 0.12), 93 mg of a mixture of chromones **5a** and **5b**, and 36 mg of hydroxychromone **5a** (R_f 0.07).

b. Dihydroxyacetophenone 2a. A 0.97-g (5 mmol) sample of **2a** was pyrolyzed with aluminum chloride (1.76 g) as described in part a. A 0.76-g portion of the crude brown solid product (0.827 g; GC analysis in Table I) was chromatographed on 100 g of silica gel. Elution with 2:1 hexane–ether gave 266 mg of a yellow-brown solid, mp 108–140 °C, composed mainly of resorcinol **4**. GC analysis revealed a purity of 78%.

c. Hydroxyacetoxyacetophenone 2b. A 1.18-g (5 mmol) sample of **2b** was pyrolyzed with aluminum chloride (1.76 g) as described in part a. The crude green solid product (0.937 g; GC analysis in Table I) was chromatographed on 100 g of silica gel. Elution with 4:1 and 2:1 hexane–ether gave 0.411 g of resorcinol **4** as a yellow solid, mp 126–136 °C, which was 91.5% pure as determined by GC analysis. Further elution with pure ether furnished 0.246 g of a solid mixture of chromones **5a** and **5b**.

1-(2,6-Dihydroxy-3,4,5-trimethylphenyl)ethanone Diacetate (6). A 0.1-g (0.52 mmol) sample of resorcinol **4** was acetylated as described above for the isomer **2a**. The crude product was recrystallized from ethanol giving 91 mg (63.6%) of diacetate **6** as a pale-yellow solid: mp 95–98 °C; IR 1765 (ester C=O), 1696 cm^{-1} (ketone C=O); UV_{max} 247 (ϵ 5650), 209 (19 200) (sh), 285 nm (1250) (sh); NMR ($CDCl_3$) δ 2.40 (s, 3, CH_3COAr), 2.26 (s, 6, Ar(OCOCH_3)$_2$), 2.24 (s, 3, ArCH_3), 2.06 (s, 6, Ar(CH_3)$_2$); MS, *m/e* 278 (M^+).

Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.94; H, 6.68.

6-Acetyloxy-2,5,7,8-tetramethyl-4*H*-1-benzopyran-4-one (5b). A 0.476-g (11.3 mmol) portion of 57% sodium hydride–oil dispersion was washed three times with hexane to remove the oil and then treated with ca. 10 drops of a solution of 0.5 g (2.58 mmol) of hydroquinone **2a** in 10 mL of dry ethyl acetate. An exothermic reaction began and the remainder of the solution was added dropwise with stirring, keeping the internal temperature below 30 °C. After stirring at room temperature for 20 min, the dark mixture was refluxed for 2 h then cooled and poured into 50 mL of ice–water containing 6 mL of glacial acetic acid. Work-up with ether in the usual manner gave a dark solid which was immediately treated with 15 mL of glacial acetic acid and 1 mL of concentrated hydrochloric acid. The mixture was refluxed for 30 min then cooled and concentrated under high vacuum. The residue was dissolved in dichloromethane and the solution was washed with saturated aqueous sodium bicarbonate solution then processed in the usual manner giving 0.5 g of a dark, solid residue. This material was chromatographed on 50 g of silica gel. Elution with 4:1 and 2:1 toluene–ethyl acetate afforded 300 mg (44.7%) of chromone **5b** as a tan solid, mp 162–171 °C. Recrystallization from ethanol yielded 230 mg (34.3%) of a colorless solid, mp 172–173.5 °C (lit.[2] mp 172 °C): IR 1760 (ester C=O), 1653 (chromone C=O), 1622 cm^{-1} (C=C); UV_{max} 228 (ϵ 24 600), 234 (24 750), 308 (6150), 246 (14 350) (sh), 252 (13 900) (sh), 265 (7900) (sh), 275 nm (5400) (sh); NMR ($CDCl_3$) δ 6.01 (s, 1, –CH=), 2.63 (s, 3, =C(O)CH_3), 2.36 (s, 3, OCOCH_3), 2.30, 2.31 (2s, 6, ArCH_3), 2.15 (s, 3, ArCH_3); MS, *m/e* 260 (M^+). This material was identical by TLC and NMR comparisons with the acetoxy chromone produced in the $AlCl_3$ rearrangements above.

6-Hydroxy-2,5,7,8-tetramethyl-4*H*-1-benzopyran-4-one (5a). A solution of 0.325 g (1.25 mmol) of acetoxy chromone **5b** prepared as in the preceding experiment and 0.345 g of potassium carbonate in 6 mL of methanol and 1 mL of water was stirred and refluxed for 1 h. The reaction mixture was cooled, diluted with water, and acidified with 1 N aqueous hydrochloric acid. The precipitated solid was filtered, washed with water, and dried giving 0.24 g (88%) of chromone **5a** as a colorless solid, mp 220–224 °C (lit.[2] mp 224 °C). Recrystallization from chloroform gave a colorless solid: mp 220–222 °C; IR 3620 (OH), 1652 (ketone C=O), 1620 cm^{-1} (C=C); UV_{max} 206 (ϵ 22 650), 238 (18 100), 330 (5480), 253 nm (14 650) (sh); NMR ($CDCl_3$) δ 6.03 (s, 1, =CH–), 5.04 (br s, 1, **OH**), 2.77 (s, 3, =C(O)CH_3), 2.34, 2.31 (2s, 9, ArCH_3); MS, *m/e* 218 (M^+).

Acknowledgments. We wish to express our gratitude to Messrs. S. Zolty and P. Riggio and Ms. F. Garlewicz for carrying out the GC and GC–MS analyses under the direction of Dr. C. G. Scott.

Registry No.—**3**, 66842-27-1; **6**, 66842-28-2.

References and Notes

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(2) F. v. Werder and F. Jung, *Chem. Ber.*, **71B**, 2650 (1938).
(3) G. Manecke and G. Bourwieg, *Chem. Ber.*, **95**, 1413 (1962).
(4) The standard procedure of R. Mozingo, "Organic Synthesis", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 387, was modified.
(5) von Werder and Jung[2] also reported an independent synthesis of **5a** involving condensation of **1a** with ethyl acetoacetate in the presence of phosphorus pentoxide, at 140 °C. However, because of the low yield reported and rather brutal conditions employed, we chose the alternative procedure described herein in order to facilitate the isolation of pure samples of chromones **5a,b** for spectral analysis.
(6) See G. P. Ellis, Ed., "Chemistry of Heterocyclic Compounds. Chromenes, Chromanones, and Chromones", Wiley, New York, N.Y., 1977, Chapter XII.
(7) Cf. (a) R. Martin, *Bull. Soc. Chim. Fr.*, 1519 (1974); (b) K. v. Auwers, H. Bundesmann, and F. Wieners, *Justus Liebigs Ann. Chem.*, **447**, 162 (1926); (c) J. N. Chatterjea, S. N. P. Gupta, and V. N. Mehrotra, *J. Indian Chem. Soc.*, **42**, 205 (1965).
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(9) Unpublished observations of N. Cohen, R. J. Lopresti, and D. Trullinger.

Diels–Alder Reaction of Pyrrole with Dimethyl Acetylenedicarboxylate

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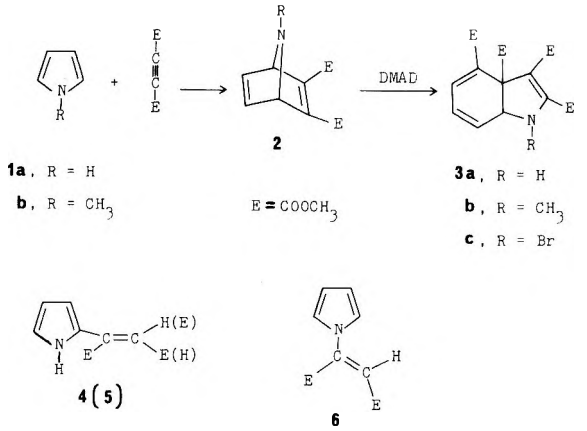
Received November 15, 1977

Pyrrole and dimethyl acetylenedicarboxylate gave the 1:2 adduct tetramethyl 3a,7a-dihydroindole-2,3,3a,4-tetracarboxylate, which has a structure similar to the known 1:2 adduct obtained from 1-methylpyrrole. The significant differences in the chemistry between the two adducts are described.

The reaction of pyrroles with common dienophiles seems to follow two different pathways, that is, [4 + 2] cycloaddition or a Michael-type addition at the α position of pyrroles.[1] Pyrroles which have aryl or electron-withdrawing substituents on the nitrogen gave 1:1 adducts of type **2** with dimethyl acetylenedicarboxylate (DMAD). With an *N*-alkyl group, the 1:1 adduct of type **2** reacted further with DMAD to give a 1:2



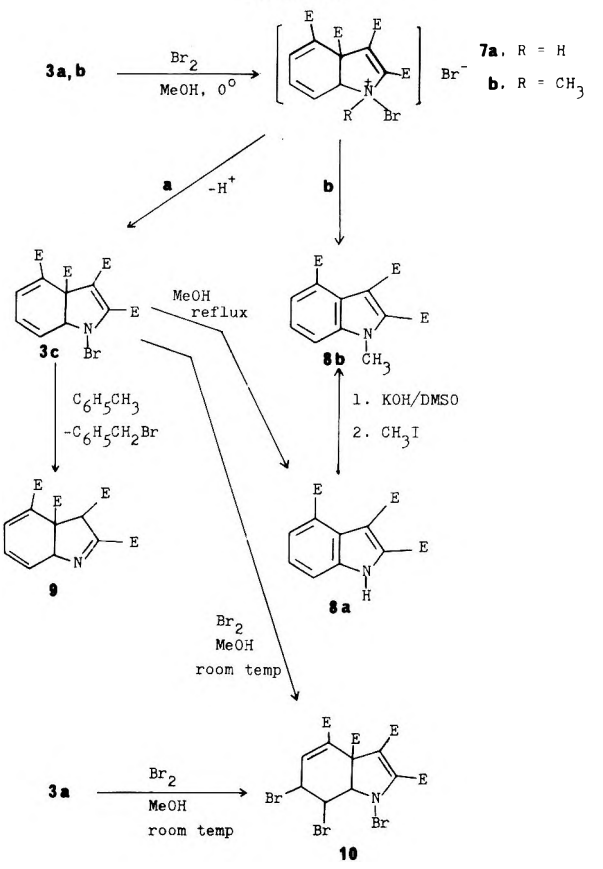
adduct of type **3**.[2] On the other hand, pyrrole (**1a**) itself was reported to give a Michael-type 1:1 adduct **5**, though the structure was not throughly established.[3] The purpose of this paper is to report that pyrrole (**1a**) also gave the 1:2 adduct **3a** when refluxed with DMAD in ether for 4 days and that the chemistry of the compound **3a** was found to be quite different from that of the *N*-methyl analogue **3b**.

Results and Discussion

Although the adduct **3a** began to form after 2 days, the yield increased to 6% in 4 days and could be improved to 10% by removing the product and refluxing for a longer period of time (7 days). The yield of **3b** was more than 80% under identical conditions. Compound **3b** formed in 70% yield after 2 days at room temperature without solvent, but **3a** could not be obtained by stirring a solution of **1a** and DMAD at room temperature for 4 days. Instead, Michael-type adducts **4** and **5** together with adduct **6**, in which the Michael-type addition took place on the nitrogen, were isolated under these conditions.

The adducts **3a** and **3b** behaved quite differently. Compound **3b** gave the oxidized product **8b** (see Scheme I) upon treatment with bromine in methanol,[2] but the 1-bromo derivative **3c** resulted when bromine was added to a suspension of **3a** in methanol at 0 °C. When the reaction of **3a** with bromine was done at room temperature, the tribromo compound **10** was formed. The same compound could also be obtained from **3c** under identical conditions. The initial reaction of bromine with **3** seems to involve the formation of an N–Br bond (cf. compound **7**). Loss of HBr from **7b** and subsequent

Scheme I



loss of a 3a-methoxycarbonyl group would give the fully aromatized indole derivative **8b**. In order to form **3c** from **7b**, a methyl carbonium ion would have to be eliminated, but this is very unlikely. On the other hand, the proton on the nitrogen in **7a** could be lost readily to give **3c**, and in fact, this process took place. Compound **3c** could be isolated almost quantitatively and recrystallized from methanol, but it gave trimethyl indole-2,3,4-tricarboxylate (**8a**) upon refluxing for 24 h in methanol. When **3c** was refluxed in toluene for 24 h, an imine derivative **9** was obtained in 47% yield. Since benzyl bromide was isolated from the reaction, we believe that the formation of **9** involves a radical process similar to the reaction of *N*-bromosuccinimide.[4] The imine was quite stable and did not tautomerize to the enamine form **3a** when refluxed in an AcOH–MeOH solution or in an AcOH–xylene solution.

In addition to similarities in spectra, the conversion of **8a** to **8b** (KOH/Me_2SO and CH_3I) provides the definite evidence that pyrrole, like 1-substituted pyrroles, undergoes initial Diels–Alder addition. However, the report that pyrrole (**1a**) gave a Michael-type 1:1 adduct with DMAD[3] and our result that a similar type of 1:2 adduct **3a** formed from the reaction

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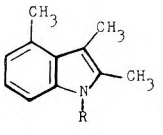
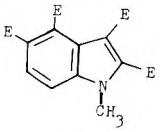
raised a suspicion of the structures of them. Although the NMR spectra and chemical degradation products are well consistent with Acheson's structure **3b**, it seemed to need an unambiguous proof. Thus, **8b** was reduced to 1,2,3,4-tetramethylindole (**11b**), which in turn was prepared by the methylation of 2,3,4-trimethylindole (**11a**).[5]



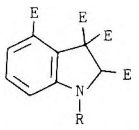
11a, R = H
b, R = CH_3



12

Compound **3a** could be converted to **8a** by sodium methoxide in methanol at room temperature. Quite to the contrary, **3b** did not react under identical conditions, but it gave **12** when the solution was refluxed for 24 h. It is interesting that both aromatization and rearrangement of a 3a-ester group to the 5 position took place. The mechanisms of both reactions are currently under investigation in our laboratory.

Compound **3b** was reported to isomerize to the indoline derivative **13b** in 4% yield upon heating at 180 °C for 6 h in the



13a, R = H
b, R = CH_3

presence of 5% palladium–charcoal.[6] The isomerization could be carried out as efficiently as 74% by refluxing **3b** in xylene for 24 h. On the other hand, **3a** did not give a similar reaction under these conditions. However, when **3a** was refluxed in pyridine for 20 min, the rearrangement took place and **13a** was isolated in 24%.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Beckman IR-18A or a Perkin-Elmer Model 257 spectrophotometer. UV and visible spectra were recorded on a Cary Model 11 or a Shimadzu double-beam spectrophotometer. NMR spectra were recorded on a Varian T-60 spectrometer in $CDCl_3$ containing Me_4Si as an internal reference. Mass spectra were obtained using an Associated Electrical Industries, Scientific Apparatus, Inc., AEI MS-30 double-beam, double focusing mass spectrometer with an AEI DS-30 data system at 70 eV and 200 °C. Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich. Thin-layer chromatography was conducted on 20 × 20 cm × 1 mm silica gel PF-254 TLC plates. Compounds were isolated from the silica gel by extraction in a Soxhlet apparatus with chloroform.

Starting Materials. Commercial pyrroles (**1a** and **1b**) and DMAD were distilled before use. Compounds **3b**, **8b**, **11a**, and **12** were prepared by following literature methods.[2,5,6]

Tetramethyl 3a,7a-Dihydroindole-2,3,3a,4-tetracarboxylate (3a). A solution of pyrrole (3.35 g, 50.0 mmol) and DMAD (14.21 g, 100.0 mmol) in ether (60 mL) was refluxed for 96 h, during which time some white precipitate formed. The precipitate was collected, washed with ether, and then recrystallized from methanol, giving **3a** as colorless prisms (1.16 g, 6%): mp 162–165 °C; IR (KBr) 1745, 1715, and 1693 (C=O), 1602 (C=C), 1337, 1225, and 1130 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 3.66 (s, 3 H), 3.77 (s, 3 H), 3.80 (s, 3 H), and 3.85 (s, 3 H, all $COOCH_3$), 4.73 (d, 1 H, N–H, $J_{1,7a}$ = 1.2 Hz), 5.18 (dd, 1 H, 7a-H, $J_{7a,7}$ = 5.4 Hz, $J_{7a,1}$ = 1.2 Hz), 6.24 (dd, 1 H, 6-H, $J_{6,5}$ = 6.0 Hz, $J_{6,7}$ = 9.5 Hz), 6.51 (dd, 1 H, 7-H, $J_{7,6}$ = 9.5 Hz, $J_{7,7a}$ = 5.4 Hz), 7.20 (d, 1 H, 5-H, $J_{5,6}$ = 6.0 Hz); UV (MeOH) nm (log *A*) 272 (4.10), 300 infl (3.76); MS *m/e* (%) 351 (1.5, M^+), 260 (100), 228 (44), 216 (21).

Anal. Calcd for $C_{16}H_{17}NO_8$: C, 54.70; H, 4.88; N, 3.99. Found: C, 54.86; H, 4.91; N, 3.99.

Tetramethyl 1-Bromo-3a,7a-dihydroindole-2,3,3a,4-tetracarboxylate (3c). Bromine (0.83 g, 5.20 mmol) was added to a suspension of **3a** (1.83 g, 5.20 mmol) in methanol (35 mL) at 0 °C. The mixture became a clear solution, and a white precipitate formed within 1 min. The mixture was stirred at 0 °C for 48 h. The solid was collected, washed with cold methanol, and then recrystallized from methanol, giving **3c** as colorless prisms (1.68 g, 75%): mp 106–107 °C; IR (KBr) 1740 and 1718 (C=O), 1275, 1195, and 1134 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 3.72 (s, 3 H), 3.80 (s, 3 H), 3.83 (s, 3 H), and 3.95 (s, 3 H, all $COOCH_3$), 5.60 (m, 1 H, 7a-H), 6.15 (m, 2 H, 6- and 7-H), 7.22 (m, 1 H, 5-H); UV (MeOH) nm (log *A*) 287 (3.75); MS *m/e* (%) 349 (16), 318 (24), 260 (90), 228 (60), 44 (100).

Anal. Calcd for $C_{16}H_{16}BrNO_8$: C, 44.67; H, 3.75; Br, 18.57; N, 3.25. Found: C, 44.62; H, 4.00; Br, 18.31; N, 3.12.

Dimethyl (*Z*)- and (*E*)-Pyrrol-2-ylbutenedioate (4 and 5) and Dimethyl (*E*)-Pyrrol-1-ylbutenedioate (6). A solution of pyrrole (0.67 g, 10.0 mmol) and DMAD (1.42 g, 10.0 mmol) was stirred under nitrogen for 90 h. The brown solution was chromatographed on a column (2.5 × 60 cm) of silica gel, eluting with the following: (1) petroleum ether (bp 60–70 °C), 0.5 L; (2) petroleum ether, 1.00 L; (3) petroleum ether–benzene (2:1), 1.00 L; (4) petroleum ether–benzene (1:1) 0.40 L; (5) petroleum ether–benzene (1:2), 0.75 L; (6) benzene, 0.50 L; (7) benzene–chloroform (2:1), 0.50 L; (8) benzene–chloroform (1:1), 1.25 L; and (9) chloroform, 0.75 L. Fraction 1 gave no organic material. Fraction 2 gave **4** as a yellow oil (0.87 g, 42%): IR (neat) 3260 (N–H), 1735 and 1690 (C=O), 1582 (C=C), 1291, 1234, 1212, 1100, and 1042 (C–O), 755 cm^{-1}; NMR ($CDCl_3$) δ 3.73 (s, 3 H) and 3.83 (s, 3 H, both $COOCH_3$), 5.92 (s, 1 H, vinyl H), 6.27 (m, 1 H, 4-H), 6.72 (m, 1 H, 3-H), 6.98 (m, 1 H, 5-H), 12.61 (broad s, 1 H, N–H); UV (MeOH) nm (log *A*) 346 (4.17); MS *m/e* (%) 210 (11, $M^+ + 1$), 209 (100, M^+), 178 (18, $M^+ - CH_3O$), 177 (44, $M^+ - CH_3OH$), 151 (12), 150 (47, $M^+ - CH_3OCO$), 119 (10), 118 (57), 91 (65).

Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.69. Found: C, 57.40; H, 5.28; N, 6.49.

Fraction 3 gave **6** as a yellow oil (0.12 g, 6%): IR (neat) 1747 and 1715 (C=O), 1630 (C=C), 1238, 1197, 1169, 1116, and 1055 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 3.73 (s, 3 H) and 3.97 (s, 3 H, both $COOCH_3$), 5.88 (s, 1 H, vinyl H), 6.28 (dd, 2 H, 3- and 4-H, J = 2.5 Hz), 6.83 (dd, 2 H, 2- and 5-H, J = 2.5 Hz); UV (MeOH) nm (log *A*) 283 (4.17), 328 infl (3.17); MS *m/e* (%) 210 (11, $M^+ + 1$), 209 (100, M^+), 178 (19, $M^+ - CH_3O$), 151 (17), 150 (30, $M^+ - CH_3OCO$), 149 (13), 94 (12).

Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.69. Found: C, 57.24; H, 5.48; N, 6.47.

Fractions 4–6 gave a trace amount of a mixture of **5** and **6**. Fractions 7–9 gave **5** as a deep yellow oil (0.53 g, 25%): IR (neat) 3350 (N–H), 1740 and 1712 (C=O), 1602 (C=C), 1234, 1200, an 1170 (C–O), 732 cm^{-1}; NMR ($CDCl_3$) δ 3.68 (s, 3 H) and 3.90 (s, 3 H, both $COOCH_3$), 5.97 (s, 1 H, vinyl H), 6.17 (m, 1 H, 4-H), 6.42 (m, 1 H, 3-H), 6.82 (m, 1 H, 5-H), 9.03 (broad s, 1 H, N–H); UV (MeOH) nm (log *A*) 335 (4.06); MS *m/e* (%) 210 (12, $M^+ + 1$), 209 (100, M^+), 178 (24, $M^+ - CH_3O$), 177 (45, $M^+ - CH_3OH$), 151 (12), 150 ($M^+ - CH_3OCO$), 119 (12), 118 (55), 91 (68).

Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.69. Found: C, 57.41; H, 5.24; N, 6.49.

Trimethyl Indole-2,3,4-tricarboxylate (8a). A. From 3a. A solution of sodium methoxide (0.16 g, 3.00 mmol) in methanol (15 mL) was added to a solution of **3a** (1.03 g, 2.90 mmol) in methanol (40 mL). As soon as a drop of sodium methoxide solution was added, the solution of the ester developed a deep blue color which persisted during the addition (10 min), and then the solution turned dark brown. The solution was stirred at room temperature for 1.5 h, and the methanol was distilled off under aspirator pressure without applying heat, leaving a black gummy material. This was dissolved in chloroform (60 mL), and the solution was washed with an acetic acid–water (1:40 v/v) solution (20 mL) and then with a saturated sodium chloride solution (20 mL). The chloroform solution was dried over sodium sulfate and evaporated to dryness, leaving a brown oil. The oil was chromatographed on a preparative silica gel TLC plate, eluting with benzene to give two bands: (1) R_f 0.12–0.23; (2) R_f 0.06–0.12. Each band was extracted with chloroform using a Soxhlet extractor. Fraction 1 gave a trace of yellow oil which could not be characterized. Fraction 2 gave **8a** as colorless prisms (0.32 g, 38%), mp 160–162 °C, having IR (KBr) and NMR ($CDCl_3$) spectra identical with those of the compound obtained below.

B. From 3c. A solution of **3c** (0.20 g, 0.48 mmol) in methanol (10 mL) was refluxed for 24 h. The solution was evaporated to dryness to give a pale yellow gummy material which was triturated with petroleum ether and then recrystallized from methanol, giving colorless prisms (0.08 g, 61%): mp 162.5–164 °C; IR (KBr) 3310 (N–H), 1733, 1720, and 1682 (C=O), 1286, 1250, 1203, 1195, 1173, and 1145 (C–O), 746 cm^{-1}; NMR ($CDCl_3$) δ 3.93 (s, 6 H) and 4.02 (s, 3 H, both $COOCH_3$), 7.33 (dd, 1 H, 6-H, $J_{6,7}$ = 8.5 Hz, $J_{6,5}$ = 7.0 Hz), 7.63 (dd, 1 H, 7-H, $J_{7,5}$ = 1.5 Hz, $J_{7,6}$ = 8.5 Hz), 7.87 (dd, 1 H, 5-H, $J_{5,7}$ = 1.5

Hz, $J_{5,6}$ = 7.0 Hz), 9.53 (broad s, 1 H, N–H); UV (MeOH) nm (log A) 224 (4.42), 245 infl (3.86), 252 infl (3.76), 314 (4.25); MS m/e (%) 291 (42, M^+), 260 (49, $M^+ - CH_3O$), 259 (34, $M^+ - CH_3OH$), 229 (11), 228 (64), 201 (31).

Anal. Calcd for $C_{14}H_{13}NO_6$: C, 57.73; H, 4.50; N, 4.81. Found: C, 57.64; H, 4.58; N, 4.81.

Trimethyl 1-Methylindole-2,3,4-tricarboxylate (8b). A mixture of freshly crushed potassium hydroxide (0.10 g, 1.75 mmol) and Me_2SO (10 mL) was stirred for 10 min. Compound **8a** (0.15 g, 0.52 mmol) was added, and the mixture was stirred for 1 h. Methyl iodide (0.80 g, 5.63 mmol) was added and the stirring continued for an additional 2 h, giving a yellow solution. Water (20 mL) was added, and the solution was extracted with chloroform (2 × 20 mL). The chloroform extract was dried over sodium sulfate. The dried extract was evaporated to about 5 mL, and the solution was kept in a refrigerator overnight, during which time some white solid formed. The solid was collected and recrystallized from methanol to give **8b** as white prisms (0.13 g, 80%), mp and mmp 122–123 °C (lit.[2] 124 °C), having IR (KBr) and NMR ($CDCl_3$) spectra identical with those of an authentic sample.

Tetramethyl 3a,7a-Dihydro-3*H*-indole-2,3,3a,4-tetracarboxylate (9). A mixture of **3c** (0.51 g, 1.18 mmol) and toluene (10 mL) was refluxed for 24 h. The resulting solution was reduced to dryness in vacuo at room temperature. The residual yellow gummy oil was suspended in ether (5 mL) for 10 min. The ethereal layer was decanted, and the undissolved gummy material was dissolved in hot methanol (2 mL). Upon cooling, crystals formed which were recrystallized from methanol to give **9** as colorless crystals (0.20 g, 47%): mp 129–129.5 °C; IR (KBr) 1735, 1724, and 1708 (C=O), 1287, 1233, 1198, and 1118 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 3.57 (s, 3 H), 3.73 (s, 3 H), 3.78 (s, 3 H), and 3.92 (s, 3 H, all $COOCH_3$), 5.03 (s, 1 H, 3-H), 5.50 (m, 1 H, 7a-H), 6.12 (m, 2 H, 6- and 7-H), 7.13 (m, 1 H, 5-H); UV (MeOH) nm (log A) 293 (3.77), 333 diffuse infl (3.13); MS m/e (%) 351 (0.1, M^+), 320 (5), 261 (14), 260 (100), 228 (65).

Anal. Calcd for $C_{16}H_{17}NO_8$: C, 54.70; H, 4.88; N, 3.99. Found: C, 54.54; H, 5.08; N, 3.87.

The ethereal layer was evaporated to dryness, leaving a yellow viscous oil. The IR (neat) and NMR ($CDCl_3$) spectra of the oil showed it to be a mixture of benzyl bromide and the ester **9**. The oil was chromatographed by preparative TLC in benzene, and the resulting bands were extracted with chloroform: (1) R_f 0.38; (2) R_f 0.09. Fraction 1 was benzyl bromide (0.01 g, 20%), having IR (neat)[8] and NMR ($CDCl_3$)[9] spectra identical with those reported in the literature. Fraction 2 was the ester **9** (total 0.29 g, 70%).

Tetramethyl 1,6,7-Tribromo-3a,6,7,7a-tetrahydroindole-2,3,3a,4-tetracarboxylate (10). A. From 3a. Bromine (0.50 g, 3.10 mmol) was added to a suspension of **3a** (0.50 g, 1.40 mmol) in methanol (20 mL) at room temperature. The mixture became a clear solution, and a white precipitate formed within 1 min. The mixture was stirred for 3 h, and then the solid was collected, washed with methanol, and recrystallized from methanol to give **10** as white leaflets (0.71 g, 86%): mp 172–175 °C; IR (KBr) 1739 and 1725 (C=O), 1320, 1244, 1197, and 1134 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 3.73 (s, 3 H), 3.80 (s, 3 H), 3.88 (s, 3 H), and 3.93 (s, 3 H, all $COOCH_3$), 4.38 (dd, 1 H, 7-H, $J_{7,6}$ = 3.5 Hz, $J_{7,7a}$ = 12 Hz), 4.90 (dd, 1 H, 6-H, $J_{6,7}$ = 3.5 Hz, $J_{6,5}$ = 7 Hz), 5.47 (d, 1 H, 7a-H, $J_{7a,7}$ = 12 Hz), 7.20 (d, 1 H, 5-H, $J_{5,6}$ = 7 Hz); UV (MeOH) nm (log A) 220 (4.04; rising end absorption); MS m/e (%) 512 (1.2), 510 (2.0), and 508 (1.0, all $M^+ - Br$), 480 (1.7), 478 (2.8), and 476 [1.4, all $M^+ - (HBr, CH_3O)$], 429 (1.3) and 427 (1.1, $M^+ - 2HBr$), 350 (11), 340 (11), 338 (11), 260 (100), 228 (57).

Anal. Calcd for $C_{16}H_{16}Br_3NO_8$: C, 32.57; H, 2.73; Br, 40.63; N, 2.37. Found: C, 32.45; H, 2.87; Br, 40.34; N, 2.21.

B. From 3c. Bromine (2 drops) was added to a suspension of **3c** (90 mg, 0.21 mmol) in methanol (2 mL) at room temperature. The mixture became a clear solution, but a precipitate did not form immediately. The solution was stirred at room temperature for 12 h. A white precipitate formed upon scratching the flask, and this was recrystallized from methanol to give **10** as white leaflets (56 mg, 45%), mp and mmp 173–175 °C, having an IR spectrum (KBr) identical with that of the sample prepared by the bromination of **3a**.

1,2,3,4-Tetramethylindole (11b). A mixture of lithium aluminum hydride (6.03 g, 160 mmol) and anhydrous ether (200 mL) was refluxed for 2 h under nitrogen and cooled to room temperature. A solution of **8b** (4.77 g, 15.6 mmol) in tetrahydrofuran (100 mL) was added slowly to the mixture so that the mixture boiled gently for 2 h. The mixture was refluxed for 5 days and cooled to 0 °C in an ice bath. A precooled solution of aluminum chloride (12.5 g, 93.7 mmol) in anhydrous ether (100 mL) was added slowly over 1 h. Then the mixture was refluxed for 2 days. After cooling in an ice bath, water (5 mL) and a 15% sodium hydroxide solution (15 mL) were added carefully. The mixture was filtered through a sintered glass funnel, and the solid was washed with ether (100 mL). The filtrate and ethereal wash were combined and dried over sodium sulfate overnight. The dried solution was evaporated, and the resulting brown oil was chromatographed on preparative TLC plates eluting with benzene. The band at R_f 0.76 was extracted with chloroform using a Soxhlet extractor. The extract gave a white powder which was recrystallized from methanol–water (7:3 v/v) to give white prisms (0.24 g, 11%): mp 77–79 °C; IR (KBr) 2920 (CH_3), 1618 and 1580 (C=C), 1470 (CH_3), 750 (=CH) cm^{-1}; NMR ($CDCl_3$) δ 2.20 (s, 3 H, 3-CH_3), 2.40 (s, 3 H, 2-CH_3), 2.67 (s, 3 H, 4-CH_3), 3.43 (s, 3 H, N-CH_3), 6.67–7.03 (m, 3 H, 5-, 6-, and 7-H); UV (MeOH) nm (log A) 232 (4.51), 282 infl (3.79), 289 (3.82), 297 infl (3.77); MS m/e (%) 174 (12, $M^+ + 1$), 173 (94, M^+), 172 (100, $M^+ - H$), 158 (55, $M^+ - CH_3$), 157 (10), 115 (14), 86 (15).

Anal. Calcd for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.08. Found: C, 83.09; H, 8.70; N, 8.13.

Compound **11b** could be obtained from **11a**[5] in 70% yield by following the similar procedure for methylation of **8a**.

Tetramethyl 1-Methylindole-2,3,4,5-tetracarboxylate (12). A solution of **3b** (1.04 g, 2.68 mmol) and sodium methoxide (0.17 g, 3.00 mmol) in methanol (55 mL) was refluxed for 24 h. The methanol was evaporated to reduce the volume of the solution to about 20 mL, and the solution was kept in a refrigerator overnight, causing a white precipitate to form. The precipitate was collected and crystallized from methanol, giving **12** as white needles (0.15 g, 14%), mp 197–198 °C (lit.[6] mp 200 °C). The structure was determined by comparison of the NMR ($CDCl_3$) and UV (MeOH) spectra with the corresponding spectra in the literature.[7]

Tetramethyl Indoline-2,3,3,4-tetracarboxylate (13a). A solution of **3a** (0.36 g, 1.00 mmol) in pyridine (25 mL) was refluxed for 20 min. The pyridine was distilled off under aspirator pressure, and the residual brown oil was dissolved in methanol, decolorized with charcoal, and kept in a refrigerator overnight, giving pale yellow prisms. The prisms were collected and recrystallized from methanol to give **13a** as pale yellow prisms (87 mg, 24%): mp 120 °C; IR (KBr) 3420 (N–H), 1722 and 1680 (C=O), 1301, 1277, 1262, 1195, and 1016 (C–O) cm^{-1}; NMR ($CDCl_3$) δ 3.62 (s, 3 H), 3.70 (s, 3 H), 3.83 (s, 3 H), and 3.88 (s, 3 H, all $COOCH_3$), 5.52 (s, 1 H, 2-H), 6.70–7.50 (m, 3 H, 5-, 6-, and 7-H), 10.00 (broad s, 1 H, N–H); UV (MeOH) nm (log A) 220 (4.23), 321 (4.20); MS m/e (%) 351 (21, M^+), 319 (23), 292 (27, $M^+ - CH_3OCO$), 260 (74), 228 (100).

Anal. Calcd for $C_{16}H_{17}NO_8$: C, 54.70; H, 4.88; N, 3.99. Found: C, 54.57; H, 4.76; N, 3.80.

Acknowledgment. C.K.L. wishes to thank the University of Minnesota for a Teaching Assistantship in 1972–1976. We wish to thank Mr. Thomas Robison for helpful suggestions in preparing the manuscript.

Registry No.—**1a**, 109-97-7; **2** (R = H; E = $COOCH_3$), 66653-21-2; **3a**, 66653-22-3; **3b**, 1444-11-7; **3c**, 66653-23-4; **4**, 66653-24-5; **5**, 66653-25-6; **6**, 66653-26-7; **8a**, 66653-27-8; **8b**, 969-47-1; **9**, 66653-28-9; **10**, 66653-29-0; **11a**, 10299-63-5; **11b**, 66653-30-3; **12**, 1244-74-2; **13a**, 66653-31-4; DMAD, 762-42-5; benzyl bromide, 100-39-0.

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Reaction of Azibenzil with Thiobenzophenone and Thiofluorenone: Isolation of 1,3-Oxathiole and α-Keto Episulfide[1]

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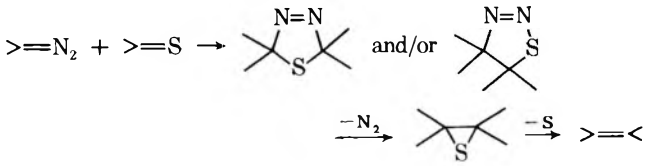
Received April 19, 1978

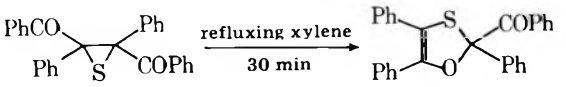
The reactions of azibenzil (**1**) with thiobenzophenone (**2**) and thiofluorenone (**6**) were investigated. In the reaction of **1** with **2**, the 1,3-oxathiole **3** and/or the 1:1 adduct **4** of diarylketene and **2** were isolated, while α-keto episulfide **7** was obtained in the reaction of **1** with **6**.

The reaction of diazo alkanes with thioketones has been extensively studied and is useful for olefin synthesis. The intermediate episulfides were often isolated, and recently even the unstable initial adducts, Δ^3-1,3,4- and/or Δ^2-1,2,3-thiadiazolines, have been isolated.[2,3]

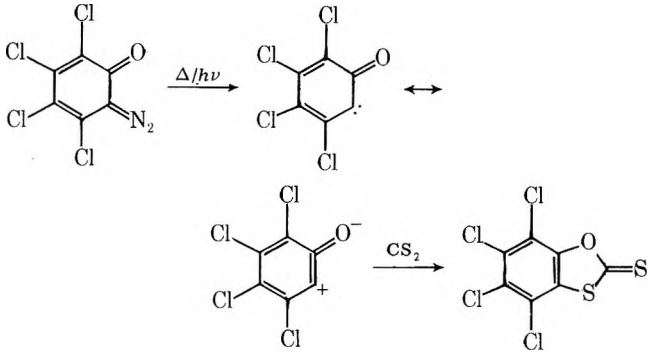


The reaction of α-diazo ketones and α-diazo esters with thiocarbonyls is considered to proceed similarly, and the α,β-unsaturated carbonyl compounds were obtained;[4] however, the intermediate α-keto episulfide has not been isolated.

Recently, the thermal conversion of *trans*-1,2-dibenzoyl-1,2-diphenyl episulfide into the corresponding 1,3-oxathiole was reported to take place smoothly and quantitatively.[5]



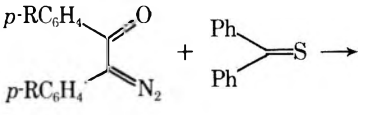
It seems curious that no paper deals with 1,3-oxathiole formation by the reaction of α-diazo compounds with thiocarbonyls except that of Huisgen et al.; the 1,3-dipolar addition of ketocarbene generated thermally and photochemically from α-diazo compounds to phenyl isothiocyanate, carbon disulfide, and o-ethyl thiobenzoate gave the corresponding 1,3-oxathioles.[6]



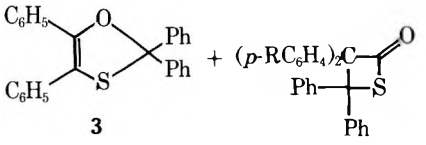
We now report the isolation of 1,3-oxathiole **3** and α-keto episulfide **7** in the reaction of azibenzil (**1**) with thiobenzophenone (**2**) and thiofluorenone (**6**).

Results and Discussion

An equimolecular mixture of azibenzil (**1a**) and **2** in benzene was heated at reflux for 30 min. After removal of the solvent in vacuo, the residue was column chromatographed on alumina using benzene as an eluent to give 2,2,4,5-tetraphenyl-1,3-oxathiole (**3**) and the 1:1 adduct **4a** of diphenylketene and **2** in 31 and 8% yields, respectively. The reaction of 4,4′-dimethoxyazibenzil (**1b**) with **2** under the same reaction conditions gave only **4b**, and no 1,3-oxathiole was isolated.



1a, R = H
b, R = CH_3O

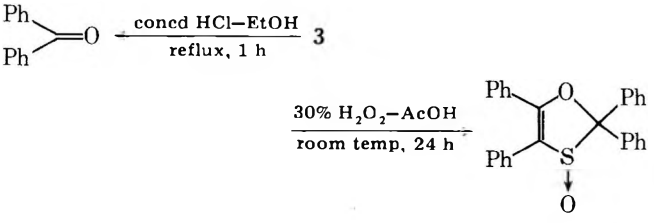


3

4a, R = H
b, R = CH_3O

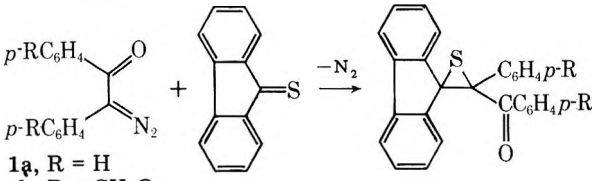
When anhydrous cuprous sulfate was added to the mixture of **1a** and **2** in order to surpress the Wolff rearrangement of **1a**, vigorous gas evolution was observed even at room temperature. The oxathiole **3** was not observed, and only a large amount of intractable resinous materials was obtained. This suggests that not ketocarbene but **1a** itself might participate in the formation of **3**.

The structure of **3** was deduced on the basis of analysis and spectral data, as well as from its chemical conversions. Comparison of the ^{13}C NMR spectrum of **3** with those of 1,3-oxathioles[5] known heretofore was especially helpful. Hydrolysis gave benzophenone, and hydrogen peroxide oxidation in acetic acid afforded the corresponding *S*-oxide **5** at room temperature in 43% yield.



5

When benzene solutions of **1a–d** were added at room temperature in one portion to a benzene solution of thiofluorenone



1a, R = H
b, R = CH_3O
c, R = CH_3
d, R = Cl

6

7a, R = H
b, R = CH_3O
c, R = CH_3
d, R = Cl

(**6**), the initial deep color of **1** and **6** disappeared immediately with evolution of nitrogen. This observation is a further indication that the reaction of **1** with **6** also does not proceed via

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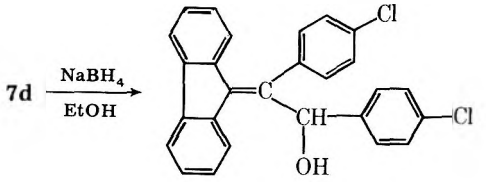
Table I. 1-Aryl-1-aroyl-2,2-fluorenylidene Episulfide (7)

Compd	Yield, %	Mp, °C	^{13}C NMR, δ			
			C_1	C_2	C=O	CH_3
7a	35	131–133	63.9	55.9	193.0	
7b	82	159–160	63.5	56.1	191.6	55.2 55.4
7c	20	182–184	63.9	55.9	192.7	21.1 21.6
7d	86	211–213	62.9	56.1	191.7	

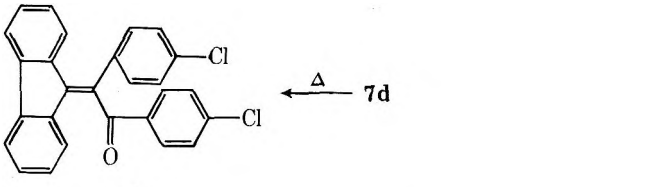
the carbene. Then the reaction mixture was heated at reflux for 30 min for the completion of the reaction. The residue obtained by removal of the solvent in vacuo was subjected to trituration with solvent and/or to silica gel column chromatography to give colorless prisms (**7a–d**) in the yields shown in Table I. The yields of **7a** and **7c** are very low compared with those of **7b** and **7d**; however, the reason for this is not clear.

The empirical formula of **7** agreed with those of 1,3-oxathioles; however, the presence of a carbonyl group was disclosed by the IR and ^{13}C NMR spectra. Reduction of **7d** with $NaBH_4$ gave the alcohol **8**. The structure of **7** was determined to be 1-aryl-1-aroyl-2,2-fluorenylidene episulfide.



8

As mentioned earlier, *trans*-1,2-dibenzoyl-1,2-diphenyl episulfide was easily converted into the corresponding 1,3-oxathiole quantitatively.[5] Thus, the pyrolysis of **7d** was studied. The compound **7d** was found to be thermally rather stable, and after being refluxed in xylene for 24 h still 9% of **7d** was recovered with the corresponding α,β-unsaturated ketone **9**; however, the corresponding 1,3-oxathiole was not isolated.[7]



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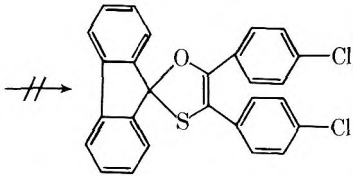
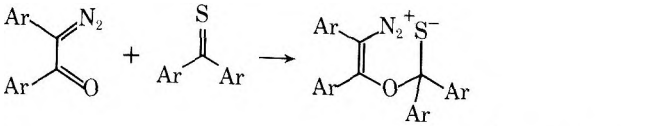
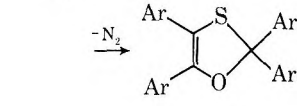


The formation of 1,3-oxathiole **3** and episulfide **7** is interpreted by the terms of the ambident electrophilic character of the thiocarbonyl group and also the ambident nucleophilic character of the diazocarbonyl function. The cyclopentadienide might be responsible for the "anomalous" behavior of thiofluorenone.

Experimental Section

All melting points are uncorrected. IR spectra were measured on a Nippon Bunko IR-A spectrometer as KBr pellets. ^{13}C NMR speetra were determined with a Nihon Denshi Jeol FT-100 spectrometer with Me_4Si as an internal standard in $CDCl_3$. Mass spectra were obtained on a Hitachi R-4 mass spectrometer at 70 eV using a direct inlet. UV spectra were measured on a Hitachi 124 spectrophotometer in ethanol.





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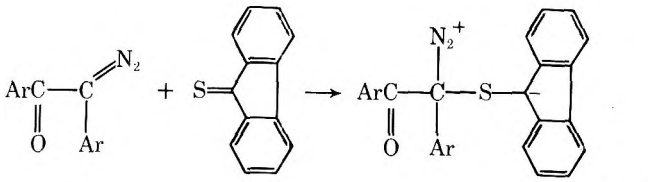

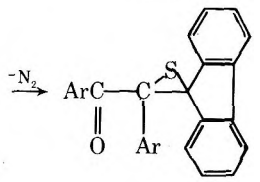

7

Reaction of Azibenzil (1a) with Thiobenzophenone[8] (2). An equimolecular mixture of **1a** (1.00 g) and **2** (0.90 g) in benzene (20 mL) was heated at reflux for 0.5 h. The reaction mixture was condensed to half of its volume and subjected to column chromatography on silica gel (Wako gel C-300) using benzene as an eluent to afford **3** (0.59 g, 31%) and **4a**[9] (0.15 g, 8%). Recrystallization of **3** from ethanol gave pale yellow prisms of mp 146–146.5 °C: IR 1610 (C=C), 1220 (C=C—O-) cm^{-1}; UV λ_{max} 343 nm (ε 7550); MS *m/e* (relative intensity) 392 (M^+, 51), 360 (M^+ − S, 100); ^{13}C NMR δ 99.7 (C_2), 111.4 (C_4), 143.8 (C_5). Anal. Calcd for $C_{27}H_{20}OS$: C, 82.63; H, 5.14. Found: C, 82.47; H, 5.12.

Reaction of 4,4'-Dimethoxyazibenzil (1b) with Thiobenzophenone (2). An equimolecular mixture (3.55 mmol) of **1b** and **2** in benzene (15 mL) was heated at reflux for 30 min. Evaporation of the solvent in vacuo and trituration of the residue with ethanol afforded **4b** in 44% yield as colorless needles from ethanol: mp 177–179 °C dec; IR 1738 (C=O) cm^{-1}. Anal. Calcd for $C_{29}H_{24}O_3S$: C, 76.97; H, 5.35. Found: C, 76.81; H, 5.32.

Oxidation of 2,2,4,5-Tetraphenyl-1,3-oxathiole (3) with Hydrogen Peroxide. A mixture of 130 mg of **3** and 0.5 mL of a 30% aqueous H_2O_2 solution in 4 mL of acetic acid was stirred at room temperature for 24 h. The reaction mixture was poured into water, and white precipitate was collected by filtration and then washed with ethanol. The ethanol washings were evaporated in vacuo, and the residue was triturated with a small amount of ethanol to give 58 mg (43%) of **5** as colorless prisms from hexane–ethanol: mp 192–193 °C; IR 1070 (S–O) cm^{-1}. Anal. Calcd for $C_{27}H_{20}O_2S$: C, 79.39; H, 4.94. Found: C, 79.42; H, 4.96.

Reaction of 1a with Thiofluorenone (6).[10] A benzene solution (25 mL) of **6** (1.65 g, 8.45 mmol) was added at room temperature to a benzene solution (25 mL) of **1a** (1.86 g, 8.45 mmol). Immediately the deep color of the starting materials faded away with evolution of nitrogen. The reaction mixture was heated at reflux for 0.5 h for the completion of the reaction. After being cooled to room temperature, the residue was treated with ether to give 545 mg of **7a**. The ether filtrate was column chromatographed on silica gel (Wako gel C-300) using benzene as an eluent to give 601 mg of **7a** as colorless prisms from ethanol; IR 1660 (C=O) cm^{-1}. Anal. Calcd for $C_{27}H_{10}OS$: C, 83.06; H, 4.64. Found: C, 83.01; H, 4.58.

Reaction of 1b with 6. A benzene solution (10 mL) of **6** (0.32 g, 1.6 mmol) was added at room temperature to a benzene solution (10 mL) of **1b** (0.46 g, 1.6 mmol), and the mixture was heated at reflux for 0.5 h. The reaction mixture was condensed to half of its volume in vacuo and column chromatographed on silica gel (Wako gel C-300) using benzene as an eluent to give 602 mg of **7b** as colorless prisms from ethanol; IR 1660 (C=O) cm^{-1}. Anal. Calcd for $C_{29}H_{22}O_3S$: C, 77.32; H, 4.92. Found: C, 76.96; H, 4.85.

Reaction of 1c with 6. A benzene solution (15 mL) of **6** (814 mg, 3.26 mmol) was added at room temperature to a benzene solution (15 mL) of **1c** (637 mg, 3.26 mmol), and the reaction mixture was heated at reflux for 0.5 h. The reaction mixture was evaporated, and the residue was column chromatographed on silica gel (Wako gel C-300) using benzene as an eluent to give 277 mg of **7c** as colorless prisms

from ethanol; IR 1660 (C=O) cm^{-1}. Anal. Calcd for $C_{29}H_{22}OS$: C, 83.22; H, 5.29. Found: C, 83.02; H, 5.17.

Reaction of 1d with 6. A benzene solution (25 mL) of **6** (1.44 g, 6.87 mmol) was added at room temperature to a benzene solution (25 mL) of **1d** (2.00 g, 6.87 mmol), and the reaction mixture was heated at reflux for 0.5 h. The reaction mixture was evaporated in vacuo, and the resultant residue was triturated with a mixture of ethanol and hexane to give 2.72 g of **7d** as colorless prisms from ethanol–benzene; IR 1670 (C=O) cm^{-1}. Anal. Calcd for $C_{27}H_{16}OCl_2S$: C, 70.59; H, 3.48. Found: C, 70.68; H, 3.50.

Reduction of 7d with $NaBH_4$. A mixture of **7d** (310 mg) and a large excess of $NaBH_4$ in ethanol (20 mL) was stirred at room temperature overnight, and ice-cold water was added to the mixture. The precipitate was collected by filtration to give 195 mg of **8** as pale yellow prisms from hexane–benzene: mp 212–213 °C; IR 3550 (OH) cm^{-1}. Anal. Calcd for $C_{27}H_{18}OCl_2$: C, 75.52; H, 4.19. Found: C, 75.54; H, 4.27.

Pyrolysis of 7d. A xylene solution (10 mL) of **7d** (425 mg) was heated at reflux for 24 h. After being cooled to room temperature, the reaction mixture was evaporated in vacuo and the resultant residue was triturated with a mixture of ether and hexane to give 38 mg (9%) of unreacted **7d**. The filtrate was chilled with dry ice–acetone to give 240 mg of **9** as pale yellow needles from benzene: mp 176–177 °C; IR 1660 (C=O) cm^{-1}. Anal. Calcd for $C_{27}H_{16}OCl_2$: C, 75.88; H, 3.74. Found: C, 75.76; H, 3.82.

Registry No.—**1a**, 3469-17-8; **1b**, 18627-14-0; **1c**, 67069-91-4; **1d**, 67069-90-3; **2**, 1450-31-3; **3**, 64801-82-7; **4a**, 67069-87-8; **4b**, 67069-86-7; **5**, 64801-83-8; **6**, 830-72-8; **7a**, 67069-82-3; **7b**, 67069-83-4; **7c**, 67069-81-2; **7d**, 67069-80-1; **8**, 67069-85-6; **9**, 67069-84-5.

References and Notes

(1) A part of this paper was reported in a preliminary communication: S. Mataka, S. Ishi-i, and M. Tashiro, *Chem. Lett.*, 955 (1977).
(2) C. E. Dieber, *J. Org. Chem.*, **35**, 1501 (1970).
(3) A. P. Krapcho, D. R. Rao, M. P. Silvon, and B. Abegaz, *J. Org. Chem.*, **36**, 3885 (1971).
(4) A. Schönberg and E. Frese, *Chem. Ber.*, **96**, 2420 (1963).
(5) U. Jacobsson, T. Kempe, and T. Norin, *J. Org. Chem.*, **39**, 2722 (1974).
(6) R. Huisgen, H. König, G. Brinsch, and H. J. S. Sturm, *Angew. Chem.*, **73**, 368 (1961).
(7) The transient formation of 1,3-oxathiole might be unlikely because no appreciable decomposition of **3** was observed when **3** was heated at reflux in xylene for 24 h.
(8) "Organic Syntheses", Collect. Vol. 4, Wiley, New York, N.Y., 1963, p 927.
(9) H. Staudinger, *Helv. Chim. Acta*, **3**, 862 (1920).
(10) E. Campaigne and W. B. Reid, *J. Am. Chem. Soc.*, **68**, 769 (1946).

Reaction of N-Substituted Thioamides with *gem*-Dicyano Epoxides: A New Synthetic Route to Anhydro-4-hydroxythiazolium Hydroxides

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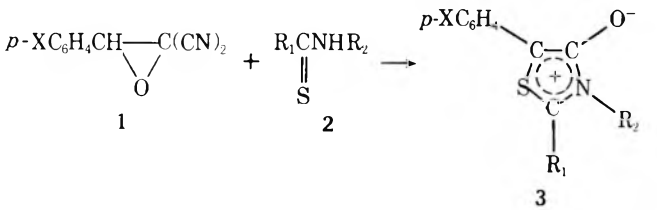
Received March 2, 1978

gem-Dicyano epoxides undergo ready reaction under neutral conditions with N-monosubstituted thioamides to provide a new, convenient synthesis of the anhydro-4-hydroxythiazolium hydroxide system. The epoxides act as potential 1,2-bielectrophiles, while the N-monosubstituted thioamides act as 1,3-binucleophiles, and in most cases excellent yields of products are obtained. The mechanism of this reaction is discussed.

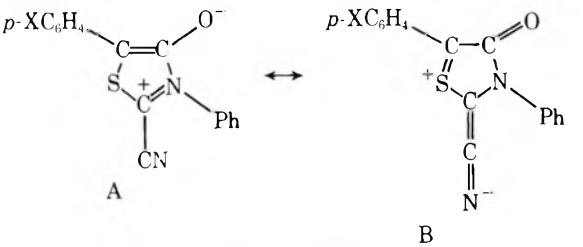
The increasing interest in the field of mesoionic compounds is evident from several recent reviews dealing with this subject.[1-3] Monocyclic anhydro-4-hydroxythiazolium hydroxides have been prepared by S-alkylation of rhodamines,[4-6] or by S-alkylation of N-substituted thioamides with an α-halo acid, followed by cyclodehydration of the resulting acid,[7-9] and recent studies have shown that this last reaction can lead to numerous mesoionic compounds when the α-halo acid is replaced by its acid chloride.[10] In a preliminary communication we described the reaction of N-substituted thioamides with *gem*-dicyano epoxides **1** as a new route to the anhydro-4-hydroxythiazolium hydroxide system[11] and in this paper elaborate further on this very useful and versatile approach to this ring system.

The reaction of the *gem*-dicyano epoxides **1** with the thiocarbonyl compounds **2** was generally carried out under neutral conditions at room temperature in acetone as solvent. The



mesoionic thiazoles obtained are described in Table I, which illustrates the general nature of the reaction and the excellent yields obtained.[13]

The mesoionic compounds **3** were generally deep red or violet in color and were characterized by IR carbonyl absorptions at 1650 cm^{-1}. The mesoionic thiazoles **3** (X = NO_2, Cl; R_1 = CN; R_2 = Ph) showed an intense nitrile absorption at 2200 cm^{-1} consistent with that described earlier for the mesoionic thiazole **3** (R_1 = CN; R_2 = Ph; X = H).[10] The presence of the strongly conjugated nitrile group in these representations of **3** is most likely indicative of a significant contribution of the resonance form B.



It is interesting to note that compound **3** (X = Cl; R_1 = CH_3; R_2 = Ph) shows two carbonyl bands in solution in CCl_4 (1628,

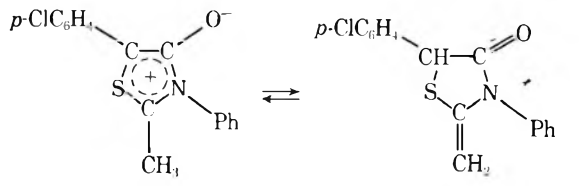


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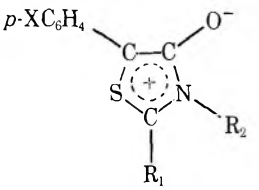
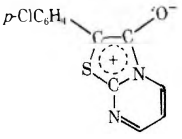
Table I. Anhydro-4-hydroxythiazolium Hydroxide Derivatives (3)



registry no.	substituents X	R_1	R_2	mp, °C	% yield
18100-80-6	H	Ph	Ph	270[a]	92
59208-06-9	Cl	Ph	Ph	300	94
66702-52-1	MeO	Ph	Ph	250	90
59208-07-0	NO_2	Ph	Ph	273	95
66702-53-2	Cl	$pNO_2C_6H_4$	Ph	242	60
66702-54-3	NO_2	$pNO_2C_6H_4$	Ph	260	65
13288-65-8	H	Ph	$PhCH_2$	164[b]	60
59208-08-1	Cl	Ph	$PhCH_2$	170	65
59208-09-2	NO_2	Ph	$PhCH_2$	210	71
59208-10-5	Cl	CH_3	Ph	180	30
59208-11-6	NO_2	CH_3	Ph	280	60
66702-55-4	Cl	Ph	Et	174	50
66702-56-5	NO_2	Ph	Et	204	60
66702-57-6	NO_2	NMe_2	Ph	287	96
66702-58-7	NO_2	SPh	Ph	210	60
66702-59-8	Cl	CN	Ph	248	40
66702-60-1	NO_2	CN	Ph	258	80
66702-61-2				278	14

[a] Lit. mp 270 °C.[7] [b] mp 164 °C.[7]

1716 cm^{-1}), whereas the solid (Nujol mull) shows only one band, at 1628 cm^{-1}. Its NMR spectrum ($CDCl_3$) shows the existence of the following tautomeric equilibrium.

The CH_3, CH_2, and CH signals are not observed when a drop of CD_3CO_2D is added in the $CDCl_3$ solution, but these signals are recovered when an excess of CH_3CO_2H is added.

The main mass fragmentations observed for the mesoionic thiazoles **3** are consistent with those described[12] (Scheme I).

The mesoionic thiazoles **3** were accompanied by a small quantity of a secondary product assigned the 2-cyanothiazolidinone (**4**) structure on the basis of their spectral characteristics (Table II).[13] The NMR spectra of the crude product (**4**, X = Cl; R_1 = Me; R_2 = Ph) showed signals which may be attributed to the presence of two diastereoisomers, but only one of the diastereoisomers was isolated by successive recrystallizations. The relative configuration of the carbons 2 and 5 has not been determined.

Scheme I. Mass Fragmentations of Mesoionic Thiazoles

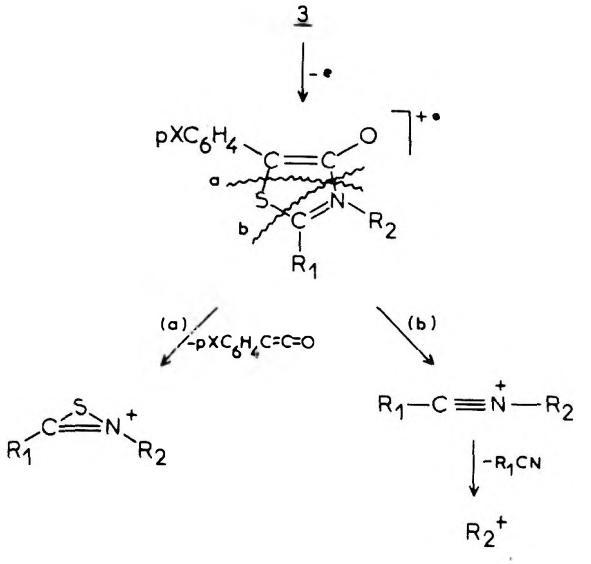
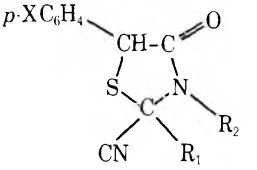


Table II. 2-Cyano-4-Thiazolidinones 4



registry no.	substituents X	R_1	R_2	mp, °C	% yield
66702-62-3	H	Ph	Ph	*a*	1
66702-63-4	Cl	Ph	Ph	191	1
66702-45-2	Cl	Ph	$PhCH_2$	158	13
66702-46-3	Cl	CH_3	Ph	174	15
66702-47-4	NO_2	CH_3	Ph	198	12

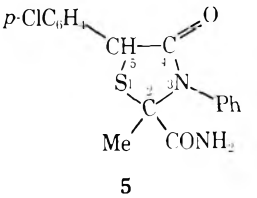
[a] Not purified.

The thiazolidinone **4** (X = Cl; R_1 = Me; R_2 = Ph) reacted with sulfuric acid to give the thiazolidinone **5**, characterized by its IR, NMR, and mass spectrum [IR (Nujol) 3395, 2380, 1702, 1654 cm^{-1}; NMR ($CDCl_3$ + CF_3CO_2H) 7.6–7 (m, 9, Ar), 5.48 (s, 1, CH), 1.82 (s, 3, Me); M^+· calcd 346.054272, found 346.0540].

Mechanism of the Reaction of the Thiocarbonyl Compounds 2 with the Epoxides 1. When the reaction of **1** (X = Cl) with **2** (R_1 = R_2 = Ph) was carried out in the presence of **4** (X = Cl; R_1 = Me; R_2 = Ph), a mixture containing exclusively **3** (X = Cl; R_1 = R_2 = Ph) and unchanged **4** (X = Cl; R_1 = Me; R_2 = Ph) was observed by NMR and TLC. This indicates that the thiazolidinone **4** was not a precursor of the mesoionic thiazole **3**. We have also shown that the mesoionic thiazoles **3** were stable under the reaction conditions and that they did not give the thiazolidinones **4**. Thus compounds **3** and **4** must arise from two different pathways.

Scheme II provides a rational mechanism for the formation of **3** and **4**. The first step, a nucleophilic opening of the epoxide **1** by the thiocarbonyl compound **2**, leads to the oxathiolane intermediate **6**. This first step is reminiscent of the well-documented ring opening of epoxides by thiourea or alkaline thiocyanate, leading to episulfide formation via an oxathiolane.[14] The intermediate **6** does not lead to an episulfide. Successive hydrocyanic acid eliminations lead first to the oxathiole **7** and then to the ketene **8** (path a) or alternatively to the α-keto nitrile **9** (path b).

Evidence in favor of the formation of the intermediate **7** comes from the isolation of 2-*N*-acyliminooxathioles **10** when the epoxides **1** were treated with KSCN in acetic anhydride.[15] We were also able to trap the intermediate **7** as its acetylated

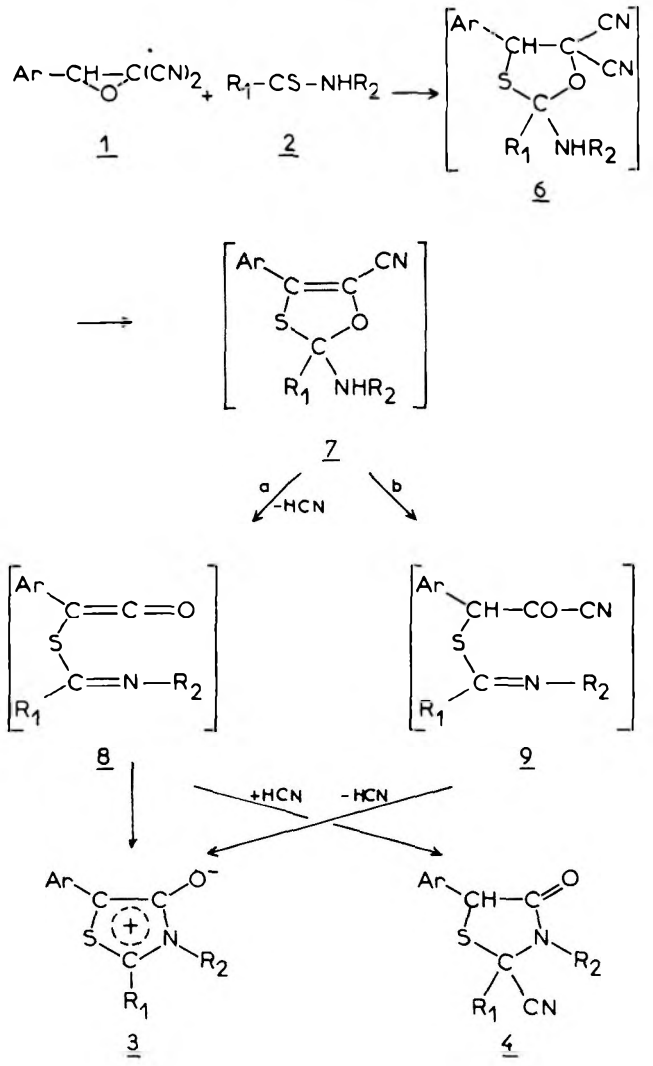


5

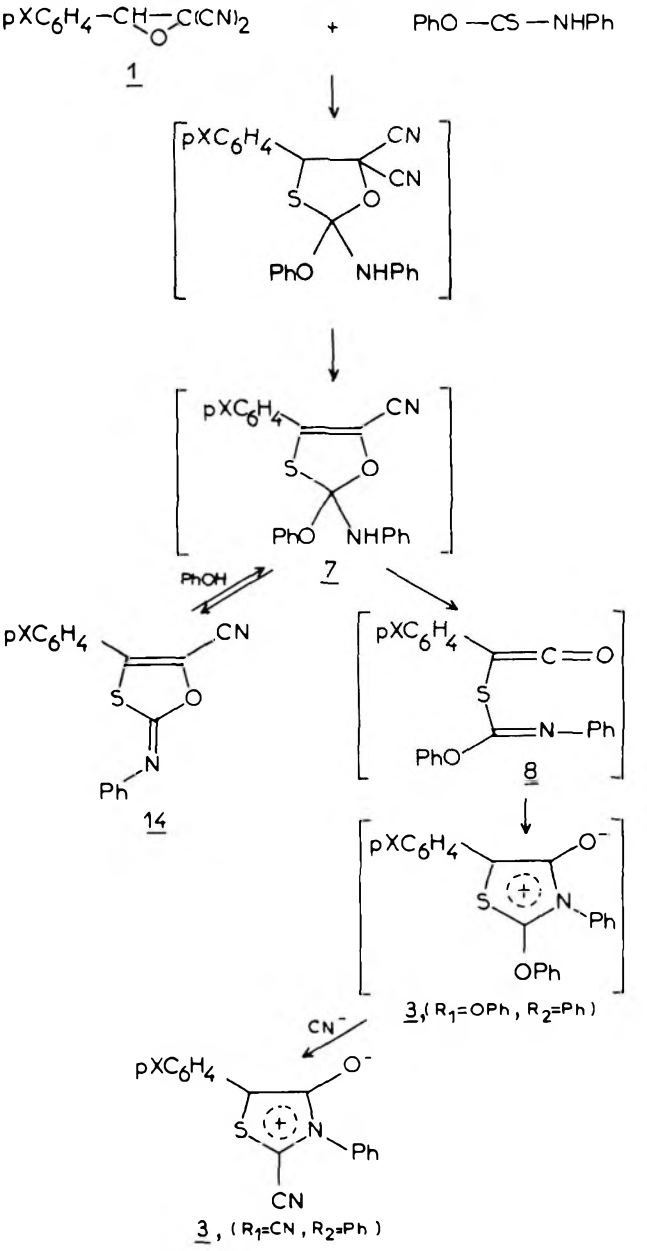
derivative **11** by reacting the epoxide **1** (X = Cl) and thiobenzanilide (**2**, R_1 = R_2 = Ph) in acetic anhydride. The compound **11** decomposed rapidly at 50 °C and gave the mesoionic thiazole **3** (X = Cl; R_1 = R_2 = Ph).

The loss of a hydrocyanic acid molecule from **7** can lead to

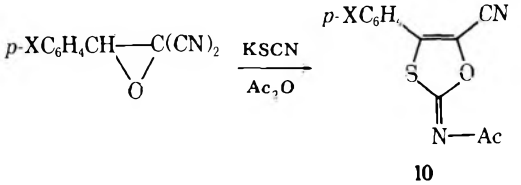
Scheme II. Mechanism of the Reaction of the Thiocarbonyl Compounds 2 with the Epoxides 1



Scheme III. Formation of 3 (R_1 = CN; R_2 = Ph)

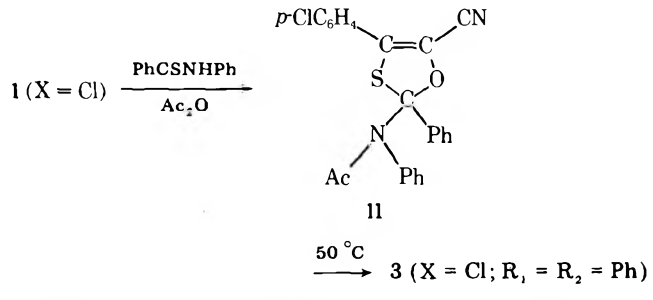


the ketene 8 (path a). However, such a ketene was not trapped by water or alcohol even when the reaction was carried out in methanol as solvent. If formed, the intermediate 8 must cyclize



10

rapidly to 3 or react with the cyanide ion present in the medium to give 4. The alternative pathway b, involving the rearrangement of 7 into the α-keto nitrile 9, cannot be definitely excluded and 9 can also be an intermediate leading to the mesoionic thiazole 3 and to the thiazolidinone 4.



It is interesting to note that the mesoionic thiazole 3 (R_1 = CN; R_2 = Ph) was obtained from *O*-phenyl phenylcarbamothioate (2) (R_1 = OPh; R_2 = Ph) and epoxide 1, whereas this same mesoionic thiazole 3 (R_1 = CN; R_2 = Ph) was not isolated from the action of thiocyananilide with epoxide 1. The particular reaction of epoxide 1 and *O*-phenyl phenylcarbamothioate gives a mixture of 2-*N*-phenyliminooxathiole (14) and mesoionic thiazole 3 (R_1 = CN; R_2 = Ph). This unexpected result can be explained by the formation of an oxathiole 7 (R_1 = OPh) as described in Scheme II. The formation of this intermediate 7 (R_1 = OPh) is linked to the presence of the leaving group, R_1 = OPh, as 7 can be an intermediate giving either 2-*N*-phenyliminooxathiole (14) by the loss of phenol, or the ketene 8 by the loss of hydrocyanic acid (Scheme III). It has been shown that 2-alkoxy-substituted mesoionic thiazoles are unstable systems[10] and we postulate that the mesoionic thiazoles 3 (R_1 = CN; R_2 = Ph) obtained arise from the reaction of the cyanide ions present in the medium with the mesoionic thiazoles 3 (R_1 = OPh; R_2 = Ph) (Scheme III).

It is of interest to note that when the reaction of 1 and *O*-phenyl phenylcarbamothioate (2, R_1 = OPh; R_2 = Ph) is carried out in the presence of phenol the yield of 14 is lowered, while the yield of mesoionic thiazole 3 (R_1 = CN; R_2 = Ph) is considerably increased. In agreement with Scheme III, this can be explained by a reversible loss of phenol from the in-

termediate 7. Indeed, whereas 14 is thermally stable, it is partially transformed into 3 (R_1 = CN) when it is heated with phenol.

Experimental Section

General. IR spectra were measured in CCl_4 on a Perkin-Elmer 225 spectrophotometer. ^1H NMR spectra were recorded on a Jeolco JNM MH 100 spectrometer using a chloroform-*d* solvent and Me_4Si as internal standard; chemical shifts are reported in δ (ppm) units. Mass spectral data were obtained on Varian Mat 311 spectrometer.

Preparation of *gem*-Dicyano Epoxides 1. The *gem*-dicyano epoxides were prepared according to a known synthetic method[16] and improvements of this procedure are detailed below. The NaClO used was a 2.5 M commercial bleach solution, diluted with water (540 mL of the 2.5 M solution and 460 mL of water).

1 (X = H). The olefin (6 g, 0.032 mol) was dissolved in 50 mL of acetonitrile and 2 mL of 2 N H_2SO_4 was added. The solution was stirred vigorously and 5 mL of the NaClO solution was added and immediately the pH of the reaction mixture was adjusted to about pH 5 with 2 N H_2SO_4. A total of 85 mL of the NaClO solution was added in this way during 10 min and, after this addition, vigorous stirring was continued for 10 min at pH 5. After adding 1000 mL of water and cooling, 4.8 g of the epoxide (X = H) was obtained (more or less rapidly). Generally the product, washed with water, is pure enough to be used without further recrystallization: mp 52–53 °C.

1 (X = Cl). The olefin (20.0 g, 0.11 mol) was dissolved in 200 mL of CH_3CN (the suspension must be warmed) and 4 mL of 2 N H_2SO_4, followed by 200 mL of the diluted bleach solution, was added in about 10 min. During the addition the pH was maintained at 5 by adding 2 N H_2SO_4. The epoxide 1 (X = Cl) readily separated on dilution of the reaction mixture with water: mp 128–129 °C (quantitative).

1 (X = NO_2). The olefin (20.0 g, 0.10 mol) was dissolved in 200 mL of CH_3CN and 7 mL of 2 N H_2SO_4, followed by 120 mL of the NaClO solution, was added rapidly. The pH was maintained at 5 by adding 2 N H_2SO_4. The epoxide 1 (X = NO_2) was obtained by dilution of the reaction mixture with water: mp 183–184 °C.

1 (X = MeO). The olefin (20.0 g, 0.10 mol) was dissolved in 200 mL of CH_3CN and 200 mL of NaClO solution was added in 50-mL portions, the pH of the reaction mixture being maintained at 5 by adding 2 N H_2SO_4. After 5 min of stirring and dilution with water the epoxide precipitated: mp 86–87 °C.

Thiocarbonyl Compounds 2. Thioacetanilide 2 (R_1 = CH_3; R_2 = Ph), thiobenzanilide 2 (R_1 = R_2 = Ph), and 2-imidazolidinethione were commercial products. The other carbonyl compounds 2 were prepared according to procedures described in the following references.

R_1	R_2	ref	R_1	R_2	ref
p-$NO_2C_6H_4$	Ph	17	$N(Me)_2$	Ph	20
Ph	$PhCH_2$	18	SPh	Ph	21
Ph	Et	19	OPh	Ph	22

General Procedure for the Reaction of N-Monosubstituted Thioamides with Epoxides. The epoxide 1 (0.005 mol) and the thioamide (0.005 mol) were dissolved in 20 mL of acetone and after 24 h at room temperature, the precipitate was separated by filtration. The mesoionic compounds 3 were recrystallized from ethanol (Table I).[13]

Modification of the above procedure for the preparation of the following mesoionic thiazoles 3: 3 (X = NO_2; R_1 = R_2 = Ph), 30 mL of acetone was used; 3 (X = NO_2; R_1 = Ph; R_2 = $PhCH_2$), 40 mL of acetone was used and the time of reaction was 160 h; 3 (X = H; R_1 = Ph; R_2 = $PhCH_2$), 3 (X = Cl; R_1 = Ph; R_2 = Et), 3 (X = NO_2; R_1 = Ph; R_2 = Et), the time of reaction was 72, 72, and 96 h, respectively; 3 (X = Cl; R_1 = *p*-$NO_2C_6H_4$; R_2 = Ph), boiling acetone; 3 (X = Cl; R_1 = Ph; R_2 = $PhCH_2$), 3 (X = Cl; R_1 = CH_3; R_2 = Ph), 40 and 20 mL of methanol was used, respectively (instead of acetone), and the time of reaction was 72 and 24 h; 3 (X = NO_2; R_1 = SPh; R_2 = Ph), the epoxide 1 (X = NO_2) and the dithiocarbamate 2 (R_1 = SPh, R_2 = Ph) were heated at 180 °C for 5 min without solvent; 3 (X = Cl; R_1, R_2 = –N=CHCH=CH–) was prepared by reacting the epoxide 1 (X = Cl) (0.005 mol) and 2(1*H*)-pyrimidinethione (0.005 mol) in solution in 20 mL of DMF for 15 min at room temperature.

2-Cyano-4-thiazolidinones 4 were obtained by refluxing the epoxides 1 (0.005 mol) and the thioamides 2 (0.005 mol) in acetone (20 mL) for 24 h. The mesoionic compounds 3 were filtered and removal of the solvent under reduced pressure and trituration of the resultant residue with ether afforded the colorless crystals of 4 (Table II).[13]

Hydrolysis of 2-(Cyanomethyl)-5-*p*-chlorophenyl-3-phenyl-4-thiazoldinone (4). The thiazolidinone (4, R_1 = CH_3; R_2 = Ph) (0.5 g, 0.0015 mol) was added to 8 mL of H_2SO_4. After 3 h of stirring the compound 5 precipitated on dilution with water: 0.4 g (80%); mp 282 °C after crystallization from EtOH.

Table III. Oxathioles 14

registry no.	X	mp, °C	% yield
62501-56-8	H	112	50
66702-48-5	Cl	120	60
66702-49-6	MeO	112	50
62501-57-9	NO_2	82	56

Stability of Mesoionic Thiazoles 3. Epoxide 1 (X = Cl) (0.005 mol), thiobenzanilide (0.005 mol), and 3 (X = Cl; R_1 = Ph; R_2 = $PhCH_2$) (0.001 mol) were dissolved in acetone (40 mL). After 27 h the solvent was removed. IR, NMR, and TLC data show that the mixture consisted of 3 (X = Cl; R_1 = R_2 = Ph), 3 (X = Cl; R_1 = Ph; R_2 = $PhCH_2$), and 4 (X = Cl; R_1 = R_2 = Ph). The formation of 4 (X = Cl; R_1 = Ph; R_2 = $PhCH_2$) was not observed.

Stability of 2-Cyano-4-thiazolidinones 4. Epoxide 1 (X = Cl) (0.005 mol), thiobenzanilide (0.005 mol), and 4 (X = Cl; R_1 = CH_3; R_2 = Ph) (0.001 mol) were dissolved in acetone (20 mL). After 24 h the solvent was removed. IR, NMR, and TLC data show that the mixture consisted of 3 (X = Cl; R_1 = R_2 = Ph), 4 (X = Cl; R_1 = R_2 = Ph), and 4 (X = Cl; R_1 = CH_3; R_2 = Ph). The formation of 3 (X = Cl; R_1 = CH_3; R_2 = Ph) was not observed.

Preparation of 2-*N*-Acyliminooxathiole 10 (X = H). Epoxide 1 (X = H) (0.005 mol) and KSCN (0.005 mol) were dissolved in acetic anhydride (6 mL). After 3 h at room temperature the mixture was cooled and the 2-*N*-acyliminooxathiole was filtered and washed with water (to eliminate CH_3CO_2K). The compound was crystallized from EtOH: mp 100 °C; yield 42%; ^1H NMR ($CDCl_3$) δ 2.42 (s, 3, CH_3); IR (CCl_4) 2229 (ν_{CN}), 1668 cm^{-1} (ν_{CO}). Anal. Calcd for $C_{12}H_8N_2O_2S$: C, 59.00; H, 3.30; N, 11.47. Found: C, 58.58; H, 3.34; N, 11.49.

Preparation of the Oxathiole 11. Epoxide 1 (X = Cl) (0.005 mol) and thiobenzanilide (0.005 mol) were dissolved in acetic anhydride (10 mL). After 24 h, successive fractions of 3 (R_1 = R_2 = Ph) were filtered and characterized by IR. After 48 h, a colorless precipitate was isolated. The compound crystallized rapidly from EtOH: mp 150 °C; IR (CCl_4) 2224 (C≡N), 1722 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.54 (s, 3, CH_3).

Compound 11 decomposed on electron impact. The observed spectrum was the same as that of the corresponding mesoionic thiazole 3 (R_1 = R_2 = Ph).

Preparation of the Mesoionic Thiazoles 3 (R_1 = CN; R_2 = Ph) and of the Oxathioles 14. When epoxides 1 (0.005 mol) and *O*-phenyl phenylcarbamothioate were heated together a mixture of the compounds 3 (R_1 = CN; R_2 = Ph) and 14 was obtained. The relative yield of these two compounds was very dependent of the reaction conditions.

Preparation of 3 (X = NO_2, Cl; R_1 = CN; R_2 = Ph). Epoxides 1 (X = NO_2, Cl) (0.005 mol), *O*-phenyl phenylcarbamothioate (0.005 mol), and phenol (0.02 mol) were heated at 180 °C for 5 min (oil bath). The mixture was then dissolved in the minimum volume of acetone and the mesoionic compound 3 (R_1 = CN; R_2 = Ph) precipitated on addition of ether (Table I).[13]

Preparation of 14 (X = H, Cl, MeO). Oxathioles 14 were obtained by fusion of epoxides 1 and *O*-phenyl phenylcarbamothioate. The mixture was purified by column chromatography (alumina, ether as eluent) (Table III).[13]

Preparation of 14 (X = NO_2). When X = NO_2, the best yield of oxathiole 14 was obtained when epoxide 1 (0.005 mol) and *O*-phenyl phenylcarbamothioate (0.005 mol) in dioxane (20 mL) were heated for 24 h. Removal of the solvent and column chromatography (alumina, ether as eluant) of the residue give the oxathiole 14 (X = NO_2) (Table III).[13]

Acknowledgment. We are grateful to Professor Kevin Potts for helpful comments.

Registry No.—1 (X = H), 33512-02-6; 1 (X = Cl), 33512-03-7; 1 (X = NO_2), 34559-52-9; 1 (X = MeO), 33441-62-2; 2 (R_1 = CH_3; R_2 = Ph), 637-53-6; 2 (R_1 = R_2 = Ph), 636-04-4; 2 (R_1 = *p*-$NO_2C_6H_4$; R_2 = Ph), 6244-77-5; 2 (R_1 = Ph; R_2 = $PhCH_2$), 14309-89-8; 2 (R_1 = Ph; R_2 = Et), 39203-76-4; 2 (R_1 = $N(Me)_2$; R_2 = Ph), 705-62-4; 2 (R_1 = SPh; R_2 = Ph), 27063-57-6; 2 (R_1 = OPh; R_2 = Ph), 2423-29-2; 5, 66702-50-9; 10 (X = H), 66702-51-0; 11, 66758-66-5; 2-imidazolidinethione, 96-45-7; 2(1*H*)-pyrimidinethione, 1450-85-7.

Supplementary Material Available: Full color, NMR, IR, UV, and mass spectral data for compounds **3** (Table I); NMR, IR, and mass spectral data for compounds **4** (Table II); IR, UV, and mass spectral data for compounds **14** (Table III) (3 pages). Ordering information is given on any current masthead page.

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Cycloaddition Reactions of Nitrile Sulfides with Acetylenic Esters. Synthesis of Isothiazolecarboxylates

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Received March 20, 1978

Evidence is reported for production of nitrile sulfides as reactive intermediates in the thermolysis of 1,3,4-oxathiazol-2-ones. The nitrile sulfides were trapped with dimethyl acetylenedicarboxylate to give good yields of dimethyl 3-substituted-4,5-isothiazoledicarboxylates **6a–t.** The diacids **7a–r** were readily converted to 3-substituted-4-isothiazolecarboxylic acids **8a–r** by thermal decarboxylation. 3-Aryl-4-isothiazolecarboxylates **9a,j,u–w** and 3-aryl-5-isothiazolecarboxylates **10a,j, u–w** were obtained in nearly equivalent amounts from nitrile sulfides and ethyl propiolate. Thermolysis of 5-methyl- and 5-phenyl-1,3,4-oxathiazol-2-ones in excess ethyl 2-butynoate and of 5-methyl-1,3,4-oxathiazol-2-one in excess ethyl phenylpropiolate resulted in excessive byproduct formation and low yields of isothiazoles. Thermolysis of 5-(α,α,α-trifluoro-*m*-tolyl)-1,3,4-oxathiazol-2-one (**5u**) in the presence of excess ethyl phenylpropiolate gave a product mixture which contained ethyl 3-(α,α,α-trifluoro-*m*-tolyl)-5-phenyl-4-isothiazolecarboxylate (**18**) (47% yield by GC) and ethyl 3-(α,α,α-trifluoro-*m*-tolyl)-4-phenyl-5-isothiazolecarboxylate (**19**) (9.5% yield by GC).

Nitrile ylides (**1**), nitrile imines (**2**), and nitrile oxides (**3**) all have been utilized in 1,3-dipolar cycloaddition reactions to form heterocycles.[1] Until very recently,[2-6] nitrile sulfides (**4**) were conspicuously missing from this series of 1,3-dipoles.

$RC{\equiv}N^+-C^-R'R''$ (**1**) $\quad RC{\equiv}N^+-N^-R'$ (**2**)

$RC{\equiv}N{\rightarrow}O$ (**3**) $\quad RC{\equiv}N{\rightarrow}S$ (**4**)

We report here evidence for the production of nitrile sulfides as reactive intermediates in the thermolysis of 1,3,4-oxathiazol-2-ones and reaction of the nitrile sulfides with acetylenic esters to form isothiazolecarboxylates in preparatively significant reactions.[7]

A report[8] that thermolysis of 5-phenyl-1,3,4-oxathiazol-2-one (**5a**) produced benzonitrile and sulfur suggested to us that benzonitrile sulfide **4a** was a possible intermediate in this reaction. Thermolysis of **5a** in the presence of dimethyl acetylenedicarboxylate (DMAD), in an experiment designed to trap the nitrile sulfide, resulted in isothiazoledicarboxylate **6a** (>90% yield); similarly, thermolysis of **5a** in the presence of ethyl propiolate gave isothiazolecarboxylates **9a** and **10a.**[2] These reactions now have been extended to a large variety of 5-substituted-1,3,4-oxathiazol-2-ones to produce the products outlined in Scheme I.

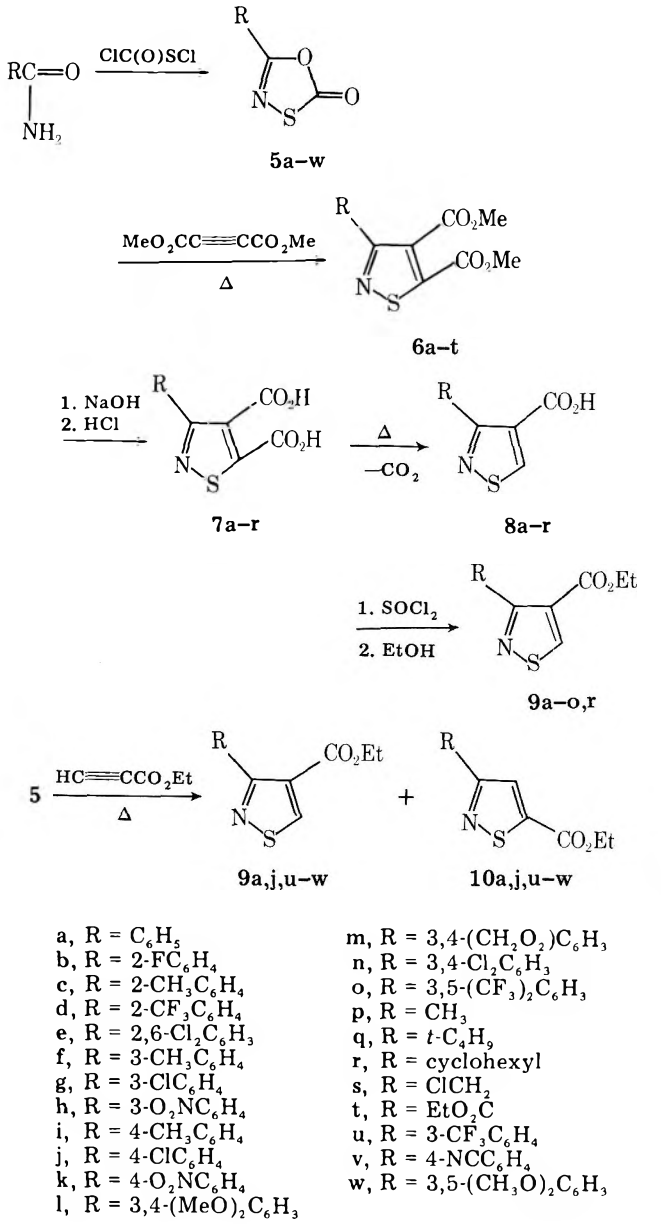
Formation of nearly equivalent amounts of **9** and **10** from ethyl propiolate and the various oxathiazolones is consistent only with a 1,3-dipolar cycloaddition reaction[9] (e.g., path A or path B, Scheme II). An alternative mechanism, path C, involving heterolysis of a bond of **5** to produce an ionic species **12,** followed by Michael addition of **12** to ethyl propiolate to give **13** and eventually **9,** is contrary to the observed formation of both **9** and **10.** Path C, as well as a similar homolytic mechanism, should produce **9** exclusively.[10]

A choice between path A and path B, which involves adduct (**11**) formation prior to loss of carbon dioxide, was made possible by the kinetic studies summarized in Table I. These studies, performed with varied concentrations of DMAD as the trapping agent, show that the rate of disappearance of **5a** is independent of the concentration of DMAD and is first order. Furthermore, the rate constants for formation of isothiazole and benzonitrile are both first order and equal to the rate constant for disappearance of **5a.** In the absence of DMAD, **5a** gave benzonitrile in 100% yield. These results rule out path B as a possible reaction mechanism and thus provide support for path A and benzonitrile sulfide as the reactive intermediate.

The order of rates of thermolysis of several 5-substituted-1,3,4-oxathiazol-2-ones is 5-CH_3 ≫ 5-$ClCH_2$ > 5-EtO_2C and 5-o-$CH_3C_6H_4$, 5-*m*-$CH_3C_6H_4$, 5-*p*-$CH_3C_6H_4$ > 5-C_6H_5 > 5-*m*-ClC_6H_4 > 5-*m*-$CF_3C_6H_4$ > 5-[3,5-$(CF_3)_2C_6H_3$], 5-*p*-NCC_6H_4, 5-*p*-$O_2NC_6H_4$, indicative of development of a partial positive charge at the 5 position in the transition state for

0022-3263/78/1943-3736$01.00/0

Scheme I



a, R = C_6H_5
b, R = 2-FC_6H_4
c, R = 2-$CH_3C_6H_4$
d, R = 2-$CF_3C_6H_4$
e, R = 2,6-$Cl_2C_6H_3$
f, R = 3-$CH_3C_6H_4$
g, R = 3-ClC_6H_4
h, R = 3-$O_2NC_6H_4$
i, R = 4-$CH_3C_6H_4$
j, R = 4-ClC_6H_4
k, R = 4-$O_2NC_6H_4$
l, R = 3,4-$(MeO)_2C_6H_3$
m, R = 3,4-$(CH_2O_2)C_6H_3$
n, R = 3,4-$Cl_2C_6H_3$
o, R = 3,5-$(CF_3)_2C_6H_3$
p, R = CH_3
q, R = t-C_4H_9
r, R = cyclohexyl
s, R = $ClCH_2$
t, R = EtO_2C
u, R = 3-$CF_3C_6H_4$
v, R = 4-NCC_6H_4
w, R = 3,5-$(CH_3O)_2C_6H_3$

decarboxylation. Also, 5-(2,6-dichlorophenyl)-1,3,4-oxathiazol-2-one thermolyzes slightly faster than 5-phenyl-1,3,4-oxathiazol-2-one, indicative of relief of steric strain in the decarboxylation and consistent with a transition state for the thermolysis that approaches the structure of the nitrile sulfide. The decarboxylation proceeds by a thermally allowed $_{\sigma}2_s + _{\sigma}2_s + _{\pi}2_s$ process.

Decarboxylation could also occur by a photochemically allowed $_{\sigma}2_s + _{\sigma}2_s + _{\pi}2_a$ process. Irradiation of **5a** and 1 equiv of DMAD in ethyl acetate solution at 253.7 nm produced benzonitrile and sulfur but no isothiazoledicarboxylate. Irradiation of the reactants at 300 or 360 nm (in the presence or absence of the triplet sensitizer benzophenone) did not result in an appreciable rate of decomposition of **5a**. Holm et al., however, reported that photolysis through Pyrex of **5a** in neat DMAD for 88 h gave isothiazole **6a** in 22% yield (based on the amount of starting material consumed).[11] In any event, photolysis of **5a** does not lead to preparatively significant yields of isothiazoles.

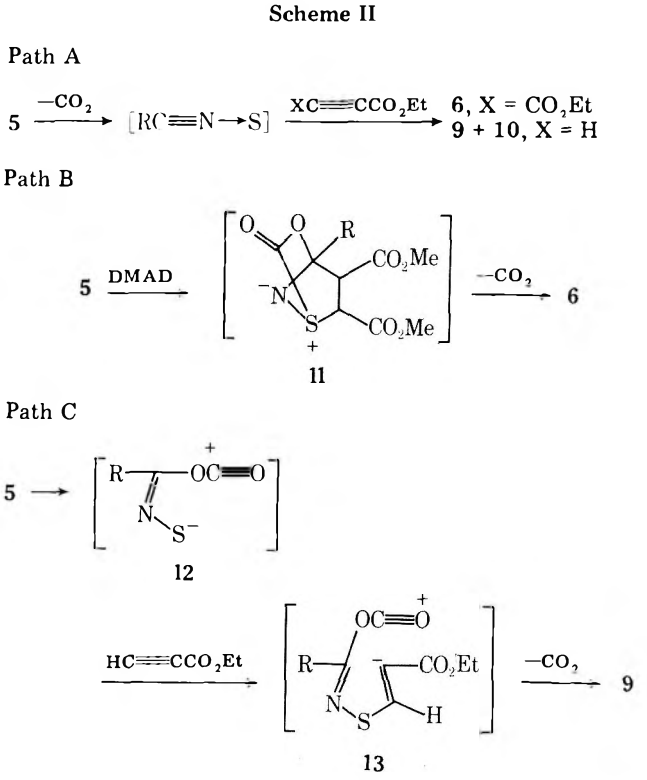
In addition to thermolysis and photolysis of 5-phenyl-1,3,4-oxathiazol-3-one, benzonitrile sulfide appears to have been generated by four other routes. Photolysis at 404–408 nm of 4-phenyl-1,3,2-oxathiazolium-5-olate (**14**) in a large excess of dimethyl acetylenedicarboxylate gave **6a** in 10% yield;[5]

Table I. First-Order Rate Constants[a] for Thermolysis of 0.103 M 5a in Chlorobenzene at 125.0 ± 0.1 °C

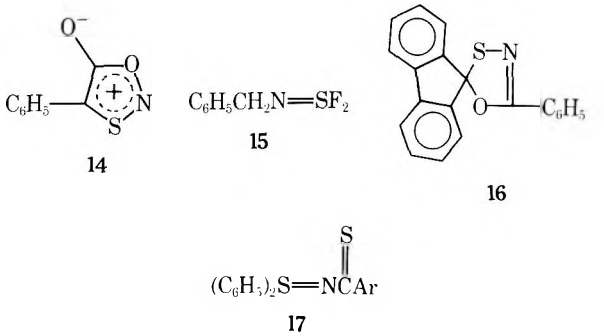
[DMAD], M[b]	k_5, 10^5 s^{-1}	k_{BN}, 10^5 s^{-1}	k_6, 10^5 s^{-1}
0	2.77 ± 0.1	2.48 ± 0.1[c]	
0.103	2.61 ± 0.12		2.63 ± 0.04[d]
0.515	2.84 ± 0.08		2.62 ± 0.09[e]

[a] Determined by gas chromatography, using least-squares method. k_5 = rate constant for disappearance of **5a**; k_{BN} = rate constant for appearance of benzonitrile; k_6 = rate constant for appearance of **6a**. [b] Initial concentration. [c] 100% yield of benzonitrile. [d] 90.5% yield of **6a**. [e] 94.7% yield of **6a**.

Scheme II



photolysis of **14** at 420 nm at 85 °K resulted in new UV absorption bands attributed to benzonitrile sulfide.[11] Thermolysis of (*N*-benzylimino)sulfur difluoride (**15**) in the presence of DMAD and sodium fluoride gave HF and **6a** in 65% yield.[6] Decomposition of **16** at room temperature gave



fluorenone, benzonitrile, and sulfur,[12] possibly via benzonitrile sulfide. Thermolysis of *N*-thiocarbonylsulfimides **17** at 50 °C in the presence of DMAD gave 3-arylisothiazoledicarboxylates in 27–34% yields, apparently via nitrile sulfide intermediates.[13]

Aliphatic nitrile sulfides also may be generated and trapped in synthetically useful reactions, as shown by thermolysis of 5-methyl- (**5p**), 5-*tert*-butyl- (**5q**), and 5-cyclohexyl-1,3,4-oxathiazol-2-one (**5r**) in 2 equiv of DMAD to give **6p, 6q,** and

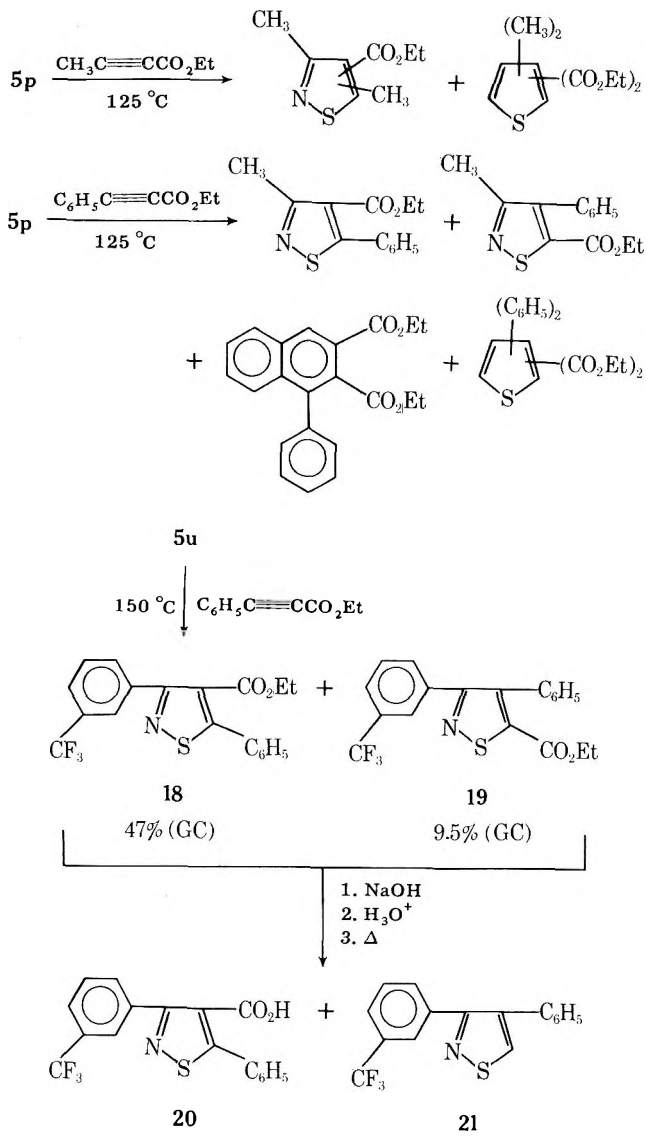
Table II. Thermolysis of Oxathiazolones in the Presence of 4 Equiv of Ethyl Propiolate in o-Dichlorobenzene at 150 °C

5	registry no.	9, % yield[a]	registry no.	10, % yield[a]	registry no.
a, R = C_6H_5	5852-49-3	40 (29)	67049-00-7	43 (31)[b]	27545-57-9
j, R = 4-ClC_6H_4	17452-79-8	44 (18)	67048-37-7	45 (26)	67048-96-8
u, R = 3-$CF_3C_6H_4$	57459-15-1	46 (34)	67048-99-1	39 (29)	67048-95-7
v, R = 4-NCC_6H_4	67048-87-7	44 (32)	67048-98-0	46 (10)	67048-94-6
w, R = 3,5-$(CH_3O)_2C_6H_3$	67048-85-5	35 (25)	67048-97-9	37 (32)	67048-93-5

[a] Yields determined by GC. Yields in parentheses are for pure isolated products. [b] Isolated as the acid.

6r in 58, 39, and 59% yields (GC analyses), respectively (Scheme I). Thermolysis of 5-aryloxathiazolones in 2 equiv of DMAD gave, with few exceptions, isothiazoledicarboxylates in >90% yields (GC analyses). The requisite oxathiazolones 5 are readily prepared from amides and chlorocarbonylsulfenyl chloride.[14] This route provides a particularly convenient synthesis of a wide range of 3-substituted-4,5-isothiazoledicarboxylates and thus the 3-substituted-4-isothiazolecarboxylates.

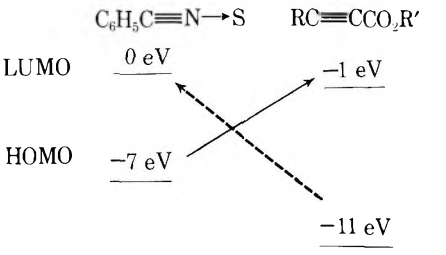
Thermolysis of the oxathiazolones in the presence of ethyl propiolate provides a quick route to samples of 3-substituted-5-isothiazolecarboxylates, as well as 3-substituted-4-isothiazolecarboxylates. Table II gives yield data for reactions in which 4 equiv of ethyl propiolate were employed. The isomers generally are readily separable by column chromatography. The 4-carboxylates are easily distinguished from the 5-carboxylates by NMR spectroscopy;[15] the 5-H of 3-aryl-4-isothiazolecarboxylates appears at δ 9.2–9.4, whereas the 4-H of 3-aryl-5-isothiazolecarboxylates appears at δ 8.0–8.2. Generally, the 5-carboxylates have longer retention times upon GC on SE-30 columns, elute faster on silica gel with benzene, have higher melting points, and are less soluble in ethanol than the corresponding 4-carboxylates.



Thermolysis of 5-methyl-1,3,4-oxathiazol-2-one at 125 °C in 10 equiv of ethyl 2-butynoate gave, based on GC–MS analyses, a complex mixture that contained a very small amount of a dimethylisothiazolecarboxylate (*m/e* 185) and larger amounts of thiophenedicarboxylates (*m/e* 256). The latter apparently arise from reaction of sulfur (from decomposition of the nitrile sulfide) with the acetylenic ester. Thermolysis of 5-methyl-1,3,4-oxathiazol-2-one at 125 °C in 10 equiv of ethyl phenylpropiolate gave a mixture of ethyl 3-methyl-5-phenyl-4-isothiazolecarboxylate and ethyl 3-methyl-4-phenyl-5-isothiazolecarboxylate, as well as ethyl phenylpropiolate dimer (*m/e* 348) and a mixture of diphenylthiophenedicarboxylates (*m/e* 380). The yield of isothiazoles appeared to be greater in the reaction with the phenylpropiolate than with the butynoate. Thermolysis of 5-phenyl-1,3,4-oxathiazol-2-one in 10 equiv of ethyl 2-butynoate gave an exceedingly complex mixture in which the isothiazolecarboxylates were minor components (GC–MS analyses).

Thermolysis of 5-(α,α,α-trifluoro-*m*-tolyl)-1,3,4-oxathiazol-2-one in 10 equiv of ethyl phenylpropiolate gave reasonable yields of isothiazolecarboxylates **18** and **19** (47 and 9.5%, respectively, GC and MS analyses), but isolation of these materials in pure form was extremely difficult due to problems in separation from large amounts of side products that included ethyl phenylpropiolate dimer and diphenylthiophenedicarboxylates; separation of a mixture of **18** and **19** was also difficult. Pure **20** (14%) was isolated by hydrolysis of the mixture of **18** and **19**, followed by selective decarboxylation of the 5-carboxylic acid and separation of **20** from **21** by crystallization.

Frontier orbital theory has been employed extensively recently to explain a wide variety of 1,3-dipolar cycloaddition data.[16–18] Since sulfur is only slightly more electronegative than carbon, nitrile sulfides should have LUMO and HOMO energy levels just slightly lower than those of nitrile ylides. From the reported[16] LUMO, HOMO energy levels for phenylnitrile ylide (0.6, −6.4 eV) and 1,3-diphenylnitrile imine (−0.5, −7.5 eV), LUMO and HOMO values of ~0 and −7 eV are to be expected for benzonitrile sulfide. Acetylenic esters should have LUMO and HOMO levels at ~−1 and −11 eV, respectively.[16] Based on these estimates and experimental results with nitrile ylides,[16] nitrile sulfides should react readily



with the electron-deficient, conjugated acetylenic esters in dipole HOMO-controlled reactions, and the reaction rate should increase as the dipolarophile LUMO energy level is decreased. Qualitatively, the acetylenic ester LUMO levels should lie in the order ethyl 2-butynoate > ethyl propiolate > ethyl phenylpropiolate > dimethyl acetylenedicarboxylate. The observed order of reactivity of the acetylenic esters with nitrile sulfides, dimethyl acetylenedicarboxylate > ethyl propiolate > ethyl phenylpropiolate > ethyl 2-butynoate, is consistent with the LUMO energy level order with a superimposed rate-retarding steric effect in the case of ethyl phenylpropiolate.

The yields of isothiazoles from nitrile sulfides depend on the relative rates of decomposition and cycloaddition of the nitrile sulfides. Alkanecarbonitrile sulfides have higher HOMO levels than arenecarbonitrile sulfides and should react faster in cycloaddition reactions with acetylenes. The lower yields of isothiazoles from alkanecarbonitrile sulfides thus indicates that they decompose more rapidly than arenecarbonitrile sulfides. The regioselectivity found for cycloaddition of benzonitrile sulfide to ethyl propiolate is less than that observed[9] for the corresponding cycloaddition of benzonitrile oxide, due undoubtedly in part to the higher reaction temperature used for the nitrile sulfide reaction.

The substituent effects observed on yields of 1,2,4-thiadiazoles formed by cycloaddition of nitrile sulfides with nitriles[4] can similarly be explained on the basis of frontier orbital theory with reinforcement by coulombic effects. This reaction also should be dipole HOMO controlled,[16] so that lowering of the nitrile LUMO level by electronegative substituents should result in a faster rate of cycloaddition and higher yield of thiadiazole, as observed.[4] The yield of thiadiazole also depends on the competition between cycloaddition of the nitrile sulfide to nitrile and decomposition of the nitrile sulfide; electronegative substituents in the nitrile sulfide should lower the dipole LUMO and HOMO levels, slowing a dipole HOMO-controlled cycloaddition. Since electronegative substituents in the nitrile sulfide were observed to increase the yield,[4a] it appears that such substituents slow the nitrile sulfide decomposition to a greater extent.

Experimental Section

Melting points were taken in open capillaries in a Mel-Temp apparatus and are corrected. Boiling points are uncorrected.

Chlorocarbonylsulfenyl chloride was prepared according to a literature procedure[14] and was employed without purification. Amides, when not available commercially, were prepared by addition of acid halides to cold solutions of ammonia in THF.

General Procedure for 1,3,4-Oxathiazol-2-ones (5). The amide and 1.25–1.50 equiv of chlorocarbonylsulfenyl chloride in toluene were stirred at 100 °C until gas evolution had nearly ceased and/or until IR spectra revealed the absence of residual amide. Up to 5.0 equiv of chlorocarbonylsulfenyl chloride were employed for the less reactive amides, such as *p*-cyanobenzamide, 3,5-bis(trifluoromethyl)benzamide, and ethyl oxamate. The reaction mixture was concentrated under vacuum, and the residue was crystallized from an appropriate solvent.

1,2-Dichloroethane at reflux was employed as the solvent in the preparation of 5-methyl- and 5-*tert*-butyl-1,3,4-oxathiazol-2-one.

5a: mp 69–71 °C (EtOAc) (lit.[8] mp 68.5–70 °C); 83% yield.

5b: mp 52–53.5 °C (MeOH) (lit.[19] mp 47.5–50 °C); 47%.

5c: mp 30.5–32 °C (cold hexane) (lit.[19] mp ~15 °C); 59%. Anal. Calcd for $C_9H_7NO_2S$: C, 55.94; H, 3.65. Found: C, 56.06; H, 3.66.

5d: mp 49–51 °C (methylcyclohexane); 32%. Anal. Calcd for $C_9H_4F_3NO_2S$: C, 43.73; H, 1.63. Found: C, 43.90; H, 1.63.

5e: mp 81–82.5 °C (methylcyclohexane); 54%. Anal. Calcd for $C_8H_3Cl_2NO_2S$: C, 38.72; H, 1.22. Found: C, 38.60; H, 1.06.

5f: mp 82.5–84 °C (methylcyclohexane) (lit.[20] mp 80 °C); 46%.

5g: mp 83–84.5 °C (EtOAc) (lit.[8] mp 81.5–83 °C); 66%.

5h: mp 95–96.5 °C (THF) (lit.[8] mp 96.5–98.5 °C); 63%.

5i: mp 91–92 °C (methylcyclohexane) (lit.[14a] mp 89 °C); 66%.

5j: mp 129–131 °C (methylcyclohexane) (lit.[8] mp 127–130 °C); 48%.

5k: mp 168–169 °C dec (THF) (lit.[14a] mp 163–164 °C); 39%.

5l: mp 143–144.5 °C (EtOAc); 68%. Anal. Calcd for $C_{10}H_9NO_4S$: C, 50.20; H, 3.79. Found: C, 49.97; H, 3.68.

5m: mp 123–124.5 °C (EtOAc); 81%. Anal. Calcd for $C_9H_5NO_4S$: C, 48.43; H, 2.26. Found: C, 48.29; H, 2.22.

5n: mp 130.5–131.5 °C (EtOAc) (lit.[8] mp 128–130 °C); 86%.

5o: mp 61–62.5 °C (methanol); 30%. Anal. Calcd for $C_{10}H_3F_6NO_2S$: C, 38.11; H, 0.96. Found: C, 38.22; H, 0.90).

5p: bp 75–76 °C (30 Torr) [lit.[14a] bp 60 °C (12 Torr)]; mp 16–17 °C; 56%.

5q: bp 35–36 °C (1.2 Torr); 33%. Anal. Calcd for $C_6H_9NO_2S$: C, 45.26; H, 5.70. Found: C, 44.99; H, 5.87.

5r was not obtained in pure form.

5s: bp 85–86 °C (4 Torr) [lit.[14a] bp 78 °C (4.5 Torr)]; 56%; NMR ($CDCl_3$) δ 4.47 (s, $ClCH_2$).

5t: mp 49–50.5 °C (methylcyclohexane); 64%. Anal. Calcd for $C_5H_5NO_4S$: C, 34.29; H, 2.88. Found: C, 34.28; H, 2.81.

5u: mp 85–86.5 °C (cold EtOAc); 86%. Anal. Calcd for $C_9H_4F_3NO_2S$: C, 43.73; H, 1.63. Found: C, 43.66; H, 1.58.

5v: mp 173 °C dec (EtOAc); 75%. Anal. Calcd for $C_9H_4N_2O_2S$: C, 52.93; H, 1.97. Found: C, 53.25; H, 2.02.

5w: mp 176–178 °C dec ($ClCH_2CH_2Cl$); 70%. Anal. Calcd for $C_{10}H_9NO_4S$: C, 50.20; H, 3.79. Found: C, 50.14; H, 3.69.

General Procedure for Dimethyl 4,5-Isothiazoledicarboxylates (6). A solution of 0.10 mol of oxathiazolone and 0.20 mol of dimethyl acetylenedicarboxylate in 60 mL of chlorobenzene was stirred at reflux until CO_2 evolution had ceased and GC analyses revealed that no residual oxathiazolone remained (5–56 h). The solvent and excess dimethyl acetylenedicarboxylate were removed under vacuum. The residue was crystallized from cold methanol and then recrystallized from an appropriate solvent.

6a: mp 72–73 °C (cold MeOH); 73%; IR (mineral oil mull) 5.8 μm; NMR ($CDCl_3$) δ 7.65 (m, 5, ArH), 4.02 (s, 3, OCH_3), 3.99 (s, 3, OCH_3); mass spectrum *m/e* 277, 262, 246, 215, 187, 159, 135, 103, 77. Anal. Calcd for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05; S, 11.56. Found: C, 56.47; H, 4.02; N, 4.93; S, 11.69.

6b: mp 73.5–75 °C (MeOH); 67%. Anal. Calcd for $C_{13}H_{10}FNO_4S$: C, 52.88; H, 3.41. Found: C, 53.08; H, 3.54.

6c: mp −33 to −31 °C (chromatographed on silicic acid with benzene–hexane); 66%. Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50. Found: C, 57.44; H, 4.64.

6d: bp 160 °C (0.015 Torr) (molecular distillation); 96%. Anal. Calcd for $C_{14}H_{10}F_3NO_4S$: C, 48.70; H, 2.92. Found: C, 48.66; H, 3.24.

6e: mp 93–94.5 °C (chromatographed on silica gel and crystallized from methylcyclohexane); 30%. Anal. Calcd for $C_{13}H_9Cl_2NO_4S$: C, 45.70; H, 2.62. Found: 45.71; H, 2.81.

6f: mp 53–54.5 °C (ether–petroleum ether); 52%. Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50. Found: C, 57.79; H, 4.20.

6g: mp 69–70 °C (ether–petroleum ether); 52%. Anal. Calcd for $C_{13}H_{10}ClNO_4S$: C, 50.09; H, 3.23. Found: C, 50.24; H, 3.42.

6h: mp 120.5–122 °C (cold MeOH); 54%. Anal. Calcd for $C_{13}H_{10}N_2O_6S$: C, 48.45; H, 3.13. Found: C, 48.51; H, 3.14.

6i: mp 92.5–93.5 °C (cold ether) (lit.[5] mp 90–91 °C); 74%. Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50. Found: C, 57.78; H, 4.67.

6j: mp 108.5–109.5 °C (cold ether); 58%. Anal. Calcd for $C_{13}H_{10}ClNO_4S$: C, 50.09; H, 3.23. Found: C, 50.23; H, 3.12.

6k: mp 142–143 °C (EtOAc); 25%; the reactants were heated in *o*-dichlorobenzene at reflux for 15 h. Anal. Calcd for $C_{13}H_{10}N_2O_6S$: C, 48.45; H, 3.13. Found: C, 48.76; H, 3.18.

6l: mp 113.5–114.5 °C (MeOH, then EtOAc); 73%. Anal. Calcd for $C_{15}H_{15}NO_6S$: C, 53.41; H, 4.48. Found: C, 53.03; H, 4.46.

6m: mp 104–105 °C (MeOH); 51%. Anal. Calcd for $C_{14}H_{11}NO_6S$: C, 52.33; H, 3.45. Found: C, 52.09; H, 3.28.

6n: mp 105–107 °C (MeOH); 71%. Anal. Calcd for $C_{13}H_9Cl_2NO_4S$: C, 45.10; H, 2.62. Found: C, 45.12; H, 2.48.

6o: mp 73–75 °C (MeOH); 53%; the reactants were heated in *o*-dichlorobenzene at reflux for 10 h. Anal. Calcd for $C_{15}H_9F_6NO_4S$: C, 43.59; H, 2.19. Found: C, 43.77; H, 2.13.

6p: Distillation of the reaction mixture, which contained **6p** in 58% yield (GC assay), gave the desired product at bp 81–83 °C (0.3 Torr) in 50% yield. The oil crystallized upon standing and was recrystallized from petroleum ether to give solid of mp 34.5–35.5 °C. Anal. Calcd for $C_8H_9NO_4S$: C, 44.64; H, 4.21; N, 6.51; S, 14.90. Found: C, 44.73; H, 4.30; N, 6.62; S, 15.08.

6q: Distillation of the reaction mixture, which contained **6q** in 39% yield (GC assay), gave the desired product at bp 95 °C (0.15 Torr), in 24% yield. Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 47.15; H, 4.84. Found: C, 47.09; H, 4.82.

6r: Distillation of the reaction mixture gave **6r** contaminated with sulfur at bp 150–165 °C (0.7 Torr), in ~59% yield. Three crystalliza-

tions of the material from methanol and once from hexane gave pure product: mp 38.5–40.5 °C; 18%. Anal. Calcd for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05. Found: C, 55.12; H, 6.02.

6s: The reactants were heated in chlorobenzene at 130–135 °C for 170 h, at which time there still was some residual oxathiazolone. Distillation of the reaction mixture gave 95.5% pure **6s**; bp 116 °C (0.1 Torr); 38% yield. Redistillation of this material gave 99% pure **6s**: bp 98 °C (0.08 Torr); 32% yield; IR (film) 5.78 μm; NMR ($CDCl_3$) δ 4.93 (s, 2, CH_2Cl), 4.00 (s, 6, OCH_3). Anal. Calcd for $C_8H_8ClNO_4S$: C, 38.49; H, 3.23. Found: C, 38.33; H, 3.23.

6t: A mixture of 8.76 g (0.050 mol) of ethyl 2-oxo-1,3,4-oxathiazole-5-carboxylate and 14.21 g (0.10 mol) of dimethyl acetylenedicarboxylate was heated at reflux for 43 min, at which time GC analysis revealed that most of the acetylenedicarboxylate was gone but much oxathiazolone was left. Another 14.2 g of dimethyl acetylenedicarboxylate was added, and the mixture was heated another 50 min at reflux. At this point, GC analysis revealed that most, but not all, of the oxathiazolone was gone, and that several oligomers of the acetylenedicarboxylate had formed in addition to the desired product. The viscous, black reaction mixture was extracted with 200 mL of 50:50 ether–hexane, and the supernatant was decanted from the black insoluble residue. The insoluble residue was dissolved in 100 mL of ethyl acetate, and 300 mL of ether and then 400 mL of hexane was added. The black, viscous gum that came out of solution contained only a trace of the desired product (GC assay). The two supernatants were combined and concentrated under vacuum to an oil. This oil was chromatographed on silica gel (Woelm material, for dry column chromatography); use of 60% ether in cyclohexane to elute the column gave 1.6 g (11.7%) of pure product as a viscous oil; IR (film) 5.83 μm; NMR ($CDCl_3$) δ 4.50 (q, 2, J = 7 Hz, OCH_2), 4.06 (s, 3, OCH_3), 4.01 (s, 3, OCH_3), 1.44 (t, 3, J = 7 Hz, CH_3). Anal. Calcd for $C_{10}H_{11}NO_6S$: C, 43.95; H, 4.06. Found: C, 43.86; H, 4.04.

General Procedure for 4,5-Isothiazoledicarboxylic Acids (7). A mixture of 0.10 mol of **6** and 0.50 mol of NaOH in 125 mL of water was held at reflux for 2 h (for very insoluble esters, a little dioxane was added to the reaction mixture). The resultant solution was acidified to pH <1 with a large excess of concentrated HCl and was extracted several times with ether. The ether layers were combined, dried ($CaSO_4$), and concentrated under vacuum. Generally, only a small sample of the crude diacid was purified for analysis. The remainder of the product was converted directly to the monoacid.

7a: mp 184–185 °C dec (CH_3CN); 90% yield. Anal. Calcd for $C_{11}H_7NO_4S$: C, 53.01; H, 2.83; N, 5.62. Found: C, 53.16; H, 2.80; N, 5.64.

7b: mp 144.5–145.5 °C dec ($ClCH_2CH_2Cl$). Anal. Calcd for $C_{11}H_6FNO_4S$: C, 49.44; H, 2.26. Found: C, 49.35; H, 2.53.

7c and **7d** were not obtained in analytically pure form.

7e: mp 159–160 °C dec (ether–methylcyclohexone). Anal. Calcd for $C_{11}H_5Cl_2NO_4S$: C, 41.53; H, 1.58. Found: C, 41.55; H, 1.61.

7f: mp 166.5–167 °C dec ($ClCH_2CH_2Cl$). Anal. Calcd for $C_{12}H_9NO_4S$: C, 54.75; H, 3.45. Found: C, 54.54; H, 3.63.

7g: mp 185–186 °C dec (rapid heating rate) ($ClCH_2CH_2Cl$). Anal. Calcd for $C_{11}H_6ClNO_4S$: C, 46.57; H, 2.13. Found: C, 46.50; H, 2.17.

7h and **7i** were not obtained analytically pure.

7j: mp 177–177.5 °C dec ($ClCH_2CH_2Cl$). Anal. Calcd for $C_{11}H_6ClNO_4S$: C, 46.57; H, 2.13. Found: C, 46.22; H, 2.26.

7k was not obtained analytically pure.

7l was obtained as a partial hydrate, mp 190.5–191.5 °C dec (rapid heating rate) (aqueous EtOH). Anal. Calcd for $C_{13}H_{11}NO_6S \cdot 0.7H_2O$: C, 48.50; H, 3.88. Found: C, 48.73; H, 4.10.

7m: mp 181.5–182.5 °C dec (rapid heating rate) (CH_3CN). Anal. Calcd for $C_{12}H_7NO_6S$: C, 49.15; H, 2.41. Found: C, 49.32; H, 2.50.

7n: mp 187.5–188.5 °C dec (rapid heating rate) (ether–$ClCH_2CH_2Cl$). Anal. Calcd for $C_{11}H_5Cl_2NO_4S$: C, 41.53; H, 1.58. Found: C, 41.56; H, 1.60.

7o; mp 193–193.5 °C dec; 93% yield. Anal. Calcd for $C_{13}H_5F_6NO_4S$: C, 40.53; H, 1.31. Found: C, 40.31; H, 1.18.

7p: mp 163 °C dec (lit.[21] mp 160 °C dec); 90%.

7q: mp 173 °C dec (ether–hexane). Anal. Calcd for $C_9H_{11}NO_4S$: C, 47.15; H, 4.84. Found: C, 47.09; H, 4.82.

7r: mp 146–147 °C dec ($ClCH_2CH_2Cl$). Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.79; H, 5.13. Found: C, 51.67; H, 5.20.

General Procedure for 4-Isothiazolecarboxylic Acids (8). The 4,5-isothiazoledicarboxylates were heated in *o*-dichlorobenzene at reflux for 15 min to effect monodecarboxylation. The solution was allowed to cool, and the solid product was collected, washed with hexane, and recrystallized. With the more soluble acids, the chlorobenzene solvent was removed under vacuum, and the residue was crystallized.

8a: mp 167–168.5 °C (50% aqueous ethanol) (lit.[15] mp 165–166 °C); 73%.

8b: mp 163.5–165 °C ($ClCH_2CH_2Cl$); 87%, Anal. Calcd for $C_{10}H_6FNO_2S$: C, 53.81; H, 2.71. Found: C, 53.50; H, 2.73.

8c: mp 157–158.5 °C ($ClCH_2CH_2Cl$); 83%. Anal. Calcd for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14. Found: C, 59.95; H, 4.10.

8d: mp 148–150 °C (benzene–heptane); 58%. Anal. Calcd for $C_{11}H_6F_3NO_2S$: C, 48.35; H, 2.21. Found: C, 48.34; H, 2.32.

8e: mp 183–185 °C (benzene) (lit.[22] mp 182–183 °C); 65%.

8f: mp 144.5–146 °C ($ClCH_2CH_2Cl$); 83%. Anal. Calcd for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14. Found: C, 60.21; H, 4.04.

8g: mp 215–216 °C ($ClCH_2CH_2Cl$–CH_3CN); 87%. Anal. Calcd for $C_{10}H_6ClNO_2S$: C, 50.11; H, 2.52. Found: C, 50.32; H, 2.47.

8h: mp 234–235.5 °C (THF–CH_3CN); 48%. Anal. Calcd for $C_{10}H_6N_2O_4S$: C, 48.00; H, 2.42; N, 11.20. Found: C, 48.08; H, 2.38; N, 11.06.

8i: mp 179.5–181 °C ($ClCH_2CH_2Cl$); 82%. Anal. Calcd for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14. Found: C, 60.49; H, 4.10.

8j: mp 177–179 °C (75% aqueous EtOH) (lit.[15] mp 172–174 °C); 89%.

8k: mp 264.5–265.5 °C dec (dioxane); 62%; did not give a satisfactory C,H analysis.

8l: mp 215.5–216 °C dec (EtOAc); 90%. Anal. Calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.18. Found: C, 54.32; H, 4.24.

8m: mp 232.5–233.5 °C dec (aqueous EtOH); 79%. Anal. Calcd for $C_{11}H_7NO_4S$: C, 53.01; H, 2.83. Found: C, 52.98; H, 2.82.

8n: mp 247–247.5 °C dec (ether–toluene). Anal. Calcd for $C_{10}H_5Cl_2NO_2S$: 43.82; H, 1.84. Found: C, 43.84; H, 1.87.

8o: mp 152–154 °C (heptane); 84%. Anal. Calcd for $C_{12}H_5F_6NO_2S$: C, 42.24; H, 1.48. Found: C, 42.13; H, 1.34.

8p: mp 235.5–237.5 °C; 99% (lit.[21] mp 236–238 °C).

8q: mp 128–130 °C; 90%. Anal. Calcd for $C_8H_{11}NO_2S$: C, 51.87; H, 5.99. Found: C, 51.77; H, 6.04.

8r: mp 155–156 °C (heptane); 68%. Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20. Found: C, 57.06; H, 6.15).

General Procedure for Ethyl 4-Isothiazolecarboxylates. Pure carboxylic acid was heated with excess thionyl chloride at reflux on a steam bath for 30 min. The resultant solution was concentrated under aspirator vacuum, and the residue was heated in excess ethanol at reflux for 30 min. The solution was concentrated under vacuum to give pure ester. In cases of solid esters, the solid was recrystallized.

9a: oil, 86%; IR (film) 5.8 μm; NMR ($CDCl_3$) δ 9.4 (s, 1, 5-H), 7.5 (m, 5, ArH), 4.3 (q, 2, OCH_2), 1.3 (t, 3, CH_3); mass spectrum *m/e* 233, 204, 188, 161, 133, 116, 104, 85, 77, 63, 57, 51. Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: C, 61.64; H, 4.93; N, 6.20.

9b: mp 29.5–31 °C (EtOH at −78 °C); 93%. Anal. Calcd for $C_{12}H_{10}FNO_2S$: C, 57.36; H, 4.01. Found: C, 57.58; H, 4.00.

9c: n^{25}_D 1.5722; 93%. Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30. Found: C, 63.15; H, 5.23.

9d: mp 57.5–59 °C (hexane); 51%. Anal. Calcd for $C_{13}H_{10}F_3NO_2S$: C, 51.82; H, 3.35; N, 4.65. Found: C, 52.07; H, 3.33; N, 4.56.

9e: mp 87.5–89.5 °C (EtOH); 86%. Anal. Calcd for $C_{12}H_9Cl_2NO_2S$: C, 47.70; H, 3.00. Found: C, 47.74; H, 3.04.

9f: n^{25}_D 1.5823; 98%. Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30. Found: C, 63.27; H, 5.38.

9g: mp 66.5–68 °C (EtOH); 95%. Anal. Calcd for $C_{12}H_{10}ClNO_2S$: C, 53.83; H, 3.76. Found: C, 53.86; H, 3.73.

9h: mp 136.5–138 °C (EtOH); 72%. Anal. Calcd for $C_{12}H_{10}N_2O_4S$: C, 51.79; H, 3.62; N, 10.07. Found: C, 51.85; H, 3.38; N, 10.07.

9i: n^{25}_D 1.5671; 90%. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30. Found: C, 62.95; H, 5.52.

9j: mp 70.5–71.5 °C (aqueous EtOH); 66%. Anal. Calcd for $C_{12}H_{10}ClNO_2S$: C, 53.83; H, 3.76. Found: C, 54.01; H, 3.90. **9j** was obtained also in a crystal form with mp 55.5–56.5 °C.

9k: mp 152–154 °C (EtOH); 63%. Anal. Calcd for $C_{12}H_{10}N_2O_4S$: C, 51.79; H, 3.62. Found: C, 51.82; H, 3.63.

9l: mp 74–75.5 °C (EtOH–hexane); 98%. Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15. Found: C, 57.36; H, 5.14.

9m: mp 119.5–120.5 °C (EtOH–EtOAc); 94%. Anal. Calcd for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05. Found: C, 56.28; H, 3.91; N, 5.04.

9n: mp 111.5–112 °C (EtOH); 88%. Anal. Calcd for $C_{12}H_9Cl_2NO_2S$: C, 47.70; H, 3.00. Found: C, 47.61; H, 3.02.

9o: mp 61.5–63 °C (96%). Anal. Calcd for $C_{14}H_9F_6NO_2S$: C, 45.53; H, 2.46. Found: C, 45.31; H, 2.51.

9r: n^{25}_D 1.5263; 88%. Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16. Found: C, 59.98; H, 5.83.

Ethyl 3-Phenyl-5-isothiazolecarboxylate (10a). A solution of 8.96 g (0.050 mol) of 5-phenyl-1,3,4-oxathiazol-2-one and 19.62 g (0.20 mol) of ethyl propiolate in 75 g of *o*-dichlorobenzene was held at reflux (150 °C) for 3.5 h. GC analysis (2 ft 10% SE-30 column) of the reaction mixture revealed that all the oxathiazolone had reacted and that ethyl 3-phenyl-4-isothiazolecarboxylate (**9a**) and ethyl 3-phenyl-5-isothi-

azolecarboxylate (**10a**) had formed in 40 and 43% yields, respectively. The reaction mixture was concentrated under vacuum to 12.2 g of black oil. Dry column chromatography of the oil on 800 g of Woelm silica gel (for dry column chromatography) with benzene gave 4.7 g of 98% pure **10a**, mp 63–65 °C, and 6.0 g of crude **9a**. Two crystallizations of the **10a** from ethanol gave 3.4 g (29%) of pure **10a**: mp 66–67 °C; IR (mineral oil mull) 5.82 μm; NMR ($CDCl_3$) δ 8.07 (s, 1, 4-H), 7.9 (m, 2, ArH), 7.4 (m, 3, ArH), 4.43 (q, 2, OCH_2), 1.37 (t, 3, CH_3). Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00. Found: C, 61.97; H, 4.71; N, 6.06.

Hydrolysis of a sample of the 5-carboxylic ester gave 3-phenyl-5-isothiazolecarboxylic acid, mp 184–185 °C (lit[23] 184–186 °C).

The 6.0 g of crude **9a** was hydrolyzed with 3.6 g (0.090 mol) of NaOH in aqueous ethanol at reflux for 1 h. The solution was cooled in ice and acidified with concentrated HCl to give 4.01 g of tan solid, mp 150–165 °C. The solid was crystallized from aqueous EtOH to give 3.45 g of tan solid, mp 162–167 °C. This material was heated in 40 mL of *o*-dichlorobenzene at reflux for 8 min. The solution was cooled, and the resultant solid was collected and washed with *o*-dichlorobenzene and then hexane to give 3.13 g (31%) of solid, mp 167–168.5°; the IR spectra of this material and of authentic 3-phenyl-4-isothiazolecarboxylic acid were identical.

Ethyl 3-(*p*-Chlorophenyl)-5-isothiazolecarboxylate (10j). A solution of 10.68 g (0.050 mol) of 5-(*p*-chlorophenyl)-1,3,4-oxathiazol-2-one and 19.62 g (0.20 mol) of ethyl propiolate in 75 g of *o*-dichlorobenzene was held at reflux (150 °C) under N_2 for 10 h and was concentrated under vacuum at 90 °C (0.2 Torr) to give 16.0 g of black oil. Dry column chromatography of the oil on silica gel with benzene and crystallizations of the fractions rich in 5-carboxylate gave 3.50 g (26% yield) of pure ethyl 3-(*p*-chlorophenyl)-5-isothiazolecarboxylate: mp 87.5–89 °C (from ethanol); NMR ($CDCl_3$) δ 8.13 (s, 1, 4-H), 7.7 (m, 4, ClC_6H_4), 4.47 (q, 2, OCH_2), 1.43 (t, 3, CH_3). Anal. Calcd for $C_{12}H_{10}ClNO_2S$: C, 53.83; H, 3.76. Found: C, 53.84; H, 3.64.

Crystallization of the fractions rich in 4-carboxylate from aqueous ethanol gave 2.45 g (18% yield) of pure ethyl 3-(*p*-chlorophenyl)-4-isothiazolecarboxylate, mp 70.5–71.5 °C.

Ethyl 3-(α,α,α-Trifluoro-*m*-tolyl)-4-isothiazolecarboxylate (9u) and Ethyl 3-(α,α,α-Trifluoro-*m*-tolyl)-5-isothiazolecarboxylate (10u). A solution of 12.36 g (0.050 mol) of 5-(α,α,α-trifluoro-*m*-tolyl)-1,3,4-oxathiazol-2-one and 19.62 g (0.20 mol) of ethyl propiolate in 75.0 g of *o*-dichlorobenzene was held at reflux under N_2 for 20 h, at which time analysis by GC revealed that the reaction was complete and that the 4-carboxylate and the 5-carboyxlate had formed in 46 and 39% yields, respectively. Concentration of the solution under vacuum gave 16.4 g of dark oil. Crystallization of the oil from 35 mL of ethanol at −20 °C gave 5.05 g (34%) of tan solid, mp 77–79 °C, that was ~98% pure 5-carboxylate (GC assay). Concentration of the filtrate gave 10.8 g of oil. Chromatography of the oil on 550 g of silicic acid with benzene gave 5.2 g (35%) of 4-carboxylate that was 97% pure (3% low boilers, no 5-carboxylate present; GC analysis): IR ($CHCl_3$) 5.83 μm; NMR ($CDCl_3$) δ 9.43 (s, 1, 5-H), 8.03–7.43 (m, 4, ArH), 4.30 (q, 2, OCH_2), 1.23 (t, 3, CH_3). Anal. Calcd for $C_{13}H_{10}F_3NO_2S$: C, 51.82; H, 3.35. Found: C, 52.09; H, 3.50.

The chromatography also gave 0.31 g (2%) of pure 5-carboxylate, mp 80–81.5 °C. Recrystallization of the 5.05 g of 5-carboxylate from ethanol gave 4.05 g (27%) of colorless crystals: mp 80–81.5 °C; IR ($CHCl_3$) 5.81 μm; NMR ($CDCl_3$) δ 8.20 (s, 1, 4-H), 8.30–7.47 (m, 4, ArH), 4.47 (q, 2, OCH_2), 1.43 (t, 3, CH_3). Anal. Calcd for $C_{13}H_{10}F_3NO_2S$: C, 51.82; H, 3.35. Found: C, 51.98; H, 3.39.

Ethyl 3-(*p*-Cyanophenyl)-4-isothiazolecarboxylate (9v) and Ethyl 3-(*p*-Cyanophenyl)-5-isothiazolecarboxylate (10v). A solution of 10.2 g (0.050 mol) of 5-(*p*-cyanophenyl)-1,3,4-oxathiazol-2-one and 19.62 g (0.20 mol) of ethyl propiolate in 75.0 g of o-dichlorobenzene was held at reflux under N_2 for 20 h, at which time GC analysis indicated that the 4-carboxylate and the 5-carboxylate had formed in 44 and 46% yields, respectively. Concentration of the reaction mixture under vacuum gave 20.3 g of brown solid. Crystallization of this material from ethanol gave 5.54 g (43%) of 5-carboxylate as a beige solid, mp 175–179 °C. Crystallization of the solid from ethanol gave 0.1 g of unidentified, fairly insoluble white solid: mp 236–237 °C; IR ($CHCl_3$) 4.50, 5.81 μm. The residue from the filtrate was chromatographed on silica gel with benzene, and the purest fractions were crystallized from ethanol to give 1.27 g (10%) of 5-carboxylate as a white solid: mp 183–184.5 °C; IR ($CHCl_3$) 4.50, 5.81 μm; NMR ($CDCl_3$) δ 8.17 (s, 1, 4-H), 7.93 (AA′BB′ m, 4, ArH), 4.43 (q, 2, J = 7 Hz, OCH_2CH_3), 1.40 (t, 3, J = 7 Hz, OCH_2CH_3). Anal. Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90. Found: C, 60.49; H, 3.98.

The filtrate from the crystallization of the 20.3 g of brown solid was concentrated under vacuum, and the residue was chromatographed on silica gel with benzene. The 4-carboxylate thus obtained was crystallized from heptane to give 4.06 g (32%) of white solid: mp 109–110 °C; IR ($CHCl_3$) 4.50, 5.81 μm; NMR ($CDCl_3$) δ 9.40 (s, 1, 5-H), 7.73 (s, 4, ArH), 4.30 (q, 2, J = 7 Hz, OCH_2CH_3), 1.27 (t, 3, J = 7 Hz, OCH_2CH_3). Anal. Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90. Found: C, 60.48; H, 3.96.

Ethyl 3-(3,5-Dimethoxyphenyl)-4-isothiazolecarboxylate (9w) and Ethyl 3-(3,5-Dimethoxyphenyl)-5-isothiazolecarboxylate (10w). By a procedure similar to that employed for **9j** and **10j**, ethyl 3-(3,5-dimethoxyphenyl)-4-isothiazolecarboxylate was obtained in 25% yield as a white solid: mp 71.5–73 °C (from ethanol); NMR ($CDCl_3$) δ 9.23 (s, 1, 5-H), 6.72 (d, 2, J = 2 Hz, ArH), 6.48 (t, 1, J = 2 Hz, ArH), 4.23 (q, 2, J = 7 Hz, OCH_2CH_3), 3.78 (s, 6, OCH_3), 1.23 (t, 3, J = 7 Hz, OCH_2CH_3). Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15. Found: C, 57.40; H, 5.21.

Ethyl 3-(3-dimethoxyphenyl)-5-isothiazolecarboxylate was obtained in 32% yield as a white solid: mp 101–103 °C (from ethanol); NMR ($CDCl_3$) δ 7.98 (s, 1, 4-H), 7.03 (d, 2, J = 2 Hz, ArH), 6.47 (t, 1, J = 2 Hz, ArH), 4.37 (q, 2, J = 7 Hz, OCH_2CH_3), 3.82 (s, 6, OCH_3), 1.40 (t, 3, J = 7 Hz, OCH_2CH_3). Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15. Found: C, 57.50; H, 5.17.

5-Phenyl-2-(α,α,α-trifluoro-*m*-tolyl)-4-isothiazolecarboxylic Acid 20. A solution of 5.44 g (0.022 mol) of 5-(α,α,α-trifluoro-*m*-tolyl)-1,3,4-oxathiazol-2-one, 38.15 g (0.22 mol) of ethyl phenylpropiolate, and 38.15 g of *o*-dichlorobenzene was held at 150 °C under N_2 for 20 h, at which time GC analysis revealed the isothiazole-4-carboxylate and isothiazole-5-carboxylate had formed in 47 and 9.5% yields, respectively. The reaction mixture was concentrated under vacuum (0.15 Torr and 180 °C bath temperature) to 12.7 g of residue (products and high-boiling side products). The residue was chromatographed on 1154 g of silica gel (Woelm, for dry column chromatography) with benzene to give 2.72 g of 91% pure 4- and 5-isothiazolecarboxylate mixture. A 2.5-g sample of the mixture was heated with 2.8 g of sodium hydroxide in 50% aqueous ethanol at reflux for 2 h. The solution was concentrated under vacuum. The residue was acidified with dilute HCl. The mixture was extracted with three 150-mL portions of ether. The ether extracts were dried ($CaSO_4$) and concentrated under vacuum to 2.1 g of solid. The solid was heated in 20 mL of *o*-dichlorobenzene at reflux for 20 min, at which time gas evolution had ceased. Concentration of the solution under vacuum gave 1.8 g of solid. Crystallization of the solid from benzene gave 1.1 g (14% yield from oxathiazolone) of solid 5-phenyl-3-(α,α,α-trifluoro-*m*-tolyl)-4-isothiazolecarboxylic acid, mp 192.5–194 °C. Recrystallization of the solid from 1,2-dichloroethane gave 0.97 g of solid: mp 194–195 °C; IR (mineral oil mull) 3.0–4.2 (m), 5.84 μm (s); mass spectrum *m/e* 349 (M^+). Anal. Calcd for $C_{17}H_{10}F_3NO_2S$: C, 58.45; H, 2.98. Found: C, 58.52; H, 3.04.

Ethyl 5-Phenyl-3-(α,α,α-trifluoro-*m*-tolyl)-4-isothiazolecarboxylate (18). A solution of 0.97 g (0.00278 mol) of 5-phenyl-3-(α,α,α-trifluoro-*m*-tolyl)-4-isothiazolecarboxylic acid and 1.58 g (5 equiv) of thionyl chloride was heated on a steam bath for 0.5 h. The reaction mixture was concentrated under vacuum. The residue in 5 cm^3 of ethanol was heated on a steam bath for 1 h. The mixture was concentrated under vacuum to give 0.65 g of oil. The oil was crystallized from hexane to give 0.13 g of solid, mp 41–45 °C. The residue from the filtrate was crystallized three times from pentane to give 0.05 g of solid: mp 44–46 °C; IR (mineral oil mull) 5.82 μm (C=O); NMR ($CDCl_3$) δ 7.99 (m, 9, ArH), 4.16 (q, 2, J = Hz, OCH_2CH_3), 1.03 (t, 3, J = 7 Hz, OCH_2CH_3). Anal. Calcd for $C_{19}H_{14}F_3NO_2S$: C, 60.47; H, 3.74; N, 3.71. Found: C, 60.32; H, 3.71; N, 3.75.

Registry No.—**5b**, 52059-63-9; **5c**, 52059-70-8; **5d**, 67048-92-4; **5e**, 67048-91-3; **5f**, 23589-68-6; **5g**, 23589-73-3; **5h**, 23589-77-7; **5i**, 17452-78-7; **5k**, 17452-80-1; **5l**, 67048-90-2; **5m**, 67048-89-9; **5n**, 67048-88-8; **5o**, 67048-86-6; **5p**, 17452-74-3; **5q**, 67049-04-1; **5r**, 67049-12-1; **5s**, 17452-75-4; **5t**, 61689-40-5; **6a**, 27545-53-5; **6b**, 67048-77-5; **6c**, 67048-73-1; **6d**, 67048-71-9; **6e**, 67048-68-4; **6f**, 67048-65-1; **6g**, 67048-62-8; **6h**, 67048-59-3; **6i**, 35550-01-7; **6j**, 67048-54-8; **6k**, 59291-74-6; **6l**, 67113-95-5; **6m**, 67048-50-4; **6n**, 59291-75-7; **6o**, 67113-94-4; **6p**, 49570-33-4; **6q**, 67049-17-6; **6r**, 67049-14-3; **6s**, 67049-11-0; **6t**, 67049-09-6; **7a**, 27545-54-6; **7b**, 67049-02-9; **7c**, 67049-10-9; **7d**, 67049-07-4; **7e**, 67048-84-4; **7f**, 67048-82-2; **7g**, 67048-79-7; **7h**, 67049-05-2; **7i**, 67049-01-8; **7j**, 67048-76-4; **7k**, 67048-83-3; **7l**, 67113-96-6; **7m**, 67048-70-8; **7n**, 67048-66-2; **7o**, 67048-64-0; **7p**, 67048-61-7; **7q**, 67048-58-2; **7r**, 67048-56-0; **8a**, 18160-82-2; **8b**, 67048-52-6; **8c**, 67048-49-1; **8d**, 67048-47-9; **8e**, 19547-33-2; **8f**, 67113-93-3; **8g**, 67049-19-8; **8h**, 67049-16-5; **8i**, 67049-13-2; **8j**, 19762-93-7; **8k**, 67049-08-5; **8l**, 67049-06-3; **8m**, 67049-03-0; **8n**, 67113-97-7; **8o**, 67048-81-1; **8p**, 15903-66-9; **8q**, 67048-75-3; **8r**, 67049-72-0; **9b**, 67048-69-5; **9c**, 67048-67-3; **9d**, 67048-63-9; **9e**, 67048-60-6; **9f**, 67048-57-1; **9g**, 67048-55-9; **9h**, 67048-53-7; **9i**, 67048-51-5; **9k**, 67048-48-0; **9l**, 67048-46-8; **9m**, 67049-21-2; **9n**, 67049-20-1; **9o**, 67049-18-7; **9r**,

67049-15-4; **18**, 67048-80-0; **19**, 67048-74-2; **20**, 67048-78-6; benzamide, 55-21-0; *o*-fluorobenzamide, 445-28-3; *o*-toluamide, 527-85-5; α,α,α-trifluoro-o-toluamide, 360-64-5; 2,6-dichlorobenzamide, 2008-58-4; *m*-toluamide, 618-47-3; *m*-chlorobenzamide, 618-48-4; *m*-nitrobenzamide, 645-09-0; *p*-toluamide, 619-55-6; *p*-chlorobenzamide, 619-56-7; *p*-nitrobenzamide, 619-80-7; 3,4-dimethoxybenzamide, 1521-41-1; 3,4-methylenedioxybenzamide, 4847-94-3; 3,4-dichlorobenzmaide, 2670-38-4; 3,5-bis(trifluoromethyl)benzamide, 22227-26-5; acetamide, 60-35-5; 2,2-dimethylpropanamide, 754-10-9; cyclohexanecarboxamide, 1122-56-1; 2-chloroacetamide, 79-07-2; ethyl oxamate, 617-36-7; α,α,α-trifluoro-*m*-toluamide, 1801-10-1; *p*-cyanobenzamide, 3034-34-2; 3,5-dimethoxybenzamide, 17213-58-0; ClCl(O)5CL, 2757-23-5; dimethyl acetylenedicarboxylate, 762-42-5; ethyl phenylpropiolate, 2216-94-6.

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Cycloaddition Reactions of Nitrile Sulfides with Olefins

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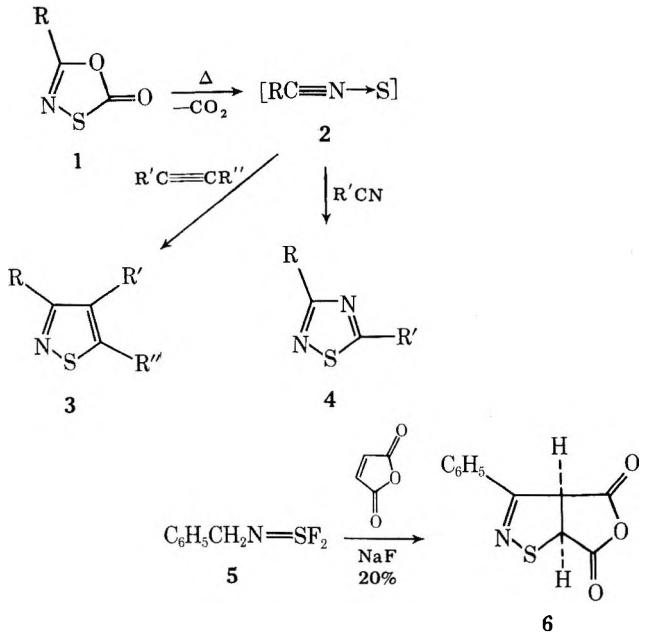
Received March 20, 1978

Dipolar cycloadditions of arenecarbonitrile sulfides to various olefins are described. Isothiazolines were obtained in fair to good yields from diethyl fumarate, phenyl acrylate, a norbornene derivative, and maleimides. Isothiazolecarboxylates were formed (via intermediate isothiazolines) from ethyl 2-chloroacrylate and ethyl β-pyrrolidinylacrylate. Significant amounts of adducts were not obtained from tetraethyl ethenetetracarboxylate, β-nitrostyrene, and 3-nitrostyrene.

We have reported previously cycloaddition reactions of nitrile sulfides (**2**), generated by thermolysis of 5-substituted-1,3,4-oxthiazol-2-ones (**1**), with acetylenic esters to give isothiazoles[1-3] (**3**) and with nitriles to give 1,2,4-thiadiazoles[4-6] (**4**) (Scheme I). We report here our studies of cycloadditions of nitrile sulfides with olefins. Subsequent to the completion of our work but prior to this account, Grunwell and Dye[7] reported cycloaddition of benzonitrile sulfide, generated from *N*-benzyliminosulfur difluoride (**5**), to maleic anhydride to give 3-phenyl-2-isothiazoline-*cis*-4,5-dicarboxylic acid anhydride (**6**) in 20% yield.

Scheme I



Thermolysis of 5-phenyl-1,3,4-oxathiazol-2-one (**1a**) at 190 °C in 4 equiv of dimethyl fumarate under nitrogen gave dimethyl 3-phenyl-2-isothiazoline-*trans*-4,5-dicarboxylate (**7**) in 55% yield (GC analysis) (Scheme II); the pure product was isolated in 45% yield. The coupling constant $J = 4$ Hz between H_4 and H_5 in the proton NMR spectrum of **7** reveals that H_4 and H_5 are trans. The corresponding coupling constant in dimethyl 3-phenyl-2-isoxazolin-*trans*-4,5-dicarboxylate is 4.9 Hz and in dimethyl 3-phenyl-2-isoxazolin-*cis*-4,5-dicarboxylate is 11.5 Hz.[8] Dehydrogenation of **7** with dichlorodicyanobenzoquinone (DDQ) gave dimethyl 3-phenyl-4,5-isothiazoledicarboxylate (**3a**), which we had prepared earlier[1-3] from **1a** and dimethyl acetylenedicarboxylate.

Thermolysis of **1a** in 4 equiv of tetraethyl ethenetetracarboxylate at 190 °C gave benzonitrile (from decomposition of benzonitrile sulfide)[1,2] in 91% yield and an unidentified high-boiling material (~6%, GC analysis). Because of steric

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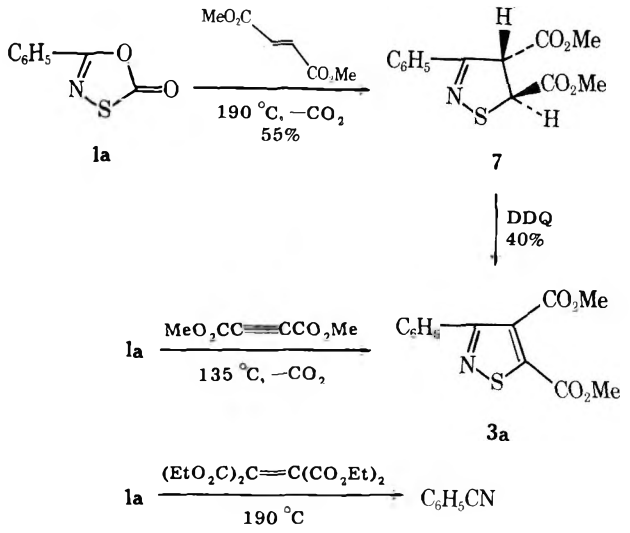
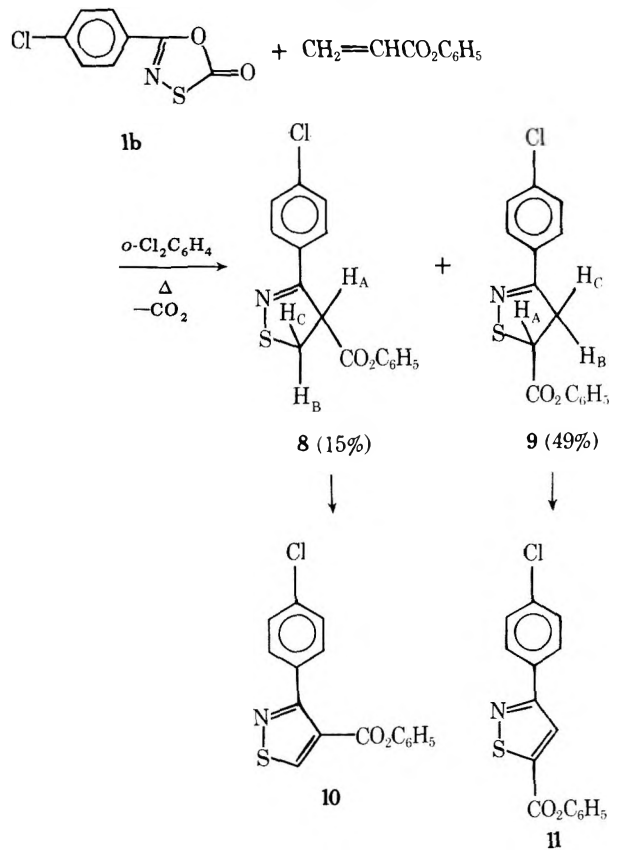
Scheme II



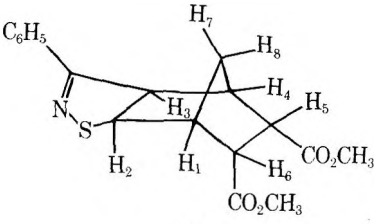
effects,[9,10] cycloaddition of benzonitrile sulfide to the ethenetetracarboxylate is less facile than addition to the fumarate ester. Earlier we found that nitrile sulfides add to the cyano group of tetracyanoethylene and not to the carbon–carbon double bond.[5]

A mixture of **1b** and 26 equiv of phenyl acrylate in *o*-dichlorobenzene heated at reflux gave isothiazolines **8** and **9** in 15 and 49% yields, respectively (GC and GC–MS analyses), and a trace (~0.8% yield) of isothiazole **10** (GC, GC–MS) (Scheme III). Pure samples of **8** (4% isolated yield) and of **9** (30% isolated yield) were obtained by fractional crystallization. Both **8** and **9** are somewhat unstable in solution and aromatize to significant extents within a few days (GC, GC–MS analyses). After 5 days at room temperature in acetone solution, **8** gave 6% of **10** and **9** produced 13% of **11**. Both **8** and **9** give ABC NMR spectra for the H_A, H_B, and H_C protons. Computer-assisted analysis of these spectra, with use of the LAOCOON III program, allowed extraction of the shifts and coupling constants for **8** and **9**. Most significantly, **8** has $J_{BC} = -11.5$ Hz, corresponding to $J_{BC} = -8.57$ Hz for the related methyl 3-phenyl-2-isoxazolin-3-ylcarboxylate,[11] and **9** has $J_{BC} = -17.7$ Hz, corresponding to -17.1 Hz for the related methyl 3-phenyl-2-isoxazolin-5-ylcarboxylate.[11] This NMR analysis secures the structural assignments for the isomers **8** and **9**.

Scheme III



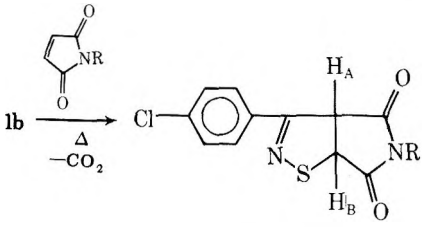
Addition of benzonitrile sulfide to dimethyl 5-norbornene-*cis*,*endo*-2,3-dicarboxylate gave **12** in 28% yield (pure isolated product). The stereochemistry of **12** was determined through analysis of the NMR spectrum of **12** in degassed



12

benzene-d_6 solvent.[12] The aromatic solvent induced shifts, $\delta(CDCl_3) - \delta(C_6D_6)$ (taken as positive when a resonance moves upfield attending the change in solvent from $CDCl_3$ to C_6D_6), were employed to aid assignments of the various protons. Selective benzene solvation of **12** about the carbonyl groups results in greater shielding of protons near the carbonyl groups. Thus, H_8 undergoes a +0.69 ppm solvent shift compared to +0.15 ppm for H_7, and protons H_5 and H_6 exhibit +0.68 and +0.48 ppm solvent shifts, respectively, compared to 0.00 and +0.07 ppm, respectively, for protons H_2 and H_3. The stereochemistry is revealed from the following data: protons H_2 and H_3 are coupled to H_8 ($J = 1.4$ Hz, $J = 1.8$ Hz), are not coupled to H_1 and H_4, and are coupled to each other with $J_{23} = 10.8$ Hz, so protons H_2 and H_3 are cis to each other and are endo; protons H_5 and H_6 are not coupled to H_7, are coupled to each other with $J_{56} = 12.0$ Hz, and H_5 couples with H_4 ($J_{45} = 4.0$ Hz) and H_6 couples with H_1 ($J_{16} = 4.4$ Hz), so H_5 and H_6 are cis,exo.[13]

Thermolysis of **1b** in the presence of 4 equiv of *N*-ethylmaleimide at 180 °C gave **13a** in 82% yield (61% isolated) and *p*-chlorobenzonitrile in 18% yield. Thermolysis of **1b** in the presence of 4 equiv of *N*-phenylmaleimide gave **13b** in 64%

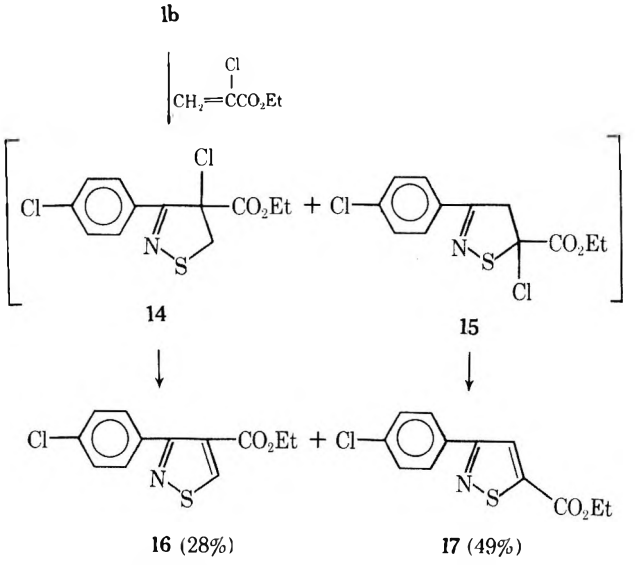


13a, R = Et
b, R = C_6H_5

yield and *p*-chlorobenzonitrile in 21% yield; the other 15% was not accounted for. Both **13a** and **13b** are cis isomers based on the observed $J_{AB} = 11$ Hz coupling in their NMR spectra. The corresponding J_{AB} in the cis anhydride **6** was reported to be 11 Hz.[7]

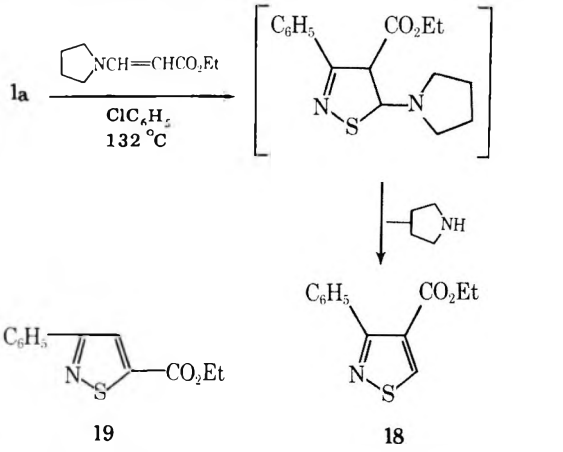
Oxathiazolone **1b** was heated in 30 equiv of ethyl 2-chloroacrylate in dodecane solvent at 165–175 °C for 55 min, resulting in ~70% reaction of **1b** (Scheme IV); **16** and **17** formed in 28 and 49% yields and were isolated in 16 and 17% yields, respectively (based on 70% reaction). No ethyl propiolate was detected in either the starting reaction mixture or in the final reaction mixture. Evidently, the reaction proceeds by cycloaddition of the nitrile sulfide to the chloroacrylate, followed

Scheme IV



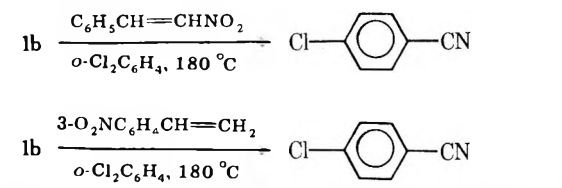
by loss of hydrogen chloride from the intermediate isothiazolines **14** and **15**. The isolated, pure samples of **16** and **17** were identical with authentic materials prepared by addition of *p*-chlorobenzonitrile sulfide to ethyl propiolate.[3]

Thermolysis to completion of **1a** in the presence of 10 equiv of ethyl β-pyrrolidinylacrylate in chlorobenzene solution at 132 °C gave ethyl 3-phenyl-4-isothiazolecarboxylate (**18**) in 8% yield. GC analysis revealed that the amount of ethyl 3-phenyl-5-isothiazolecarboxylate (**19**) present amounted to



≤2% of the amount of **18** present. Nitrile oxides have been reported to add regiospecifically to β-aminoacrylates to give exclusively 3-substituted-4-isoxazolecarboxylates.[14]

A mixture of **1b** and 4 equiv of β-nitrostyrene heated in o-dichlorobenzene at 180 °C gave *p*-chlorobenzonitrile in



98.5% yield from nitrile sulfide decomposition. Similarly, reaction of **1b** in the presence of 4 equiv of 3-nitrostyrene gave no significant amount of cycloadduct.

From the reactions reported here, it appears that nitrile sulfides react best with very electron-deficient olefins. This result is consistent with dipole–HOMO control[15] of these cycloadditions, similar to the cycloadditions of nitrile sulfides with acetylenes[3] and nitriles.[3,4]

Experimental Section

Dimethyl 3-Phenyl-2-isothiazoline-4,5-dicarboxylate (7). Technical grade dimethyl fumarate (Pfizer) was recrystallized twice (with filtration) from methylcyclohexane to give solid, mp 101–103 °C.

To 23.0 g (0.16 mol) of dimethyl fumarate stirred at 190 °C under nitrogen was added 7.16 g (0.040 mol) of 5-phenyl-1,3,4-oxthiazol-2-one. The solution was stirred at 190 °C for 10 min, and then the light amber solution was cooled and dissolved in 60 mL of warm THF. Chlorobenzene, 6.0 g, was added as an internal GC standard. An aliquot of the solution was diluted with more THF and was analyzed by GC; this analysis revealed that 6.17 g (55% yield) of product had formed.

The reaction mixture was concentrated under vacuum to remove the THF, and 60 mL of o-dichlorobenzene was added. The solution was concentrated under vacuum to remove the o-dichlorobenzene and dimethyl fumarate. The addition of o-dichlorobenzene and the concentration was repeated twice. The residue was triturated with 20 mL of methanol, the insoluble sulfur was removed by filtration, and the filtrate was concentrated under vacuum to 6.5 g of oil. The oil was chromatographed on 350 g of silicic acid (Mallinckrodt SilicAR CC-7). After elution with 1 L of 50:50 hexane–benzene, the column was eluted with benzene. The first 1300 mL of benzene eluate gave no material. The next 100 mL of benzene eluate gave 0.33 g of 98% pure product; the next 660 mL of benzene eluate gave 3.1 g (28% yield) of 100% pure (GC assay) product as a viscous oil of mp ~6 °C. The next 1350 mL of benzene eluate gave 1.6 g of 98% pure product. The total amount of product was 5.03 g (45% yield); IR (mineral oil mull) 5.8 μm; NMR ($CDCl_3$) δ 7.96 (m, 2, ArH), 7.61 (m, 3, ArH), 5.22 (d, 1, J = 4 Hz, SCH), 4.81 (d, 1, J = 4 Hz, SCCH), 3.79 (s, 3, OCH_3), 3.69 (s, 3, OCH_3); mass spectrum *m/e* 279, 247, 220, 188, 176, 161, 135, 103; UV (CH_3CN) max (log ε) 222 (4.00), 313 nm (4.05). Anal. Calcd for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69. Found: C, 56.05; H, 4.80.

Dehydrogenation of 7. A mixture of 1.93 g (0.00692 mol) of dimethyl 3-phenyl-2-isothiazoline-4,5-dicarboxylate, 2.36 g (0.014 mol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), and 40 mL of chlorobenzene was held at reflux for 5 h. The mixture was allowed to cool and was filtered. The insoluble gray solid, after washing with chlorobenzene and hexane, weighed 1.5 g and appeared to be 2,3-dichloro-5,6-dicyano-1,4-hydroquinone (IR identification). The filtrate and washings were combined and concentrated under vacuum to 2.65 g of dark oil. This oil was extracted with 150 mL of hexane and then with three 40-mL portions of hot hexane to give 0.6 g of insoluble solid that appeared to be slightly impure DDQ. The hexane extracts were combined, concentrated, and cooled in ice to give 0.95 g of solid, mp 68–70 °C. This solid was dissolved in hexane, the mixture was filtered to remove a few milligrams of insoluble solid, and the filtrate was concentrated and cooled in ice to give 0.77 g (40% yield) of white solid dimethyl 3-phenyl-4,5-isothiazoledicarboxylate, mp 71–72 °C (lit.[1] mp 71–73 °C); the IR spectra of this and of authentic material were identical.

Phenyl 3-(*p*-Chlorophenyl)-2-isothiazoline-4-carboxylate (8) and Phenyl 3-(*p*-Chlorophenyl)-2-isothiazoline-5-carboxylate (9). A solution of 0.20 g of hydroquinone, 35.7 g (0.241 mol) of redistilled phenyl acrylate (Monomer-Polymer Laboratories), 2.0 g (0.00935 mol) of 5-(*p*-chlorophenyl)-1,3,4-oxthiazol-2-one, and 45.0 g of o-dichlorobenzene was heated rapidly to reflux and was held at reflux under N_2 for 20 min. GC analysis of the reaction mixture revealed that the 4-carboxylate and the 5-carboxylate had formed in 15 and 49% yields, respectively. Further GC and GC–MS analyses revealed the presence of a trace (~0.8% yield) of **10** (m/e 315). The reaction mixture was concentrated under vacuum to 5.3 g of grape colored gum. The gum was extracted with two 125-mL portions of hot heptane. Upon cooling, the heptane deposited 1.35 g (45%) of 98% pure 5-carboxylate **9**. Recrystallization of the solid from ethanol gave 0.89 g (30% yield) of white crystals, mp 127.5–129 °C, that was 100% pure 5-carboxylate (GC assay): IR ($CHCl_3$) 5.70 μm; NMR ($CDCl_3$) δ 7.73 (m, 2, one-half of an AA'BB' multiplet, Ar**H**), 7.53–7.07 (m, 7, Ar**H**), 4.82 (dd, 1, J_{AB} = 5.2, J_{AC} = 11.3 Hz, $CH_ACH_BH_C$), 4.10 (m, 1, J_{BC} = −17.7, J_{AB} = 5.2 Hz, $CH_ACH_BH_C$), 3.60 (m, 1, J_{AC} = 11.3, J_{BC} = −17.7 Hz, $CH_ACH_BH_C$). Anal. Calcd for $C_{16}H_{12}ClNO_2S$: C, 60.47; H, 3.81. Found: C, 60.22; H, 3.72.

Fractional crystallization from ethanol of the residue from the combined heptane filtrates gave 100% pure (GC assay) 4-carboxylate **8** in 4% yield as white needles: mp 123.5–125 °C; IR ($CHCl_3$) 5.70 μm; NMR ($CDCl_3$) δ 7.87 (m, 2, one-half of an AA'BB' multiplet, Ar**H**), 7.53–6.87 (m, 7, Ar**H**), 4.88 (dd, 1, J_{AB} = 6.3, J_{AC} = 10.2 Hz, $CH_ACH_BH_C$), 4.01 (m, 1, J_{AB} = 6.3, J_{BC} = −11.5 Hz, $CH_ACH_BH_C$), 3.93 (m, 1, J_{AC} = 10.2, J_{BC} = −11.5 Hz, $CH_ACH_BH_C$). Anal. Calcd for $C_{16}H_{12}ClNO_2S$: C, 60.47; H, 3.81. Found: C, 60.64; H, 3.76.

A dilute solution of **8** in acetone was allowed to stand 5 days at room temperature. After this time GC and GC–MS analysis revealed formation of ~6% of **10** (*m/e* 315). Similarly, after 5 days in acetone, **9**

produced ~13% of **11** (*m/e* 315). Retention times on a 2-ft long GC column packed with 10% SE-30 on Chromosorb W, 60 mL/min He flow, at 240 °C for **8**, **9**, **10**, and **11** were 4.2, 6.2, 3.3, and 4.7 min, respectively.

Dimethyl *exo*-3a,4,5,6,7,7a-Hexahydro-3-phenyl-4,7-methano-1,2-benzisothiazole-*endo,cis*-5,6-dicarboxylate (12). A solution of 6.0 g (0.0335 mol) of 5-phenyl-1,3,4-oxthiazol-2-one and 100.0 g (0.476 mol) of dimethyl 5-norbornene-*endo,cis*-2,3-dicarboxylate[13b] (Frinton Laboratories) was stirred at 190 °C under N_2 for 10 min, allowed to cool, and concentrated under vacuum to 10.0 g of oil that contained ~45% of product. Crystallization of the oil from methanol gave 3.7 g of white solid, mp 149–153 °C. Recrystallization of the solid from methanol gave 3.2 g (28%) of pure product as a white solid: mp 155–156.5 °C; IR ($CHCl_3$) 5.77 μm; NMR (benzene-d_6) δ 8.33 (m, 3, ArH), 7.23 (m, 2, ArH), 4.70 (dd, 1, J = 1.4, 10.8 Hz, H_2), 4.27 (dd, 1, J = 1.8, 10.8 Hz, H_3), 3.47 (s, 3, OCH_3), 3.31 (s, 3, OCH_3), 2.77 (dd, 1, J = 4.4, 12.0 Hz, H_6 or H_5), 2.60 (bm, 1, H_4 or H_1), 2.35 (dd, 1, J = 4.0, 12.0 Hz, H_5 or H_6), 2.33 (bm, 1, H_1 or H_4), 1.77 (dt, 1, $J + J'$ = 3.2 Hz, J = 11.0 Hz, H_7), 0.68 (dp, 1, J_{78} = 11.0 Hz, H_8). Anal. Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; 5.54. Found: C, 62.41; H, 5.72.

3-(*p*-Chlorophenyl)-*N*-ethyl-2-isothiazoline-4,5-dicarboximide (13a). To a solution of 25.0 g (0.20 mol) of *N*-ethylmaleimide in 100 g of *o*-dichlorobenzene stirred at reflux (180 °C) under N_2 was added 10.68 g (0.050 mol) of 5-(*p*-chlorophenyl)-1,3,4-oxathiazol-2-one. The solution was stirred at reflux for 30 min and concentrated under vacuum at 90 °C (0.35 mm) to give 25.8 g of solid residue. Trituration of the solid with 125 mL of ethanol followed by cooling of the mixture gave 11.7 g (79%) of solid, mp 176–179 °C. Crystallization of the solid from ethanol (hot filtration) gave 9.02 g (61%) of white solid: mp 179–181 °C; IR ($CHCl_3$) 5.61 (w), 5.83 μm (s); NMR ($CDCl_3$) δ 7.67 (m, 4, $ClC_6\mathbf{H}_4$), 5.02 (s, 2, **CHCH**), 3.58 (q, 2, J = 7 Hz, $NC\mathbf{H}_2CH_3$), 1.17 (t, 3, J = 7 Hz, $NCH_2C\mathbf{H}_3$); NMR (50:50 $CDCl_3$–benzene-d_6) δ 7.57 (m, 4, $ClC_6\mathbf{H}_4$), 4.40 (d, 1, J = 11 Hz, $C\mathbf{H}_aCH_b$), 4.23 (d, 1, J = 11 Hz, $CH_aC\mathbf{H}_b$), 3.37 (q, 2, J = 7 Hz, $NC\mathbf{H}_2CH_3$), 1.00 (t, 3, J = 7 Hz, $NCH_2C\mathbf{H}_3$).

3-(*p*-Chlorophenyl)-*N*-phenyl-2-isothiazoline-4,5-dicarboximide (13b). A solution of 13.85 g (0.080 mol) of *N*-phenylmaleimide in 80 g of *o*-dichlorobenzene was heated rapidly to reflux (180 °C), and then 4.27 g (0.020 mol) of 5-(*p*-chlorophenyl)-1,3,4-oxthiazol-2-one was added. The solution was held at reflux under N_2 for 20 min. GC analysis indicated that 0.0448 mol of *N*-phenylmaleimide was left, that *p*-chlorobenzonitrile had formed in 21% yield, and that the dicarboximide had formed in 64% yield. The reaction mixture was concentrated under vacuum at 90 °C (0.2 mm). The residue was boiled with 375 mL of ethanol, and the mixture was filtered. The insoluble solid, 0.70 g, appeared from the IR spectrum to be polymeric *N*-phenylmaleimide. The filtrate was cooled to give 2.34 g of crude product, mp ~150–170 °C. Concentration of this filtrate gave a solid residue, which was stirred with 12 g of sodium metabisulfite in 70 mL of water–30 mL of ethanol for 25 min in order to convert the residual *N*-phenylmaleimide to the water-soluble sodium sulfonate derivative. The mixture was diluted with water and extracted three times with ether. The ether extracts were combined, washed with water, filtered, and concentrated under vacuum. The residue was crystallized from ethanol to give 1.0 g of crude product, mp 164–169 °C. Several crystallizations of the combined crude products, 3.34 g, from ethanol gave 2.41 g (35%) of solid, mp 173–175 °C, which gave 1.91 g (28%) of solid, mp 174–175 °C, upon recrystallization: IR (mineral oil mull) 5.61 (w), 5.84 μm (s); NMR ($CDCl_3$) δ 8.00 (m, 2, $ClC_6\mathbf{H}_a\mathbf{H}_a\mathbf{H}_b\mathbf{H}_b$), 7.40 (m, 7, $NC_6\mathbf{H}_5$, $ClC_6H_aH_aH_b\mathbf{H}_b$), 5.20 (s, 2, $C\mathbf{H}_aC\mathbf{H}_b$). Addition of an equal volume of benzene to the $CDCl_3$ solution caused the δ 5.20 singlet to become an AB quartet, δ 4.37 (d, 1, J = 11 Hz, $C\mathbf{H}_aCH_b$), 4.27 (d, 1, J = 11 Hz, $CH_aC\mathbf{H}_b$). Anal. Calcd for $C_{17}H_{11}ClN_2O_2S$: C, 59.56; H, 3.23; S, 9.35. Found: C, 59.43; H, 3.16; S, 9.43.

Reaction of 1b with Ethyl 2-Chloroacrylate. A solution of 40.4 g (0.30 mol) of ethyl 2-chloroacrylate and 2.14 g (0.010 mol) of 5-(*p*-chlorophenyl)-1,3,4-oxathiazol-2-one (**1b**) in 75 g of dodecane was held at reflux (165–175 °C) for 55 min, at which time GC analysis indicated ~70% reaction of **1b**. The reaction mixture was allowed to cool, and the supernatant was decanted from polymeric ester and concentrated under vacuum. The residue was chromatographed on silicic acid (Mallinckrodt SilicAR CC-7). Elution with 25% benzene in hexane gave unreacted **1b**. Elution with 40% benzene in hexane gave the 5-carboxylate **17**. Elution with 75% benzene in hexane gave 0.46 g of the 4-carboxylate **16**. Crystallization of the **16** from aqueous ethanol gave 0.30 g (16%) of solid, mp 55.5–56.5 °C, that changed after several days to mp 69–70 °C (lit.[3] mp 70.5–71.5 °C). Crystallization of the **17** from ethanol gave 0.31 g (17%) of solid, mp 87–89 °C (lit[3] mp 87.5–89 °C). The IR and NMR spectra of these materials were identical with those of authentic materials.

Registry No.—**1a**, 5852-49-3; **1b**, 17452-79-8; **3a**, 27545-53-5; **7**, 67048-45-7; **8**, 67048-44-6; **9**, 67048-43-5; **10**, 67048-41-3; **11**, 67048-42-4; **12**, 67048-40-2; **13a**, 67048-39-9; **13b**, 67048-38-8; **16**, 67048-37-7; **17**, 67048-96-8; dimethyl fumarate, 624-49-7; dimethyl 5-norbornene-*endo,cis*-2,3-dicarboxylate, 39589-98-5; *N*-ethylmaleimide, 128-53-0; *N*-phenylmaleimide, 941-69-5; ethyl 2-chloroacrylate, 687-46-7.

References and Notes

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(12) Degassing removes paramagnetic oxygen which causes peak broadening and loss of resolution of multiplets with J values approximately ≤1 Hz. The spectrum of **12** in $CDCl_3$ was not sufficiently simple to analyze by a first-order treatment.
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Peroxide-Initiated Cyclizations of Olefinic *N*-Chloro Amides. Electronic Configuration of Amido Radicals

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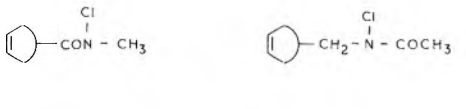
Received December 30, 1977

It is shown that intramolecular additions of *N*-methylcarboxamido radicals are conveniently achieved in high yields by benzoyl peroxide initiation, whereas the analogous acetamido radicals either do not cyclize or cyclize less efficiently under the same conditions. In a few cases, a comparison is made with photochemically initiated cyclizations. Some mechanistic and stereoelectronic aspects are discussed, leading to the conclusion that a Σ_N electronic configuration of the carboxamido radicals could be involved.

Introduction

Extensive experimental studies on amido radicals have shown that these species do react similarly to aminium radicals in nonactivated hydrogen abstraction processes.[2-6] Concerning the reactivity toward double bonds, aminium radicals are known to add efficiently to olefins,[7,8] but the reactivity of amido radicals was shown to depend markedly on the presence or absence of an *N*-alkyl substituent. Thus, the intermolecular radical additions of primary *N*-halo amides (additions of unsubstituted amido radicals) to olefins, either photochemically induced[9] or initiated by chromous chloride,[10] proceed in good to excellent yields, whereas *N*-alkyl-*N*-halo amides (*N*-alkylamido radicals) do not usually add under the same conditions.[6,9-11] However, intramolecular additions of a few *N*-alkylamido radicals have recently been reported; these amido radicals were photochemically generated from olefinic *N*-chloro amides[12,13] or *N*-nitroso amides.[12,14,15]

The purpose of the present work was to make a comparative study of the radical cyclization of olefinic *N*-chloro carboxamides A and of the corresponding *N*-chloro acetamides B



A B

using various methods of initiation. Cyclizations initiated by chromous chloride reduction are described and discussed in the accompanying paper.[16] In this paper, we wish to report that, as in the case of olefinic *N*-chloramines,[17] cyclization of olefinic *N*-chloro carboxamides A can efficiently be achieved by using benzoyl peroxide as initiator. However, cyclization of the corresponding olefinic *N*-chloro acetamides B was far from being as efficient. Our results give interesting information on the electronic structure of *N*-alkylamido radicals and their relative reactivity toward double bonds and/or allylic hydrogens.

Results

We have studied the cyclization of *N*-chloro carboxamides **1b, 4b,** and **7b,** and of the corresponding *N*-chloro acetamides **9b, 11b,** and **12b** (Table I). These *N*-chloro compounds have been easily prepared by treatment of the corresponding amides with commercial bleach and the crude products were used without further purification. Full details about the preparation, yields, and purity of the *N*-chloro derivatives are given in the accompanying paper.[16]

Benzoyl peroxide initiated reactions were performed by heating (80 °C) a dioxane solution of the *N*-chloro amide under a nitrogen atmosphere. Addition of bases (e.g., calcium carbonate) and water in the reaction medium, which was shown to increase markedly the yield of transannular cyclization reactions of *N*-chloro lactams,[18] was unnecessary. In order to allow comparison of the yields and of the structures of the products, we also performed the photolysis of *N*-chloro carboxamides **1b, 4b,** and **7b.** The results are recorded in Table I together with literature data on the photolysis of *N*-chloro amides **1b** and **9b.**

Model compound **1b** was chosen in order to compare our results with those already described in the literature.[12,13] Photolysis of *N*-chloro carboxamide **1b** in methylene chloride solution led to a 97% cyclization yield. An identical yield (95%) was obtained by the dioxane–benzoyl peroxide method. Two isomers, **2** and **3,** were obtained along with traces of parent amide **1a.**

Model compound **4b** was studied because, in this system, intramolecular allylic hydrogen abstraction by the amido radical could "a priori" compete more effectively with the intramolecular addition to the double bond than in the *N*-chloro carboxamide **1b** (see discussion below). Cyclization of this compound by irradiation led to a 55% yield of isomers **5** and **6,** whereas the peroxide initiated reaction afforded 79% of these bicyclic amides. The material balance (cyclization products plus parent amide) was much higher in the peroxide-initiated cyclization. No attempt was made to isolate the other products from the photolysis.

Similarly, cyclization of *N*-chloro carboxamide **7b** led, under photolysis, to a 70% yield of tricyclic chloride **8,** whereas benzoyl peroxide initiated cyclization gave a much higher yield (92%) of the same product[19] and again a much better material balance. The benzoyl peroxide initiated cyclization of the corresponding *N*-chloro acetamide **12b** was much less efficient, however, leading to the formation of only 50% of tricyclic chloride **13.** The exclusive formation of the exo isomers **8** and **13** can be assigned to steric factors[20] as well as to the probable pyramidal structure of the intermediate adduct radical.[21] The same stereoselectivity was observed for the cyclization of the corresponding *N*-chloramine.[17]

Surprisingly, the parent amides **9a** and **11a** were the sole products isolated from the treatment of *N*-chloro acetamides **9b** and **11b** with benzoyl peroxide. Cyclization of **9b** has been achieved by photolysis[13] and more efficiently using chromous chloride.[16]

Discussion

The possible reactions of the olefinic amido radicals are depicted in Scheme I with the amido radical I derived from

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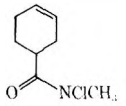
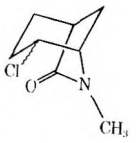
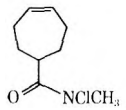
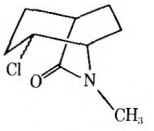
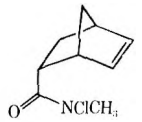
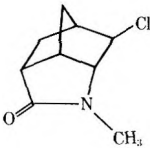
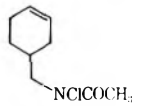
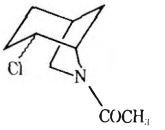
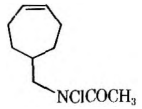
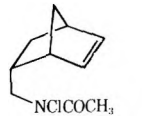
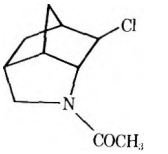
Table I. Radical Cyclization of Olefinic *N*-Chloro Amides

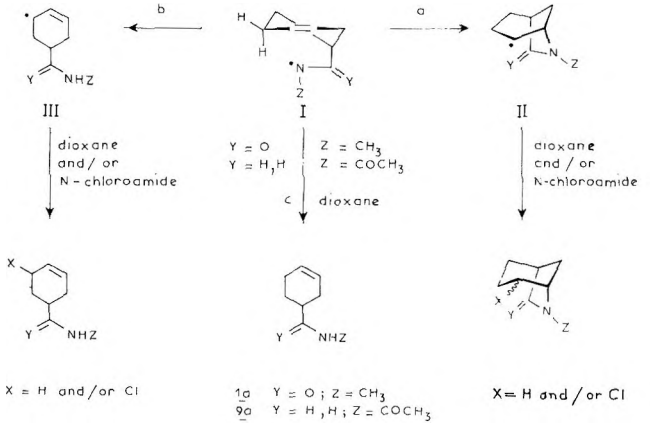
N-chloro amide	no.	cyclization products	no.	% yield[a] of cyclization products Bz_2O_2	$h\nu$	lit. ($h\nu$)[b]	% parent amide no.	Bz_2O_2	$h\nu$
	**1b**		**2** (exo) **3** (endo)	51 44	42 55	47,[c] 39[d] 44,[c] 30[d]	**1a**	3	tr
	**4b**		**5** (exo) **6** (endo)	57 22	35 20		**4a**	18	12
	**7b**		**8**	92	70		**7a**	5	<5
	**9b**		**10**	0		55[d,c]	**9a**	90	
	**11b**			0			**11a**	90	
	**12b**		**13**	50			**12a**	20	

[a] Yields based on the *N*-chloro amide and determined by VPC. [b] Photolyses carried out in benzene. [c] Reference 12. [d] Reference 13; yields of isolated products after distillation. [e] Probably a mixture of endo and exo isomers.

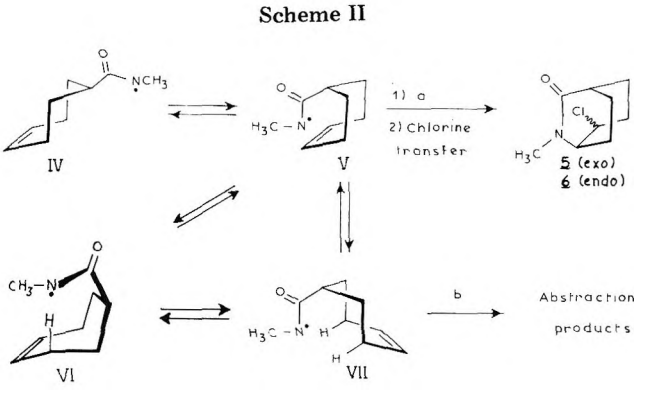
N-chloro carboxamide **1b**: intramolecular addition to the double bond (path a); intramolecular allylic hydrogen abstraction through the normally highly favored six-membered ring transition state[22,24] (path b); and hydrogen abstraction from the solvent to yield the parent amide (path c). The carbon-centered radicals II and III resulting from paths a and b, respectively, could abstract hydrogen from the solvent and/or react with another *N*-chloro amide molecule by chlorine-atom transfer.

Interestingly, the *N*-methylamido radicals I (Y = O, Z = CH_3; Scheme I) and IV (Scheme II) derived from *N*-chloro carboxamides **1b** and **4b**, respectively, follow almost exclusively path a, a result which is in marked contrast with the assumed preference for allylic hydrogen abstraction in intermolecular reactions of *N*-alkylamido radicals with olefins.[6,25] This high preference for path a is particularly noteworthy in the case of **4b**, since this process would be expected to be less favorable than in the case of **1b** and **7b** because of the formation of a six-membered ring (**5** and **6**, Scheme II), usually less favored than the formation of a five-membered ring in intramolecular radical additions to double bonds;[27] furthermore, the cycloheptene ring has to adopt a boat-like conformation[28] (V, Scheme II). On the other hand the intramolecular allylic hydrogen abstraction process involves the normally prefered 1,5-transfer[22,24] with either a twist-boat form (VI) or a chair-like conformation (VII) of the seven-membered ring (Scheme II).

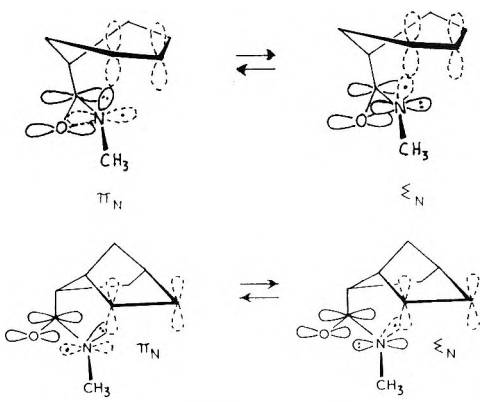
Scheme I



Scheme II



Scheme III



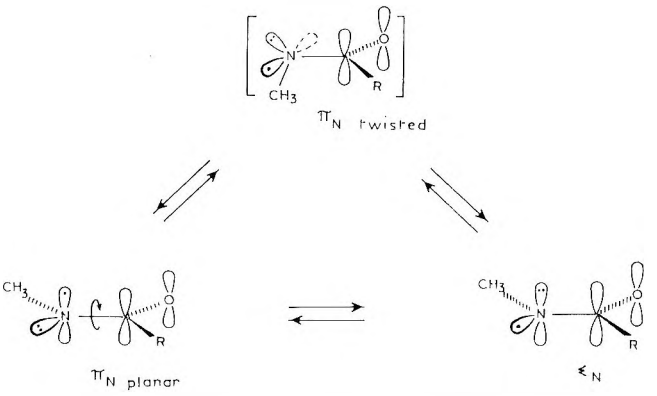
The contrasting behavior of the *N*-alkenylacetamido radicals derived from *N*-chloro acetamides **9b** and **11b** is also very interesting; they do not follow path a. The sole products isolated in high yields were the parent amides **9a** and **11a.** These amides could have arisen directly via path c and/or via path b. Their formation presumably occurs via path c for the following reasons. First of all, since the carbon-centered radicals II (Scheme I) obtained via path a did react exclusively by chlorine-atom transfer, there is no reason to believe that the more stable allylic radicals III formed via path b would prefer to abstract hydrogen from dioxane. Secondly, it will be shown, by chromous chloride reduction of **11b** carried out in a fully deuterated medium, that such an allylic radical is not formed.[16]

The less efficient cyclization of *N*-chloro acetamide **12b,** as compared to *N*-chloro carboxamide **7b,** and the failure to cyclize *N*-chloro acetamides **9b** and **11b,** suggest that an *N*-alkylamido radical would be less reactive toward a double bond on the *N*-alkyl chain than toward a double bond on the acyl chain.[16]

Our results show that benzoyl peroxide cyclization of the olefinic *N*-chloro carboxamides leads to better yields than photochemical cyclization. This can be easily understood as chlorine atoms are formed in the initiation step of the photochemical process. These are known to be quite reactive hydrogen abstractors[29] and may perform competing reactions of the type proposed by Goldfinger et al.[30] They are also known to add efficiently to olefins.[31] On the other hand no such chlorine atoms are formed during the peroxide initiation process.

One of the main points of interest concerns the electronic structure of the amido radical. ESR evidence and calculations suggest that the ground-state electronic configuration of amido radicals is of the Π_N type.[32] This has recently been used by Chow et al.[4] to satisfactorily explain, on the basis of stereoelectronic arguments, the behavior of *N*-halo carboxamides in intramolecular hydrogen abstraction processes. Examination of Dreiding models of the *N*-methylcarboxamido radicals derived from *N*-chloro carboxamides **1b** and **7b** show that, for a Π_N configuration, the Π orbital of the carbon–carbon double bond and the orbital containing the unpaired electron would be about orthogonal (Scheme III); in contrast, for a Σ_N configuration, there is maximum overlap[33,34] (Scheme III). In the case of the *N*-methylcarboxamido radical derived from **4b,** the overlap appears to be better for the Σ_N configuration. As for the acetamido radicals derived from **9b, 11b,** and **12b,** a good overlap is possible with both the Π_N and Σ_N configurations (there seems to be more nonbonded interactions with the Π_N configuration, however). Hence the failure to cyclize **9b** and **11b** and the less efficient cyclization of **12b** (as compared to **7b**) do not seem to be related to the electronic structure of the amido radicals; it is most probably due to steric effects.[16]

Scheme IV



If we assume that, in the cyclization of the amido radicals derived from **1b, 4b,** and **7b,** the Σ_N configuration is the reacting species and the Π_N planar configuration is nevertheless more stable,[4,32] the former could be in equilibrium with the latter through the Π_N twisted configuration[32b] (Scheme IV). The activation energy for the rotation around the C–N bond should be quite low because, according to ESR experiments,[32a] there is no extensive delocalization of the unpaired electron onto the carbonyl group. The Π_N planar and Σ_N configurations could also be directly interconverted by electronic reorganization (Scheme IV) as recently suggested by Goosen et al.[35] to explain their results on the intramolecular reactions of *N*-methylcarboxamido radicals with aromatic rings. Finally, the amido radical could react in a Π_N twisted configuration without rehybridization to a Σ_N configuration.[4] Interestingly, ab initio calculations predict the most stable configuration of the formamido radical as being the 50° Π_N twisted configuration.[32b]

Experimental Section

Infrared spectral data were obtained from a Perkin-Elmer 257 spectrophotometer. Routine ^1H NMR spectra were recorded on a Varian A60 or on a Varian XL100 WG spectrophotometer, and 250 MHz ^1H NMR spectra were obtained from a Cameca spectrophotometer. Mass spectra were taken on a Hitachi RMU-6E or on a AEI-MS9 spectrometer. All melting points and boiling points are uncorrected. VPC analyses and separations were performed on the following columns: OS-138 (15% on AW–DMCS Chromosorb W); OV-17 (3% on AW–DMCS Chromosorb W).

Preparation of Olefinic Amides. *N*-Methyl-3-cyclohexenecarboxamide (1a) and *N*-[(3-Cyclohexen-1-yl)methyl]acetamide (9a). Amide **1a** was prepared from 3-cyclohexenecarboxylic acid: 78% yield; mp 88–89 °C (lit.[13] mp 89–90 °C). Amide **9a** was prepared from 3-cyclohexenecarbonitrile: 63% yield; bp 109–114 °C (0.15 mm) [lit.[13] bp 88–95 °C (0.07 mm)].

***N*-Methyl-4-cycloheptenecarboxamide (4a).** A solution of 1.94 g (0.014 mol) of 4-cycloheptenecarboxylic acid[36] in 10 mL of dry benzene was cooled at 0 °C and 2.3 g (0.018 mol) of freshly distilled oxalyl chloride was added slowly with stirring. The mixture was stirred overnight at room temperature. The benzene and the excess oxalyl chloride were then stripped off. The crude acid chloride was distilled to give 1.87 g (85%) of colorless liquid: bp 80 °C (10 mm). A solution of 1.87 g (0.012 mol) of distilled acid chloride in 5 mL of dry benzene was added dropwise to 10 mL of dry benzene saturated at 0 °C with methylamine. The solution was stirred for 1 h, water was added, and the organic layer was dried over magnesium sulfate. The solvent was evaporated and the crude residue was crystallized from hexane to give 1.65 g (92%) of *N*-methyl-4-cycloheptenecarboxamide (**4a**): mp 125–127 °C; IR ($CHCl_3$) 3460, 3300, 1660 and 1520 cm^{-1}; NMR ($CDCl_3$) δ 1.4–2.5 (m, 9 H), 2.8 (d, 3 H), 5.8 (m, 2 H), and 6.5 (br, 1 H).

***N*-Methyl-5-bicyclo[2.2.1]hept-2-eneearboxamide (7a).** This amide has been prepared following standard procedures: 57 g (0.4 mol) of *endo*-5-carbomethoxybicyclo[2.2.1]hept-2-ene[37] was treated with an excess of saturated solution of methylamine in methanol at room temperature during 5 days. The solvent was stripped off to leave 44 g (78%) of a white solid which was recrystallized from a methylene chloride–pentane mixture: mp 104 °C; IR (CCl_4) 3450, 3300, 1645, and 1530 cm^{-1}; NMR δ 1.2–2.2 (m, 5 H), 2.75 (d, 3 H), 3.0 (m, 2 H), 6.1 (ddd, 2 H), and 6.5 (br, 1 H).

***N*-[(4-Cyclohepten-1-yl)methyl]acetamide (11a).** 4-Cycloheptenecarboxamide was prepared by bubbling ammonia into a solution of 5 g (0.031 mol) of the acid chloride in dry tetrahydrofuran. The solvent was stripped off and the residue was recrystallized in hexane to give 3.77 g (86%) of the amide: mp 176 °C; IR ($CHCl_3$) 3560, 3440, and 1690 cm^{-1}; NMR (Me_2SO-d_6) δ 1.2–2.55 (m, 9 H), 5.75 (m, 2 H), 6.6 (br, 1 H), and 7.15 (br, 1 H). This amide (7.36 g, 0.053 mol) was placed in a Soxhlet apparatus and reduced by means of lithium aluminium hydride in boiling tetrahydrofuran during 50 h. After normal workup and distillation under vacuum [bp 37 °C (4 mm)] one gets 5.13 g (78%) of (4-cyclohepten-1-yl)methylamine: IR (CCl_4) 3420, 3050, and 710 cm^{-1}; NMR ($CDCl_3$) δ 0.9–2.3 (m, 7 H), 1.22 (s, 2 H), 2.57 (d, 2 H), and 5.5 (m, 2 H). Treatment of 4.9 g (0.039 mol) of the primary amide by 4 g of acetic anhydride dissolved in dry benzene afforded, after workup and recrystallization from cyclohexane, 6.3 g (96%) of the pure acetamide **11a**: mp 52 °C; IR ($CHCl_3$) 3460, 1670, and 1520 cm^{-1}; NMR ($CDCl_3$) δ 1.0–2.2 (m, 9 H), 2.0 (s, 3 H), 3.12 (t, 2 H), and 5.8 (m, 3 H).

***N*-[(2-Bicyclo[2.2.1]hepten-5-yl)methyl]acetamide (12a).** 5-Bicyclo[2.2.1]hept-2-enecarboxamide was obtained by a Diels–Alder reaction between cyclopentadiene and acrylamide.[38] Reduction of this primary amide following the above described procedure (using a Soxhlet apparatus) gave the primary amine in 40% yield. Acetylation by means of acetic anhydride afforded the acetamide **12a**, which was distilled under vacuum: bp 125–126 °C (0.3 mm); IR ($CHCl_3$) 3450, 3330, 1660, and 1520 cm^{-1}; NMR ($CDCl_3$) δ 0.55 (ddd, 1H), 1.15–3.1 (m, 8 H), 1.98 (s, 3 H), and 6.05 (ddd + br, 3 H).

Preparation of Olefinic *N*-Chloro Amides. The various *N*-chloro amides have been obtained by treating the olefinic amides, dissolved in methylene chloride, with an excess of commercial bleach. Full details about the preparation, the yields, and the purity of the *N*-chloro compounds are given in the accompanying paper.[16]

Typical Procedure for the Photolysis of Olefinic *N*-Chloro Amides. Cyclization of *N*-Chloro-*N*-methyl-4-cycloheptenecarboxamide (4b). In a 50-mL Vycor irradiation cell, 1 g (0.0053 mol) of **4b** was dissolved in 20 mL of methylene chloride (freshly distilled over phosphorus pentoxide). Oxygen-free dry nitrogen was bubbled through the solution for 10 min and the solution was then irradiated in a Rayonet reactor (2500-Å lamps). Irradiation was carried out at room temperature during 1 h (until a negative starch–iodide paper test). The solution was concentrated and transfered in a 10-mL volumetric flask. The yields were determined by VPC (OS-138) using authentic samples as standards: 35% of exo isomer **5**, 20% of endo isomer **6**, and 12% of parent amide **1a**. Minor products have not been identified. The authentic samples were obtained by preparative VPC on a 5-mL aliquot.

The less polar isomer was identified as *exo*-4-chloro-6-methyl-6-azabicyclo[3.2.2]nonan-7-one (**5**). It was recrystallized from hexane: mp 67–68 °C; IR (CCl_4) 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.7–2.9 (m, 9 H), 3.05 (s, 3 H), 3.65 (m, 1 H), and 4.0 (m, 1 H).

Anal. Calcd for $C_9H_{14}ClNO$: C, 57.60; H, 7.52; N, 7.46. Found: C, 57.53; H, 7.33; N, 7.46.

The more polar isomer was *endo*-4-chloro-6-methyl-6-azabicyclo[3.2.2]nonan-7-one (**6**): IR (CCl_4) 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.6 (m, 8 H), 2.8 (m, 1 H), 3.18 (s, 3 H), 3.85 (m, 1 H), and 4.25 (m, 1 H).

Anal. Calcd for $C_9H_{14}ClNO$: C, 57.60; H, 7.52; N, 7.46. Found: C, 56.74; H, 7.40; N, 7.04.

The mass spectra of the two isomers were identical: *m/e* (rel intensity) 187 (M^+, 27), 151 (100), 109 (40), 95 (37), 57 (41); for these and all the other cyclization products, P/(P + 1) = 2.8–3.

The olefinic *N*-chloro amides **1b** and **7b** were irradiated respectively for 1.5 and 2 h under the same conditions. Yields were determined by VPC analyses (see Table I) and authentic samples were obtained either by preparative VPC or by preparative TLC.

Cyclization of *N*-Chloro-*N*-methyl-3-cyclohexenecarboxamide (1b). The bicyclic exo isomer **2** was recrystallized from hexane, mp 37–40 °C. The endo isomer **3** was obtained as an oil. IR and ^1H NMR spectra were consistent with those reported.[12,13]

Cyclization of *N*-Chloro-*N*-methyl-5-bicyclo[2.2.1]hept-2-enecarboxamide (7b). The tricyclic exo isomer **8** has been recrystallized from hexane to give pure *exo*-9-chloro-3-methyl-3-azatricyclo[4.2.1.$0^{1,5}$]nonan-2-one (**8**): mp 57–59 °C; IR (CCl_4) 1710 and 1400 cm^{-1}; NMR ($CDCl_3$) δ 1.5–1.63 (2 m, 2 H), 1.84–2.65 (m, 5 H), 2.85 (s, 3 H), 3.04 (m, 1 H), 3.58 (m, 1 H), and 3.64 (m, 1 H); mass spectrum *m/e* (rel intensity) 185 (M^+, 36), 150 (17), 122 (31), 110 (100), 43 (31).

Anal. Calcd for $C_9H_{12}ClNO$: C, 58.23; H, 6.52; Cl, 19.1. Found: C, 58.27; H, 6.36; Cl, 18.97.

Typical Procedure for Benzoyl Peroxide Initiated Reactions of Olefinic *N*-Chloro Amides. Cyclization of *N*-Chloro-*N*-methyl-5-bicyclo[2.2.1]hept-2-enecarboxamide (7b). In 10 mL of peroxide-free dioxane (distilled over sodium and passed through alumina) containing a catalytic amount (10 mg) of benzoyl peroxide was dissolved 927 mg (0.004 mol) of **7b**. Dry nitrogen was bubbled through the solution for 5 min. The solution was then stirred at 80 °C under nitrogen. The reaction took 29 h as checked by an iodometric test. The solvent was stripped off and the crude product dissolved in a 10-mL volumetric flask. VPC analyses were carried out as in the photochemical reaction and gave 92% of the tricyclic exo isomer 8 and <5% of the starting amide. The same procedure was used with the olefinic *N*-chloro amides **1b**, **4b**, **9b**, **11b**, and **12b**; the reactions took respectively 4.5, 21, 22, 48, and 48 h. No cyclizations have occurred for the *N*-chloro compounds **9b** and **11b** and the parent amides were recovered in a 90% yield.

Cyclization of *N*-Chloro-*N*-[(2-bicyclo[2.2.1]hepten-5-yl)-methyl]acetamide (12b). Cyclization of the olefinic *N*-chloro amide **12b** afforded only the tricyclic exo isomer **13** in a 50% yield plus 20% of the starting amide **12a**. Recrystallization from cyclohexane gave the pure *exo*-9-chloro-3-acetyl-3-azatricyclo[4.2.1.$0^{1,5}$]nonane (**13**): mp 87–88 °C; IR ($CHCl_3$) 1630 cm^{-1}; NMR ($CDCl_3$, 250 MHz) δ 1.0 (d, 1 H), 1.6 (d, 1 H), 1.9–2.9 (m, 5 H), 2.05 and 2.2 (2 s, 3 H). 3.35 (q, 1 H), 3.4 (s, 1 H), 3.6 (s, 1 H), 4.2 (d, 1 H); mass spectrum *m/e* (rel intensity) 201 (43), 199 (M^+, 93), 159 (45), 157 (100), 110 (47), 80 (98), 43 (53).

Anal. Calcd for $C_{10}H_{14}ClNO$: C, 60.15; H, 7.07; Cl, 17.75. Found: C, 60.22; H, 6.93; Cl, 17.78.

Registry No.—**1a**, 54385-24-9; **1b**, 36393-98-3; **2**, 36294-04-4; **3**, 36394-03-3; **4a**, 53102-89-9; **4b**, 66769-77-5; **5**, 66769-88-8; **6**, 66791-98-8; **7a**, 13295-40-4; **7b**, 66769-79-5; **8**, 66769-89-9; **9a**, 54385-23-8; **9b**, 54385-09-0; *endo*-**10**, 66769-87-7; *exo*-**10**, 66769-86-6; **11a**, 66769-67-3; **11b**, 66769-78-6; **12a**, 66769-68-4; **12b**, 66769-80-0; **13**, 66769-90-2; 3-cyclohexenecarboxylic acid, 4771-80-6; 3-cyclohexenecarbonitrile, 100-45-8; 4-cycloheptenecarboxylic acid 1614-73-9; oxalyl chloride, 79-37-8; 4-cycloheptenecarbonyl chloride 3454-74-8; *endo*-5-carbomethoxybicyclo[2.2.1]hept-2-ene, 2903-75-5; 4-cycloheptenecarboxamide, 1626-63-7; (4-cyclohepten-1-yl)methylamine, 38288-79-8; 5-bicyclo[2.2.1]hept-2-enecarboxamide, 51757-85-8.

References and Notes

(1) (a) This work was carried cut within the framework of the "Coopération franco-québécoise" ("projet intégré" No. 01 05 **15** between the University of Sherbrooke (Professor J. Lessard) and the University of Aix-Marseille III (Professor B. Waegell)); a "stage de recherche" was granted to Ph. Mackiewicz (Marseille) at the Chemistry Department, University of Sherbrooke, in 1974–1975. (b) Supported in part (in Quebec) by grants from the "Ministère de l'Education du Québec" and the National Research Council of Canada, and in part (in France) by grants from the CNRS and the DGRST (Scholarship to Ph. Mackiewicz). (c) The use of the French German sattelite Symphony for discussions is gratefully acknowledged. (d) Abbreviated from Ph. Mackiewicz, Thèse d'Ingénieur-Docteur, Université d'Aix-Marseille III, 1977. (e) We thank Dr. Tordo and Professor Pujol of Université d'Aix-Marseille I for fruitful discussions.

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Chromous Chloride Promoted Cyclization of Olefinic *N*-Chloro Amides. Synthesis of Nitrogen Heterocycles[1]

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Received December 30, 1977

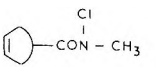
The chromous chloride promoted cyclization of a variety of olefinic *N*-chloro-*N*-methyl carboxamides was compared to the cyclization of the analogous *N*-chloro-*N*-alkenylacetamides. In all cases but one, the yields were higher with the former than with the latter. The high yield of cyclization (95%) of *N*-chloro-*N*-methylcycloheptenecarboxamide (**13b**) is noteworthy since a six-membered ring is formed and contrasts with the failure of the analogous *N*-chloro-*N*-cycloheptenylacetamide (**16b**) to cyclize. A number of nitrogen heterocycles were synthesized in good to excellent yields, including the azahomoadamantanone derivative **28** and the azaadamantane derivatives **30** and **31**. An attempt to prepare an azatwistanone derivative from *N*-chloro carboxamide **26b** failed. Comparison with photochemical and peroxide cyclizations of a few *N*-chloro amides showed that better yields were usually obtained with the chromous chloride method. The reaction mechanism is discussed from the following points of view: comparison of reactivity of the *N*-chloro carboxamides and *N*-chloro acetamides; comparison of the relative reactivity of amido radicals (complexed or not) in intramolecular addition to double bonds and intramolecular allylic hydrogen abstraction; stereochemistry; nature of the transfer step of the radical chain reaction.

Introduction

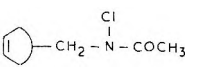
The chromous chloride promoted intermolecular addition of *N*-halo amides (ZCONHX) to a variety of olefins has been shown to proceed in good to excellent yields,[2] whereas *N*-alkyl-*N*-halo amides (ZCONRX) failed to add under the same conditions.[2a] This failure could be due to the fact that chromium(II) reduction of an *N*-alkylamido radical would be faster than its addition to the olefin as already suggested.[2b] However, intramolecular addition of *N*-alkylamido radicals would be expected to compete favorably with their chromium(II) reduction (an intermolecular process). Indeed, as we will see, the chromous chloride promoted cyclization of olefinic *N*-chloro amides does occur in good to excellent yields.

In the preceding paper,[3] we have compared the intramolecular behavior of *N*-chloro amides toward double bonds under photochemically and peroxide-initiated decomposition. Due to the special design of the models used, it was possible to gain information on the electronic structure of *N*-alkylamido radicals. Because of the possible complexation of these radicals with chromium ions,[2b] their electronic structure will not be considered in this paper.

In the present paper, we are going to (i) evaluate the scope and limitations of the chromous chloride method for the synthesis of nitrogen heterocycles, comparing the cyclization of olefinic *N*-chloro carboxamides A and *N*-chloro acetamides B; (ii) see whether the cyclization would occur when a six-membered transition state is involved; (iii) examine the competition between intramolecular abstraction of allylic hydrogens by the amido radical, and its intramolecular addition to double bonds; and (iv) study the stereochemistry of the cyclization reaction.



A



B

As will be seen, most of the questions raised could be answered in a satisfactory manner and an efficient process for the synthesis of functionalized nitrogen heterocycles was devised. This method constitutes a useful complement to the synthesis of azabicyclic and polycyclic molecules efficiently

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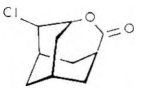
achieved by intramolecular reactions of olefinic *N*-chloramines.[4,5]

Results

Preparation of *N*-Chloro Amides. The N-chlorination of olefinic amides is more difficult than that of the corresponding amines because amides are less reactive than amines toward the various chlorinating agents generally used. Two methods gave satisfactory results: room temperature treatment of the amide by sodium hypochlorite, and treatment of the lithium amide salt by *N*-chlorosuccinimide in ether, a method developed by Kuehne and Horne.[6] The yields as well as the purity of the *N*-chloro amides are recorded in Table I. The N-chlorination of the olefinic *N*-methyl carboxamides by the first method was usually faster than that of the corresponding *N*-alkenyl acetamides. It was necessary to follow the reaction by ^{1}H NMR spectroscopy or by TLC, since partial hydrolysis of the amide to the carboxylic acid occurred, particularly in the case of the *N*-methyl carboxamides.[7] Buffering the chlorinating solution at pH 12.5 was expected to reduce the amide hydrolysis. This occurred efficiently in the case of the preparation of **1b**, but presented no real advantage over the standard method for the preparation of *N*-chloro carboxamides **7b** and **17b**. The crude *N*-chloro amides prepared by the sodium hypochlorite method were used without further purification, the unreacted amide being essentially the sole other product present according to the ^{1}H NMR spectra. The second method proved to be efficient to prepare **26b**, **27b**, and **29b** where the sodium hypochlorite method, with or without buffer, and other methods[8] have failed. In the case of **27b**, these methods gave the chloro lactone **32** (54% yield with sodium hypochlorite). This product is most likely to be formed by the hydrolysis of the *N*-chloro amide and electrophilic chlorination of the double bond, followed by trapping of the intermediate cation by the carboxylate anion. The source of positive halogen is not clear, but it might be the *N,N*-dichloromethylamine formed by hydrolysis of the amide[7] or eventually the acylhypochlorite.



32

Cyclization of Olefinic *N*-Chloro Amides. The results of the chromous chloride promoted cyclization of various olefinic *N*-chloro amides are summarized in Table I.[10] The reactions were carried out as described for the intermolecular additions[2a] at −78 °C (cooling bath temperature) in a chloroform/methanol mixture, adding the chromous chloride slowly and monitoring the reaction by an iodometric test. The various examples studied illustrate the synthetic potential of the method, as the yields of cyclization vary from good to excellent (except for the *N*-chloro amides **16b** and **26b**, which did not cyclize).

Inspection of Table I leads to the following general comments. It is noteworthy that the cyclization of the olefinic *N*-chloro-*N*-methyl carboxamides is generally more efficient than the cyclization of the analogous *N*-chloro-*N*-alkenyl acetamides. The material balance (cyclized products plus recovered parent amide) is very good (>90% in most cases) as in the peroxide-initiated cyclizations[3] and thus generally much better than in the photochemical cyclizations.[3,12] The chromous chloride method appears to be the most efficient except in the case of *N*-chloro carboxamide **7b**, where the three methods gave similar yields, and of *N*-chloro acetamide **16b** where the chromous chloride and benzoyl peroxide methods failed (the photochemical cyclization of **16b** was not studied).

The cyclization of *N*-chloro amides **1b** and **4b** led to a relatively large proportion of the nonchlorinated products **3** and **6** (1,H cyclic adducts), respectively, whereas no such product was isolated in the case of the other *N*-chloro amides.

The *N*-chloro amides **13b** and **16b** were chosen to test the hydrogen abstraction ability of the amido radical vs. its addition to double bonds in intramolecular reactions. As already pointed out in the preceding paper,[3] the cyclization was expected to be more difficult than that of *N*-chloro amides **7b** and **10b** (formation of a six-membered ring, boat-like conformation of the cycloheptene ring in the transition state), whereas the intramolecular allylic hydrogen abstraction process should involve the normally preferred 1,5 transfer.[13] Surprisingly, cyclization of **13b** was very efficient (95%). In contrast, **16b** gave only the parent amide **16a** as in the case of the peroxide-initiated reaction.[3]

The *N*-chloro amides **17b**, **19b**, **21b**, and **24b** were studied to see if their behavior would parallel that of the corresponding *N*-chloramines.[4d,e] As in the case of *N*-chloramines, the cyclization was almost quantitative and the chlorine-atom transfer onto the intermediate adduct radical occured almost exclusively from the less-hindered exo face, leading to the tricyclic products **18**, **20**, **22**, and **25**, respectively. Interestingly, *N*-chloro amides **7b** and **10b** yielded a mixture of endo and exo epimers in contrast to the corresponding *N*-chloramine, which has been reported to give exclusively the exo derivative.[5a]

We had hoped to obtain an azatwistanone derivative from *N*-chloro amide **26b**, but its cyclization failed. The *N*-chloro amides **27b** and **29b** led, in good yields, respectively, to the azahomoadamantanone derivative **28** and to the azaadamantanes **30** and **31**.

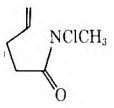
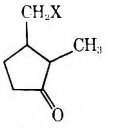
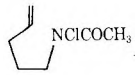
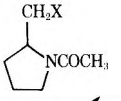
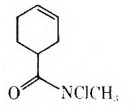
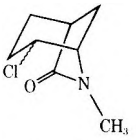
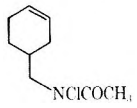
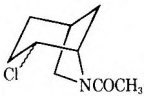
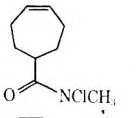
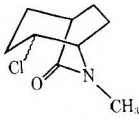
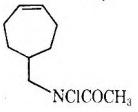
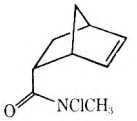
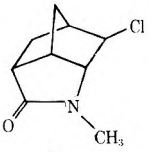
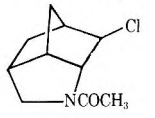
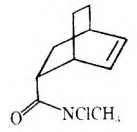
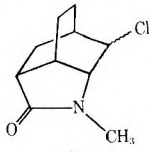
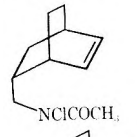
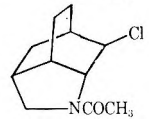
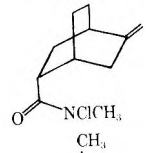
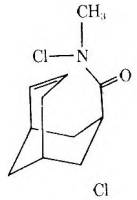
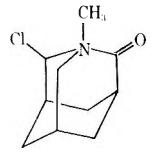
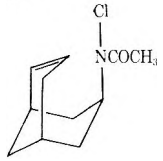
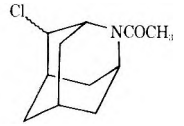
Discussion

The emphasis of this work had initially been placed on the synthetic aspects and the results clearly show the synthetic potential of the chromous chloride promoted cyclization of olefinic *N*-chloro amides for the synthesis of nitrogen heterocycles. This method turns out to be generally more efficient than the corresponding photocyclization[3,6] or benzoyl peroxide initiated cyclization.[3] It compares well with the cyclization of olefinic and enol ether *N*-chloramines,[4] although it was not possible to use an enol ether *N*-chloro amide because of the difficulty in chlorinating the corresponding amides [e.g., *N*-methyl(4-methoxy-3-cyclohexenyl)carboxamide].

The reactivity of amido radicals and the reaction mechanism of the chromous chloride promoted additions of *N*-halo amides to olefins have been already discussed.[2] However, the results obtained during the present work allow some further comments.

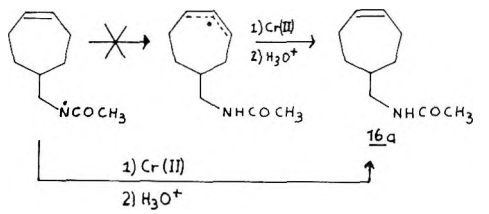
Comparative Reactivity of *N*-Chloro Acetamides and *N*-Chloro Carboxamides. The difference in favor of a greater reactivity of *N*-chloro carboxamides is particularly clear if the behavior of **13b** and **16b** is compared (Table I). This difference cannot be attributed to the greater reactivity of an amido radical toward an allylic hydrogen on the alkyl moiety than toward an allylic hydrogen on the acyl moiety (compare also the cyclization of **7b** and **10b**) as has been shown to be the case for intramolecular abstraction of nonactivated hydrogens by *N*-alkylamido radicals,[15] since a 1,5-hydrogen transfer is not operating in the case of **16b** (see below). Furthermore, the amido radicals derived from **17b** and **19b** (or **21b** and **24b**) have no hydrogen suitably oriented for the usual 1,5-transfer into the nitrogen,[13] and those derived from **1b** and **4b** have only an unreactive vinylic hydrogen in a 1,5 relationship with respect to the nitrogen, but the same difference in reactivity is still observed. Although electronic factors could be involved, this difference can be explained in terms of steric (torsional and nonbonded) interactions which would be expected to be larger for the cyclization of an *N*-alkenylace-

Table I. Preparation and Chromous Chloride Promoted Cyclization of Olefinic *N*-Chloro Amides

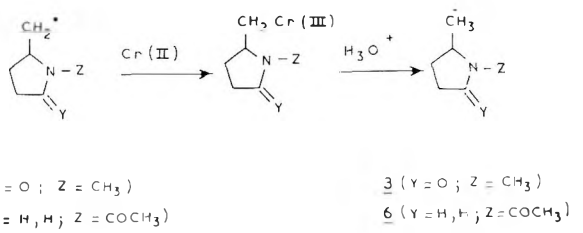
N-chloro amide	*N*-chloro amide no.	*N*-chloro amide preparation method[a]	*N*-chloro amide reaction time, h	*N*-chloro amide yield, %	*N*-chloro amide iodometric purity, %	cyclization products: product	cyclization products: no.	cyclization products: yield,[b] %	parent amide: no.	parent amide: yield,[b] %
	**1b**	NaOCl	8	23	70		**2** (X = Cl)	44	**1a**	0
		buff. NaOCl	3	74	84		**3** (X = H)	61		
	**4b**	NaOCl	9.5	90	100		**5** (X = Cl)	0	**4a**	90
							6 (X = H)	6		
	**7b**	NaOCl	18	71	92		**8** (exo)	28	**7a**	0
		buff. NaOCl	11	76	79		**9** (endo)	70		
	**10b**	NaOCl	100	83	96		**11** (exo)	44	**10a**	20
							12 (endo)	36		
	**13b**	NaOCl	40	82	91		**14** (exo)	70	**13a**	tr
							15 (endo)	25		
	**16b**	NaOCl	100	90	92			0	**16a**	95
	**17b**	NaOCl	34	70	80		**18**	92[c]	**17a**	7
		buff. NaOCl	78	64	100					
	**19b**	NaOCl	100	85	91		**20**	85[d]	**19a**	20
	**21b**	NaOCl	48	76	89		**22** (exo)	80	**21a**	<2
							23 (endo)	5		
	**24b**	NaOCl	100	81	91		**25**	80	**24a**	10
	**26b**	*n*-BuLi/NCS		73	100			0	**26a**	70[e]
	**27b**	*n*-BuLi/NCS		54	100		**28** (exo)	74	**27a**	15
	**29b**	*n*-BuLi/NCS		52	100		**30** (exo)	19	**29a**	21
							31 (endo)	43		

[a] See text. [b] Yields based on the *N*-chloro amide present in the starting product and determined by VPC. [c] This corresponds to a quantitative yield of cyclization considering that the parent amide contained 8–10% of unseparable exo isomer. [d] Another unidentified product containing chlorine (*m/e* 185, 187) was isolated in about 12% yield. [e] The sample of amide **26a** used to prepare **26b** contained about 10% of the isomer with the amido group exo and this 10% was still present in the recovered parent amide (^{1}H NMR spectra); in addition to **26a**, we isolated (preparative VPC and TLC) 32% of the isomer with the double bond endo.

Scheme I



Scheme II



33 (Y = O; Z = CH_3) 3 (Y = O; Z = CH_3)
34 (Y = H, H; Z = $COCH_3$) 6 (Y = H, H; Z = $COCH_3$)

tamido radical than for the cyclization of the analogous olefinic *N*-methylcarboxamido radical according to the inspection of models. This led us to hypothesize that *N*-alkylamido radicals would be less reactive toward a double bond on the alkyl moiety than toward a double bond on the acyl moiety. Work is in progress to verify this hypothesis on substrates where an amido radical will have the choice between the two possibilities in an intramolecular process.

Five- or Six-Membered Transition State Leading to Cyclization. It is well known that radical cyclizations usually lead to five-membered rings.[17] Our results essentially confirm this trend. However, we noticed three exceptions with the cyclization of **13b**, **27b**, and **29b**. Cyclization of **29b** through a five-membered transition state would have led to a protoadamantane skeleton known to be more strained than the adamantane skeleton.[18] Cyclization of **27b** could have led either to a six-membered ring or to a seven-membered ring. The seven-membered ring was preferred (e.g., **28**) probably as a result of the greater stability of an homoadamantane derivative relative to a homoprotoadamantane derivative. *N*-Chloro amide **13b** can only give a six-membered ring. The entropy factor and the absence of strain in the transition state seem in fact to be the most important factors allowing or forbidding the cyclization.

Addition to Double Bond vs. Allylic Hydrogen Abstraction. The efficient cyclization of *N*-chloro amides **7b**, **10b**, and **13b** shows that the amido radical prefers to add to a double bond rather than to abstract an allylic hydrogen in intramolecular processes, even if the abstraction would involve the prefered 1,5 transfer to the nitrogen,[13] and even when the cyclization occurs through a six-membered transition state and a less favorable conformation of the ring as in the case of **13b**. This behavior cannot be attributed to the complexation of the amido radicals by chromium ions, since it has been observed in the peroxide-induced cyclization of **7b** and **13b**,[3] and in the photochemical cyclization of **7b**;[3,11] it is marked contrast with the assumed preference of *N*-alkylamido radicals for allylic hydrogen abstraction in intermolecular reactions with olefins.[14c] In the case of *N*-chloro amide **16b**, the parent amide **16a**, the sole product isolated, could have been formed by allylic hydrogen abstraction followed by chromium(II) reduction of the resulting allylic radical then protonolysis[19] (Scheme I). However, when compound **16b** was submitted to chromous chloride cyclization conditions in totally deuterated medium,[2b] then the workup carried out with D_2O, and the crude product passed over a silica gel column (in order to exchange the amide deuterium and also for purification purposes), the resulting product did not contain any deuterium as shown by mass spectroscopy. Consequently, the parent amide **16a** is most likely to be formed by chromium(II) reduction of the amido radical followed by protonolysis[2b] (Scheme I).

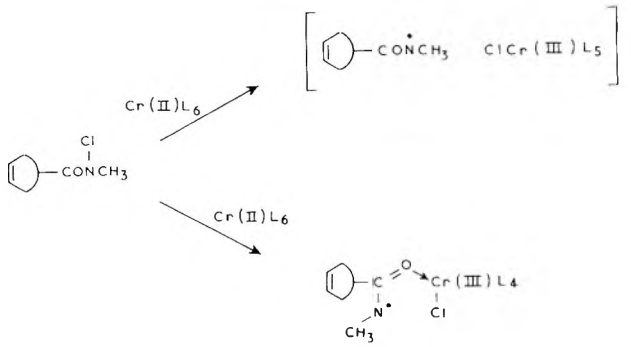
It therefore appears that, in the radical decomposition of olefinic *N*-chloro amides, the amido radical shows little reactivity in intramolecular abstraction of allylic hydrogens so that its intramolecular addition to the double bond competes mainly with intermolecular processes. In the chromous chloride promoted reactions, the main intermolecular competing process is most probably chromium(II) reduction of the amido radical leading to the formation of the parent amide. In the peroxide-initiated reactions,[3] it is most likely the abstraction of hydrogen from dioxane by the amido radical, which leads also to the parent amide. In the photochemical cyclizations,[3,12] the most probable intermolecular process is the abstraction of allylic hydrogen by chlorine atoms formed in the initiation step, which leads to chlorinated derivatives and the parent amide according to the Goldfinger mechanism.[20] This then would explain the poorer material balance, cyclized products plus parent amide, obtained with the photochemical method as compared to the other two methods.

1,H-Cyclic Adducts. In intermolecular additions initiated by chromous chloride, nonhalogenated adducts, termed 1,H-adducts, were currently observed.[2a] Deuterium incorporation experiments have shown that their formation results mainly from chromium(II) reduction of an intermediate adduct–radical followed by protonolysis.[2b] By analogy, we propose a similar mechanism (Scheme II) for the formation of the 1,H-cyclic adducts **3** and **6** in the cyclization of **1b** and **4b**, respectively. A primary carbon radical should be reduced more readily than a secondary one. Indeed, no 1,H-cyclic adducts were isolated in the cyclization of the other olefinic *N*-chloro amides where the intermediate adduct–radical is secondary. A primary carbon radical should also be a more efficient hydrogen abstractor than a secondary one. This accounts for the fact that, whereas no 1,H-cyclic adduct was isolated from the photochemical cyclization of **7b**, **13b**, and **17b**,[3] some 15% of **3** and 9% of **6** was obtained from **1b** and **4b**, respectively.[12]

Stereochemistry. The stereochemistry is strongly dependent on the substrate (Table I). Interestingly, only two *N*-chloro amides gave predominantly the endo isomer, *N*-chloro carboxamide **7b** (endo/exo = 2.5) and *N*-chloro carboxamide **29b** (endo/exo = 2.3). The stereochemistry was found to be also dependent on the method of initiation in the case of *N*-chloro amides **7b** and **13b**. For **7b**, the endo/exo ratio varies from 2.5 with chromous chloride to 1.3 by irradiation in methylene chloride[3] (0.94 in benzene[11]), and 0.86 with benzoyl peroxide.[3] For **13b**, the following endo/exo ratios were observed: 0.35 with chromous chloride, 0.57 by irradiation in methylene chloride,[3] and 0.39 with benzoyl peroxide.[3] In order to see whether these differences in stereoselectivity could be due, at least in part, to variations of solvent and temperature, we carried out the photochemical cyclization of **7b** under conditions similar to those used for chromous chloride cyclization, and obtained an endo/exo ratio (2.0) close to that observed with chromous chloride (2.5).[21]

Reaction Mechanism. The fact that the chromous chloride method generally gives better yields of cyclization than the benzoyl peroxide method[3] and the photochemical method[3,12] could be due, to some extent, to an association complex between the metal ion and the amido radical. The "complexed radical" could then be more reactive toward a double bond than a "noncomplexed radical". The generation of an amido radical in the presence of chromous chloride is in itself quite different from the same generation in the presence of peroxides or under photochemical conditions. As already suggested for intermolecular additions,[2b] the formation of a monodentate complex, in the initiation step, will liberate an amido radical which could remain associated with the metal ion[23]

Scheme III



(Scheme III); and/or the *N*-chloro amide could also act as a bidentate ligand leading to an amido radical bonded to the chromium ion (Scheme III), a process which would be more favorable than the former because of the entropy factor. Whether or not the geometry of the substrate can accommodate the octahedral structure of chromium(II), a tridentate complex could also be involved as depicted in Scheme IV. This would be the case for *N*-chloro amides **7b** and **29b** according to the inspection of models. The formation of such a complex could result in a larger proportion of endo epimer by allowing an intramolecular ligand (chlorine) transfer as shown in Scheme IV. The *N*-chloro amides **7b** and **29b** are the two *N*-chloro amides that did give predominantly the endo isomer as already pointed out. However, as mentioned above, the photochemical cyclization of **7b** under conditions of solvent and temperature similar to those used for the chromous chloride reactions led to an endo/exo ratio of 2.0 as compared to 2.5 with chromous chloride. We therefore have no conclusive evidence for or against a ligand-transfer mechanism. The same situation was encountered for the intermolecular additions;[2b] a classical chain mechanism was considered more probable than a ligand-transfer mechanism mainly on the basis of the low redox potential of the chromic ion. However, it is likely that both mechanisms are involved.

Conclusion

The present work allowed us to show the synthetic potential of the chromous chloride promoted cyclization of olefinic *N*-chloro amides for the preparation of functionalized nitrogen heterocycles. It also allows us to compare the effectiveness and convenience of three methods of cyclization.

The benzoyl peroxide method appears to be quite effective for the cyclization of olefinic *N*-chloro carboxamides (e.g., **7b**, **13b**, and **17b**).[3] Whenever it works, it could be the method of choice, since it is very simple (technical operation and workup are easy) and amenable to large-scale reactions.

The chromous chloride method is more general, giving good to high yields of cyclization with olefinic *N*-chloro acetamides as well as with olefinic *N*-chloro carboxamides. It is amenable to large-scale work and furthermore, the larger the scale, the higher the yield of cyclization. Indeed, the reduction of the amido radical competes with its intramolecular addition to the double bond. Thus the smaller the relative amount of chromous chloride added at a time (which can be achieved by working on larger scales and adding the chromous chloride solution slowly), the better should be the yield of cyclization (as in the case of intermolecular additions[2a]). For instance, the cyclization of *N*-chloro acetamide **4b** carried out on a 3.5-mmol scale, adding the chromous chloride solution over 45 min led to 6% of **6** (Table I). When the reaction was carried out on a 8-mmol scale, adding the chromous chloride solution over 90 min, a 20% yield of **6** was obtained.

The photochemical method is very simple from the point of view of technical operation and workup. However, it is limited to small-scale reactions and proved generally less effective than the two other methods.[3,12] In addition, it may give a more complex mixture of products due to the competing reactions of the chlorine atoms produced in the initiation step.

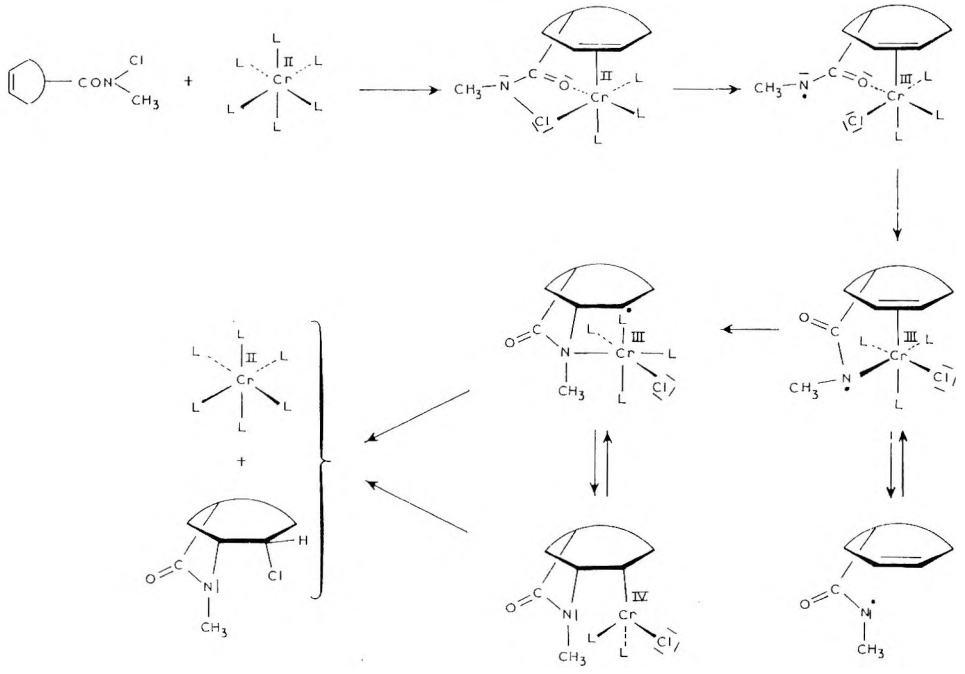
Experimental Section

The pertinent general information has been given in the preceding paper.[3]

Preparation of Olefinic Amides. The preparation of amides **7a**, **10a**, **13a**, **16a**, **17a**, and **19a** has been described in the preceding paper,[3] and that of amide **21a** in ref 4d. Amides **1a** and **4a** have been prepared from 4-pentenoic acid by standard procedures: **1a**,[24] 75% yield; **4a**,[6] 52% yield [after purification by microdistillation at 55–60 °C (1 mm)]. Amide **29a** was prepared according to the method described by Staas and Spurlock:[25] 55% yield; mp 89–92 °C (lit.[25] mp 94–96 °C).

***N*-[(2-Bicyclo[2.2.2]octen-5-yl)methyl]acetamide (24a).** A Diels–Alder reaction between acrolein and cyclohexadiene afforded

Scheme IV



5-formylbicyclo[2.2.2]oct-2-ene.[26] Treatment of this aldehyde by means of hydroxylamine hydrochloride in methanol gave a quantitative yield of oxime. Reduction of this oxime by aluminum hydride afforded the primary amine in 24% yield. Acetamide **24a** was obtained by the usual acetylation procedure in 77% yield: mp 75–77 °C; IR ($CHCl_3$) 3460, 3380, 1670, and 1520 cm^{-1}; NMR ($CDCl_3$) δ 0.8 (m, 1 H), 1.1–2.6 (m, 8 H), 1.98 (s, 3 H), 2.92 (t, 2 H), and 6.2 (m, 3 H).

N-Methyl-2-methylene-5-bicyclo[2.2.2]octanecarboxamide (26a). 5-Carbomethoxybicyclo[2.2.2]octan-2-one was prepared as described by Lee.[27] A Wittig reaction on this ketone (8 g, 44 mmol) in dry benzene (200 mL) using methyltriphenylphosphonium iodide (41.6 g, 103 mmol) and potassium *tert*-butoxide (11.2 g, 0.1 mol) afforded 5-carbomethoxy-2-methylenebicyclo[2.2.2]octane (5.5 g, 70%). Treatment with methylamine (50 mL of a 30% solution in methanol) for 10 days gave, after sublimation of the crude product, the amide **26a** (30% yield): mp 79–85 °C (sealed tube); IR ($CHCl_3$) 3460, 1650, and 1530 cm^{-1}; NMR ($CDCl_3$) δ 1.45–2.8 (m, 11 H), 2.74 (d, 3 H), 4.50 and 4.68 (two m, 2 H), and 7.45 (m, 1 H); mass spectrum *m/e* (rel intensity) 179 (M^+, 14), 24 (18), 86 (100), 79 (26).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.71; H, 9.56; N, 7.81. Found: C, 73.92; H, 9.51; N, 7.82.

N-Methyl-3-bicyclo[3.3.1]non-6-enecarboxamide (27a). This amide was prepared from 6-bicyclo[3.3.1]non-3-enecarboxylic acid.[28] The preparation of the acid chloride gave a mixture containing 60% of the acid chloride and 37% of 4-chloroadamantan-2-one.[29] Addition of the acid chloride to a dry solution of methylamine in benzene afforded amide **27a** in 60% yield. The crude amide was recrystallized from cyclohexane: mp 74 °C; IR ($CHCl_3$) 3520, 3440, 1675, and 1540 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.5 (m, 11 H), 2.75 (d, 3 H), and 5.6 (m, 3 H).

Preparation of Olefinic N-Chloro Amides. The *N*-chloro amides **26b**, **27b**, and **29b** were prepared from the parent amide by the method described by Kuehne and Horne.[6] The yields are recorded in Table I.

Typical Procedure for the Sodium Hypochlorite Method. N-Chloro-N-methyl-5-cycloheptenecarboxamide (13b). Amide **13a** (0.775 g, 5 mmol) dissolved in methylene chloride (10 mL) was treated with sodium hypochlorite (12.1 mL of a 0.83 N solution, 10 mmol). Sulfuric acid (1.2 mL of a 1 N solution) was then added. The mixture was stirred vigorously at room temperature in the dark. The reaction was followed by NMR until the complete disappearance of the *N*-methyl doublet at 2.8 ppm. The organic layer was separated and the aqueous solution extracted with methylene chloride (5 × 10 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvent gave **13b** (0.865 g, 91% active chlorine by iodometry, 82% yield): NMR ($CDCl_3$) δ 2.2 (m, 6 H), 3.1 (m, 1 H), 3.4 (s, 3 H), and 5.8 (m, 2 H).

The *N*-chloro amides **4b** to **24b** (Table I) were prepared in the same way on a 5–10-mmol scale with 0.8–1.3 M sodium hypochlorite solutions. Better yields could be obtained by stopping the reaction before the complete disappearance of the starting amide.

2-Chloro-4-oxahomoadamantane-5-one (32). An attempt to N-chlorinate amide **27b** by the above method led to a mixture which after separation on silica gel plates (ether–hexane 1:1) gave the chloro lactone **32** (54%). The analytical sample was obtained after recrystallization from cyclohexane (it sublimed readily and no melting point was recorded): IR ($CHCl_3$) 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.4–2.6 (10 H), 3.09 (m, 1 H), 4.26 (m, 1 H), and 4.46 (m, 1 H); mass spectrum *m/e* (rel intensity) 200 (M^+, 2), 156 (8), 121 (30), 79 (100), and 39 (42); *m/e* calcd for $C_{10}H_{13}ClO_2$ 200.060404, found 200.059763.

Anal. Calcd for $C_{10}H_{13}ClO_2$: C, 59.86; H, 6.53. Found: C, 59.46; H, 6.81.

Typical Procedure for the Buffered Sodium Hypochlorite Method. N-Chloro-N-methyl-4-pentenecarboxamide (1b). The phosphate buffer (3 M solution) was prepared by adding a saturated potassium hydroxide solution to phosphoric acid until pH 12.5. The amide **1a** (1.50 g, 13 mmol) was dissolved in chloroform (10 mL). The buffer (37 mL) was added, then sodium hypochlorite (37 mL of a 0.71 N solution). The reaction was followed by NMR and was stopped when the integration ratio of the singlet at 3.33 ppm and the doublet at 2.75 ppm reached a maximum. Workup as above gave *N*-chloro amide **1b** (2.04 g, 84% active chlorine, 74% yield). The crude product still contained chloroform and 14% of parent amide **1a** by NMR. It was used without further purification.

Chromous Chloride Promoted Cyclizations. Typical Procedure. Cyclization of N-Chloro-N-methyl-4-pentenecarboxamide (1b). The reaction was carried out as described for the intermolecular additions,[2a] adding slowly a 1 M methanolic chromous chloride solution (10 mL added over 90 min) to a solution of **1b** (2.17 g, 78% active chlorine, 11.5 mmol) in chloroform (10 mL)–methanol (2 mL) cooled at −78 °C (dry ice–methanol bath) until a negative starch–iodide test. The crude product obtained after the usual workup and methylene chloride extraction was diluted in a 10-mL volumetric flask. An aliquot (2 mL) was separated by preparative TLC (hexane–ether–methanol 10:10:1) to yield three fractions. The less polar fraction consisted of *N*-methyl-5-chloromethyl-2-pyrrolidone (**2**; 0.121 g, 36%), which was purified by microdistillation at 70 °C (0.5 mm): NMR ($CDCl_3$) δ 1.9–2.7 (m, 4 H), 2.79 (s, 3 H), 3.64 (m, 2 H), and 3.80 (m, 1 H); mass spectrum *m/e* 147, 149 (3:1, M^+). The second fraction consisted of *N*-methyl-5-methyl-2-pyrrolidone (**3**; 0.131 g, 50%), which proved identical (IR, ^1H NMR) with an authentic sample (Aldrich). The third fraction consisted of the parent amide **1a** (0.063 g). Continuous extraction of the aqueous phases (from the extraction above) with methylene chloride yielded additional quantities of **1a**, **2**, and **3**. VPC analysis (OS-138) of this fraction and of the crude product obtained above, using authentic samples as standards, gave the following results: **1a**, 22% (amount present in the starting material); **2**, 44%; **3**, 61%.

The same procedure was followed for the cyclization of *N*-chloro amide **4b** (addition of the chromous chloride solution over 45 min). For the other *N*-chloro amides of Table I, it was not necessary to carry out a continuous extraction of the aqueous phases. The yields were determined by VPC using authentic samples as standards. These samples were obtained either by preparative VPC or preparative TLC.

Cyclization of N-Chloro-N-(4-penten-1-yl)acetamide (4b). The cyclic products **5** and **6** proved identical (IR, ^1H NMR) with samples prepared as follows. (2-Pyrrolidino)methanol was converted to its diacetate (95%) by acetylation under the usual conditions (1 h). Mild hydrolysis (potassium hydroxide, 1 equiv, in aqueous methanol) at room temperature for 3 h afforded *N*-acetyl(2-pyrrolidino)methanol (quantitative). It was treated with triphenylphosphine and chlorine in dry methylene chloride at 25 °C for 3 h. The solution was washed with a saturated solution of sodium bisulfite and dried, and the solvent was evaporated. Most of the triphenylphosphine oxide was removed by crystallization. Short-path distillation at 68°C (0.5 mm) afforded pure **5** in 58% yield: IR ($CHCl_3$) 1645 and 1405 cm^{-1}; NMR ($CDCl_3$) δ 2.00 (m, 4 H), 2.08 (s, 3 H), 3.50 (t, 2 H), 3.76 (m, 2 H), and 4.30 (m, 1 H); *m/e* 161, 163 (3:1, M^+). 5-Methyl-2-pyrrolidone was reduced with $LiAlH_4$ in ether to 2-methylpyrrolidine, which was then acetylated (Ac_2O, aqueous Na_2CO_3) to afford pure *N*-acetyl-2-methylpyrrolidine (**6**) as a liquid (26% yield): IR (CCl_4) 1645 and 1405 cm^{-1}; NMR ($CDCl_3$) δ 1.17 (d, 3 H), 1.5–2.3 (m, 4 H), 2.0 and 2.06 (two s, 3 H), 3.43 (m, 2 H), and 4.06 (br m, 1 H).

Cyclization of N-Chloro Amides 7b, 13b, 17b, and 19b. The physical constants and characterization of the corresponding cyclization products have been already described in the preceding paper.[3]

Cyclization of N-Chloro-N-[(3-cyclohexen-1-yl)methyl]-acetamide (10b). Cyclization of the olefinic *N*-chloro acetamide **10b** afforded a mixture of the two isomers **11** and **12**. The less polar isomer **11** was identified as exo-4-chloro-6-acetyl-6-azabicyclo[3.2.1]octane: mp 35 °C; IR ($CHCl_3$) 1630 cm^{-1}; NMR ($CDCl_3$, 250 MHz) δ 1.5–2.1 (m, 5 H), 2.11 and 2.06 (2 s, 3 H), 2.42 (m, 2 H), 3.31 and 3.37 (2 d, 1 H), 3.51 and 3.56 (2 q, 1 H), 4.18 and 4.38 (2 t, 1 H), 4.08 and 4.5 (2 t, 1 H).

Anal. Calcd for $C_9H_{14}ClNO$: C, 57.60; H, 7.52; N, 7.46. Found: C, 57.83; H, 7.13; N, 7.26.

The more polar isomer **12** was *endo*-4-chloro-6-acetyl-6 azabicyclo[3.2.1]octane: IR ($CHCl_3$) 1625 cm^{-1}; NMR ($CDCl_3$, 250 MHz) δ 1.5–2.18 (m, 5 H), 2.23 (br, 1 H), 2.27 (s, 3 H), 2.5 (br, 1 H), 3.34 (m, 1 H), 3.6 (q, 1 H), 4.05 (q, 1 H), and 4.26 (d, 1 H). The mass spectra of the two isomers were identical: *m/e* (rel intensity) 187 (M^+, 18), 110 (53), 68 (100), 43 (20); for these and all the other cyclization products P/(P + 2) = 2.8–3.

Reaction of N-Chloro-N-[(4-cyclohepten-1-yl)methyl]-acetamide (16b) in a Deuterated Medium. Chromous Chloride Solution (1 M). Anhydrous chromous chloride (2.46 g, 20 mmol) (Merck) was dissolved in 20 mL of methanol-d_1 containing 2 mL of heavy water and 0.3 mL of deuterated hydrochloric acid (37%) under nitrogen atmosphere.

Reaction. Olefinic *N*-chloro amide **16b** (1.03 g, 5 mmol) was dissolved in a chloroform–methanol-d_1 (5:1) mixture and the solution was cooled to −78 °C (methanol–dry ice). Then 10 mL (10 mmol) of the chromous chloride solution was added very slowly. The reaction was followed by iodometric test and stopped after completion; 20 mL of heavy water was added before the reaction mixture was allowed to warm up to room temperature. Extraction followed by silica gel column chromatography afforded quantitatively the parent amide **16a**. The mass spectrum of the reaction product showed no incorporation

of deuterium in the molecule and was identical with the mass spectrum of an authentic sample of **16a**.

Cyclization of *N*-Chloro-*N*-methyl-5-bicyclo[2.2.2]oct-2-enecarboxamide (21b). Cyclization of *N*-chloro amide **21b** gave 85% of cyclized products. One could isolate 80% of the tricyclic exo isomer **22** and detect a product (5%) which could be the endo isomer **23** on the basis of its mass spectrum. The exo isomer **22** was recrystallized from cyclohexane to give pure *exo*-10-chloro-3-methyl-3-azatricyclo[4.3.1.0^{1,5}]decan-2-one (**22**): mp 65–66 °C; IR ($CHCl_3$) 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.3–2.43 (m, 9 H), 2.9 (s, 3 H), 3.46 (d, 1 H), and 4.0 (d, 1 H). The mass spectra of **22** and **23** were identical: *m/e* (rel intensity) 199 (M^+, 69), 164 (53), 136 (68), 96 (100), 78 (21), 42 (34).

Cyclization of *N*-Chloro-*N*-[(2-bicyclo[2.2.2]octen-5-yl)-methyl]acetamide (24b). *exo*-10-Chloro-3-acetyl-3-azatricyclo[4.3.1.0^{1,5}]decane (**25**) was obtained from the cyclization of olefinic *N*-chloro amide **24b** in 85% yield: IR ($CHCl_3$) 1635 cm^{-1}; NMR ($CDCl_3$, 250 MHz) δ 1.28 (m, 2 H), 1.6–2.5 (m, 7 H), 2.03 and 2.19 (2 s, 3 H), 2.84 and 3.20 (2 d, 1 H), 3.29 and 3.4 (2 q, 1 H), 3.84 and 4.19 (2 d, 1 H); mass spectrum *m/e* (rel intensity) 213 (M^+, 26), 178 (19), 136 (61), 80 (100), 68 (48), 43 (34).

Reaction of *N*-Chloro-*N*-methyl-2-methylene-5-bicyclo[2.2.2]octanecarboxamide (26b). Attempts to cyclize the *N*-chloro amide **26b** yielded a mixture containing 70% of parent amide **26a** and 32% of a product which was identified as *N*-methyl-2-methyl-5-bicyclo[2.2.2]oct-2-enecarboxamide: IR ($CHCl_3$) 1660, 1520 cm^{-1}; NMR ($CDCl_3$) δ 1.1–2.88 (m, 9 H), 1.83 (d, 3 H), 2.77 (d, 3 H), 5.5 (m, 1 H), and 5.83 (br, 1 H); mass spectrum *m/e* (rel intensity) 139 (M^+, 18), 94 (48), 86 (100), 79 (58).

Cyclization of *N*-Chloro-*N*-methyl-3-bicyclo[3.3.1]non-6-enecarboxamide (27b). Cyclization of *N*-chloro amide **27b** afforded 74% of *anti*-5-chloro-3-methyl-3-azahomoadamantan-2-one (**28**) and 15% of parent amide **27a**. The tricyclic lactam **28** was recrystallized from cyclohexane: mp 98 °C; IR ($CHCl_3$) 1650 cm^{-1}; NMR ($CDCl_3$, 250 MHz) δ 1.47–2.45 (m, 10 H), 2.88 (m, 1 H), 3.02 (s, 3 H), 3.45 (m, 1 H), and 4.22 (br, 1 H); mass spectrum *m/e* (rel intensity) 213 (39), 178 (100), 122 (21), 80 (23), 57 (26).

Anal. Calcd for $C_{11}H_{16}ClNO$: C, 61.83; H, 7.55; N, 6.55. Found: C, 61.69, H, 7.24; N, 6.28.

Cyclization of *N*-Chloro-*N*-(6-bicyclo[3.3.1]nonen-3-yl)-acetamide (29b). Cyclization of the olefinic *N*-chloro amide **29b** afforded a mixture of 62% of isomers **30** and **31**, 21% of parent amide **29a**, and 15% of an unidentified product. The less polar isomer was identified as *anti*-4-chloro-2-acetyl-2-azaadamantane (**30**): IR ($CHCl_3$) 1625 cm^{-1}; NMR ($CDCl_3$, 250 MHz) δ 1.56–2.46 (m, 10 H), 2.09 (s, 3 H), 3.98 (br, 1 H), 4.18 and 4.22 (2 br, 1 H), 4.81 and 4.86 (2 br, 1 H).

Anal. Calcd for $C_{11}H_{16}ClNO$: C, 61.83; H, 7.55; N, 6.55. Found: C, 61.66; H, 7.55; N, 6.52.

The more polar isomer was *syn*-4-chloro-2-acetyl-2-azaadamantane (**31**): mp 35 °C; IR ($CHCl_3$) 1630 cm^{-1}; NMR ($CDCl_3$, 250 MHz) δ 1.52–2.52 (m, 10 H), 2.12 (s, 3 H), 4.01 and 4.1 (2 br, 1 H), 4.31 (br, 1 H), 4.86 and 5.0 (2 br, 1 H).

Anal. Calcd for $C_{11}H_{16}ClNO$: C, 61.83; H, 7.55; N, 6.55. Found: C, 61.85; H, 7.50; N, 6.51.

The mass spectra of the two isomers were identical: *m/e* (rel intensity) 213 (M^+, 41), 178 (80), 171 (52), 136 (96), 94 (30), 80 (100), 43 (35).

Registry No.—**1a**, 52565-61-4; **16**, 66769-76-4; **2**, 66769-85-5; **3**, 5075-92-3; **4a**, 54385-21-6; **4b**, 54385-04-5; **5**, 54385-06-7; **6**, 18912-61-3; **7a**, 54385-24-9; **7b**, 36393-98-3; **8**, 36394-04-4; **9**, 36394-03-3; **10a**, 54385-23-8; **10b**, 54385-09-0; **11**, 66769-86-6; **12**, 66769-87-7; **13a**, 53102-89-9; **13b**, 66769-77-5; **14**, 66769-88-8; **15**, 66791-98-8; **16a**, 66769-67-3; **16b**, 66769-78-6; **17a**, 13295-40-4; **17b**, 66769-79-7; **18**, 66769-89-9; **19a**, 66769-68-4; **19b**, 66769-80-0; **20**, 66769-90-2; **21a**, 62460-73-5; **21b**, 66769-81-1; **22**, 66769-91-3; **23**, 66791-99-9; **24a**, 66769-69-5; **24b**, 66769-82-2; **25**, 66792-17-4; **26a**, 66769-70-8; *exo*-**26a**, 66791-96-6; **26b**, 66769-83-3; **27a**, 66769-71-9; **27b**, 66787-43-7; **28**, 66769-65-1; **29a**, 53092-79-8; **29b**, 66769-84-4; **30**, 66769-66-2; **31**, 66791-95-5; **32**, 66769-72-0; 5-formylbicyclo[2.2.2]oct-2-ene, 40570-95-4; 5-formylbicyclo[2.2.2]oct-2-ene oxime, 66769-73-1; bicyclo[2.2.2]oct-2-ene-5-methanamine, 66791-97-7; 5-carbomethoxybicyclo[2.2.2]octan-2-one, 49826-55-3; 5-carbomethoxy-2-methylenebicyclo[2.2.2]octane, 66769-74-2; 6-bicyclo[3.3.1]non-3-enecarboxylic acid, 21932-98-9; 6-bicyclo[3.3.1]non-3-enecarbonyl chloride, 57438-49-0; (2-pyrrolidino)methanol, 498-63-5; (2-pyrrolidino)-methanol diacetate, 42366-60-9; *N*-acetyl-(2-pyrrolidino)methanol, 27822-68-0; *N*-methyl-2-methyl-5-bicyclo[2.2.2]oct-2-enecarboxamide, 66769-75-3; chromous chloride, 10049-05-5.

References and Notes

(1) (a) See ref 1a to 1c of the preceding paper in this issue. (b) Most of the work reported here is part of Ph. Mackiewicz, "Thèse d'ingénieur—Docteur", University d'Aix-Marseille III, 1977. (c) Part of this work has been presented at the Congress of Heterocyclic Chemistry, Teheran, Iran, July, 1977, and at the 2nd International Symposium on Organic Free Radicals, Aix-en-Provence, France, July, 1977.

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(8) We have tried different additional chlorinating agents next to the previously described ones, i.e., calcium hypochlorite, *tert*-butyl hypochlorite,[9] *N*-chlorosuccinimide, and tetra-*n*-butylammonium hypochlorite.

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(10) All the cyclization products reported in Table I had IR and ^{1}H NMR spectra, and elemental analysis, and/or a mass spectrum consistent with their structure and stereochemistry. The interpretation and analysis of the ^{1}H NMR and IR spectra are generally quite straightforward and are presented in the Experimental Section. Compounds **8** and **9** had spectral data similar to those reported.[6,11] The *N*-acetyl derivatives are of particular interest from the ^{1}H NMR point of view as the two rotamers could be observed. These data will be reported in full details elsewhere.

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(12) We have also performed the photochemical cyclization of *N*-chloro amides **1b** and **4b**, as described in the preceding paper,[3] and obtained the following results: from **1b**, 56% of **2**, 15% of **3**, no parent amide; from **4b**, 6% of **5**, 21% of **6**, 10% of parent amide. Kuehne and Horne[6] reported a 35% yield of **5** after distillation. However we obtained, under the same conditions, a mixture of products.

(13) The preference for 1,5 transfer of hydrogen in amido radicals[14,15] and other heteroradicals[16] is documented by many examples.

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Effect of Substituents in Controlling the Rate of the Intramolecular Cycloaddition Reaction of Allyl-Substituted 2*H*-Azirines[1]

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Received February 10, 1978

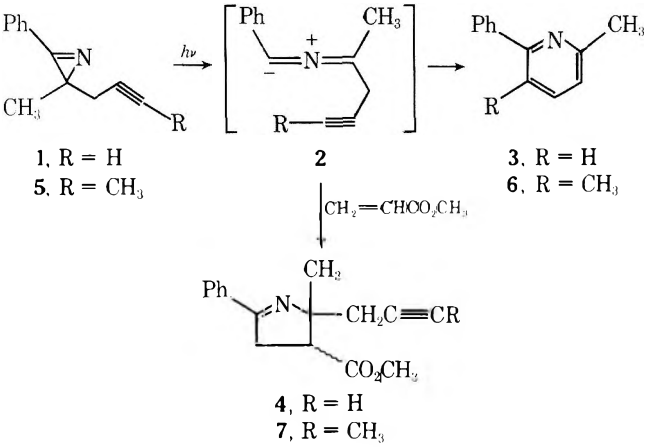
The intramolecular photocycloaddition reactions of a number of allyl-substituted 2*H*-azirines have been investigated in mechanistic detail. Irradiation of these systems gives rise to 2-azabicyclo[3.1.0]hex-2-enes which are readily oxidized to 2,6-disubstituted pyridines. The rearrangements proceed via a nitrile ylide intermediate which can be intercepted with added dipolarophiles to give Δ^1-pyrroline derivatives. A kinetic investigation, involving Stern–Volmer plots and relative reactivity studies, shows that the internal cycloadditions are controlled by interaction of the HOMO of the dipole with the LUMO of the dipolarophile. Thus, methyl (*E*)-4-(2-methyl-3-phenyl-2*H*-azirin-2-yl)-2-butenoate (**14**) was found to undergo internal cycloaddition at a faster rate (tenfold) than 2-allyl-2-methyl-3-phenyl-2*H*-azirine (**8**). The relative reactivity studies show that there is a marked leveling of the rate profile associated with these internal cycloadditions when compared with their bimolecular counterparts. The data suggest that the internal cycloaddition reactions involve appreciable interaction of both the in-plane and out-of-plane π-unoccupied orbitals of the dipole with the dipolarophile-filled orbitals. This secondary orbital interaction significantly enhances the rate of internal cycloaddition of the simple olefinic azirines and can account for the marked leveling effect noted with these systems.

In earlier papers we have shown that there are two pathways by which nitrile ylides react with multiple π bonds.[2-5] The most frequently encountered path involves a "parallel-plane approach of addends" [6] and can be considered to be an orbital symmetry allowed [4 + 2] concerted process.[7] With this path, the relative reactivity of the nitrile ylide toward a series of dipolarophiles will be determined primarily by the extent of stabilization afforded the transition state by interaction of the dipole highest occupied (HOMO) and dipolarophile lowest unoccupied (LUMO) orbitals.[8-12] Substituents which lower the dipolarophile LUMO energy will accelerate the 1,3-dipolar cycloaddition reaction.[13] Nitrile ylides are known to react most rapidly with electron-deficient alkenes since such a pair of addends possesses a narrow dipole HOMO–dipolarophile LUMO gap.[14,15] Bimolecular reactions of nitrile ylides with electron-rich olefins have never been observed, thereby indicating that the dipole LUMO–dipolarophile HOMO interaction is never large. Because of their high nucleophilicities, nitrile ylides generally undergo reactions with their precursors, dimerize, or isomerize faster than they undergo reactions with electron-rich alkenes.[16-18]

The other path by which nitrile ylides react with π bonds occurs only in certain intramolecular cases and has been designated as a 1,1-cycloaddition reaction.[2-5] It occurs when the p orbitals of the olefinic group have been deliberately constrained to attack perpendicular to the nitrile ylide plane. Houk and Caramella have suggested that the 1,1-cycloaddition reaction is initiated by interaction of the terminal carbon of the olefin with the second LUMO of the nitrile ylide.[19] The second LUMO of the dipole is perpendicular to the ylide plane and presents a large vacancy at C_1 of the dipole for attack by the terminus of the neighboring double bond, without the possibility of simultaneous bonding at the C_3 carbon. In fact, the HOMO and second LUMO of the bent nitrile ylide bear a strong resemblance to the HOMO and LUMO of a singlet carbene. According to this argument, the effect of substituents upon the rate of the intramolecular carbene-like cycloaddition should be controlled by the interaction of the alkene HOMO and the second LUMO of the nitrile ylide. Since electron-releasing substituents raise both the HOMO and LUMO orbital energies of ethylene,[9] one might expect that attachment of alkyl groups on the double bond would facilitate the rate of the 1,1-cycloaddition reaction. Electron-withdrawing substituents, on the other hand, would be expected to diminish the rate of the 1,1-cycloaddition reaction. In order to assess the effect of substituents on the rate of the 1,1-cycloaddition reaction, we have examined the photochemistry of a series of olefinic 2*H*-azirines containing unsaturation two bonds away from the azirine ring. We report here the results of these studies.

Results

Product Studies. As a continuation of our studies dealing with the carbenic behavior of nitrile ylides, we became interested in examining the photochemistry of 2-propargylic 2*H*-azirines in order to determine whether internal cycloaddition of the nitrile ylide would take place across the acetylenic π bond. Our initial experiments revealed that the 2-propargylic-substituted 2*H*-azirines were highly photochemically reactive. Thus, direct irradiation of 2-methyl-2-propargyl-3-phenyl-2*H*-azirine (**1**) with light of wavelength >250 nm for



1, R = H
5, R = CH_3

2

3, R = H
6, R = CH_3

4, R = H
7, R = CH_3

15 min resulted in the formation of 2-phenyl-6-methylpyridine (**3**; 48% isolated yield). Similar irradiation of 2-(2-butynyl)-2-methyl-3-phenyl-2*H*-azirine (**5**) afforded the analogous pyridine **6** in good yield. Chemical confirmation of these structures was obtained by comparison with authentic samples. Photolysis of **1** (or **5**) in the presence of methyl acrylate resulted in the trapping of nitrile ylide **2** and produced cycloadduct **4** (or **7**) in high yield. Under these conditions, the formation of pyridine **3** (or **6**) is completely suppressed. This result implicates nitrile ylide **2** as an intermediate in the formation of the pyridine ring. The formation of **3** (or **6**) can be postulated to arise by attack of the terminal carbon atom of the acetylene onto the nitrile ylide followed by a 1,2-hydrogen shift of the resulting carbene intermediate.

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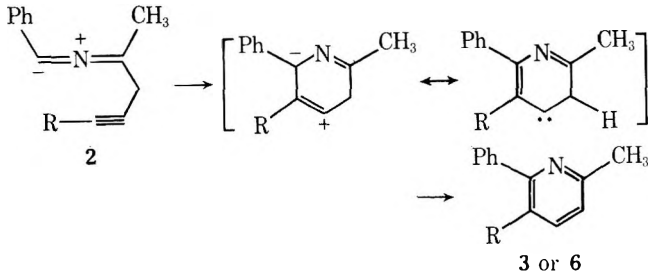
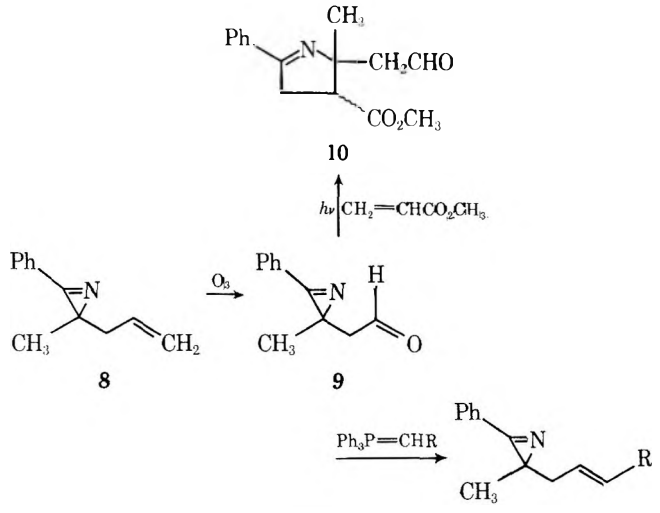


2 3 or 6

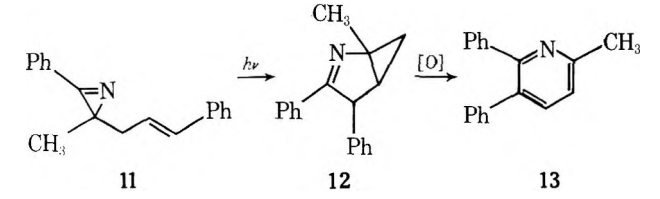
Attention was next turned to the synthesis of 2-allyl-substituted 2*H*-azirines which contain electron-withdrawing groups on the double bond. A convenient method for preparing these systems involved ozonization of the parent 2-allyl-substituted 2*H*-azirine followed by reaction of the resulting aldehyde with various Wittig reagents. All attempts to detect an intramolecular cycloadduct from the photolysis of aldehyde **9** failed. The initially generated nitrile ylide de-



8 **9** **10**

rived from **9** could be trapped, however, with methyl acrylate to afford the normal Δ^1-pyrroline adduct **10** as a mixture of stereoisomers.

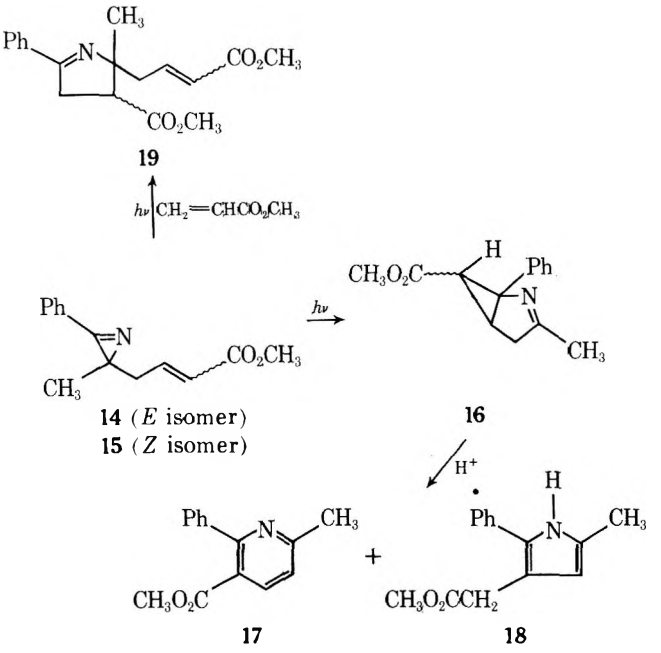
When a thoroughly deaerated solution of (*E*)-2-cinnamyl-2-methyl-3-phenyl-2*H*-azirine (**11**) was irradiated in cyclo-



11 **12** **13**

hexane, an extremely rapid conversion to *exo*-3,4-diphenyl-1-methyl-2-azabicyclo[3.1.0]hex-2-ene (**12**) occurred. The identity of azabicyclohexene **12** was determined by its straightforward NMR spectrum (CCl_4, 60 MHz), which showed signals at τ 9.76 (t, 1 H, J = 4.5 Hz), 9.07 (dd, 1 H, J = 8.0 and 4.5 Hz), 8.31 (s, 3 H), 7.72 (dd, 1 H, J = 8.0 and 4.5 Hz), 5.83 (s, 1 H), and 2.8 (m, 5 H). Upon standing or on chromatographic separation, the initially produced azabicyclohexene was converted to 2,3-diphenyl-6-methylpyridine (**13**) in quantitative yield. It is interesting to note that the irradiation of **11** resulted in the exclusive formation of cycloadduct **12**. This result stands in marked contrast to the photochemistry of the related 2-allyl-substituted 2*H*-azirine system **8**, which produced a mixture of azabicyclohexenes.[2]

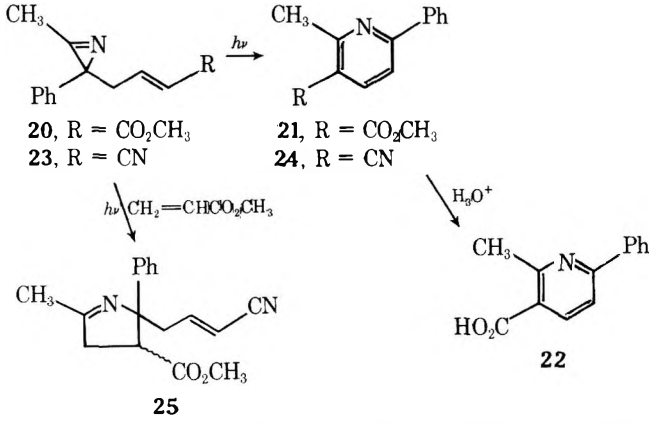
The intramolecular photocycloaddition reaction of methyl (*E*)-4-(2-methyl-3-phenyl-2*H*-azirin-2-yl)-2-butenoate (**14**) was also studied in order to assess the effect of electron-withdrawing groups on the double bond. Irradiation of **14** in cyclohexane using a 450-W Hanovia immersion apparatus



19 **14** (*E* isomer) **15** (*Z* isomer) **16** **17** **18**

equipped with a Vycor filter sleeve led to the complete consumption of reactant in 20 min and produced a mixture of *endo*- and *exo*-6-carbomethoxy-3-methyl-1-phenyl-2-azabicyclo[3.1.0]hex-2-ene (**16**) in high yield. The same epimeric mixture of isomers was produced from the irradiation of the corresponding *Z* isomer **15**. The epimeric mixture of azabicyclohexenes was converted to 2-phenyl-3-carbomethoxy-6-methylpyridine (**17**; 60%) and methyl (2-phenyl-5-methylpyrrol-3-yl)acetate (**18**; 40%) on silica gel chromatography. It should be pointed out that no equilibration of the starting azirines was detected, and the only product that was formed when methyl acrylate was used as the trapping agent was the usual Δ^1-pyrroline **19**.

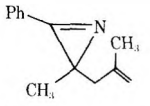
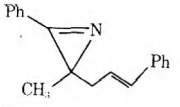
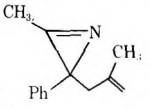
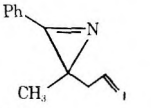
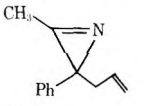
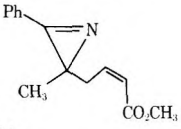
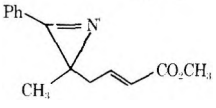
The photochemical behavior of the closely related methyl (*E*)-4-(3-methyl-2-phenyl-2*H*-azirin-2-yl)-2-butenoate (**20**)



20, R = CO_2CH_3 **21**, R = CO_2CH_3
23, R = CN **24**, R = CN
25 **22**

was also studied in order to assess the generality of the internal cycloaddition reaction. Photolysis of **20** gave 2-methyl-3-carbomethoxy-6-phenylpyridine (**21**) as the only characterizable material. The structure of **21** was verified by hydrolysis to the known carboxylic acid **22**.[20] With this system there were no detectable quantities of a 2-azabicyclohexene in the crude reaction mixture. It would appear as though the initially formed azabicyclohexene is rapidly converted to pyridine **21** during photolysis. We also studied the photochemistry of the closely related butenonitrile **23** and found that it was converted to 2-methyl-3-cyano-6-phenylpyridine (**24**) in high yield. Chemical support for structure **24** was obtained by its hydrolysis to carboxylic acid **22**. Irradiation of **23** in the presence of methyl acrylate was found to afford Δ^1-pyrroline **25** in excellent yield.

Table I. Kinetic Data from the Stern–Volmer Analysis of the Internal Photocycloaddition Reactions of 2-Allyl-Substituted 2*H*-Azirines

Compd	No.	Φ_o	Slope	Intercept	Slope/intercept	k_{rel}
	26	0.11	2200	9.1	233	1.0
	11	0.014	9160	70	130	1.8
	27	0.21	212	4.9	43	5.4
	8	0.26	152	3.8	40	5.8
	28	0.30	112	3.3	34	6.8
	15	0.049	960	20	48	4.9
	14	0.06	73	17.5	4.2	55.4

Rate Studies. In order to derive additional mechanistic information concerning the intramolecular dipolar cycloaddition reaction, a more quantitative investigation of these cycloadditions was undertaken. Quantum yields for product formation were determined using cyclopentanone as the chemical actinometer.[21] Degassed and sealed quartz tubes containing solutions of the azirines were irradiated with actinometer tubes in a rotating photochemical assembly. Reactions were carried out to low conversions to prevent appreciable light absorption by the products, and yields were determined by quantitative NMR analysis. The quantum yield for product formation as a function of the concentration of added methyl acrylate was also studied. The results of the quantum yield measurements for the seven azirines studied are given in Table I. Several features become apparent upon examination of the data. Good linear relationships are observed between the inverse of the quantum yield for product formation and the concentration of added methyl acrylate. The slopes and intercepts of the plots depend on the structure of the azirine used. At zero dipolarophile concentration, the quantum yield for internal cycloaddition varies between 0.014 and 0.30. The relatively high quantum efficiencies observed with these systems indicate that a significant path from the electronically excited state of the unsaturated azirine involves bond rupture and formation of a nitrile ylide. The initially generated 1,3 dipole is either trapped internally by the adjacent π bond or else undergoes bimolecular cycloaddition with the added dipolarophile.

The results obtained using these unsaturated azirines as nitrile ylide precursors are consistent with the mechanism outlined in Scheme I. In this scheme, A_o = unsaturated azirine, NY = nitrile ylide, P = product, and O = dipolarophile (i.e., methyl acrylate). By making the usual steady state assumption, we can write eq 1, where k_d represents the nonradiative

$$1/\Phi_p = [(k_d + k_r)/k_r][1 + (k_2[O]/k_1)] \quad (1)$$

Scheme I

$$A_o \xrightarrow{h\nu} A^*$$

$$A^* \xrightarrow{k_d} A_o$$

$$A^* \xrightarrow{k_r} NY$$

$$NY \xrightarrow{k_1} P$$

$$NY + O \xrightarrow{k_2} \text{adduct}$$

decay of excited azirine, k_r is the rate of C–C bond cleavage of the excited azirine ring, k_1 is the rate of internal cycloaddition, k_2 is the rate of 1,3-dipolar cycloaddition with methyl acrylate, and Φ_p is the quantum yield of product formation.

From the slope and intercept of the Stern–Volmer analysis for product formation with a given azirine, we find that the slope/intercept = k_2/k_1. Thus, for the case of azirine 8, k_2/k_1 = 40, while with azirine 14, k_2/k_1 = 4.2. These values indicate that the nitrile ylide intermediate obtained from azirine 8 is much more easily trapped with an added dipolarophile than the 1,3 dipole derived from the carbomethoxy-substituted 2*H*-azirine 14. If we assume that the rate of cycloaddition (i.e., k_2) of both nitrile ylides with methyl acrylate is the same, we can obtain the relative rate difference for internal cycloaddition of these two azirines (eq 2). It should be pointed out that

$$[k_2/k_1 \text{ (for azirine 8)}/k_2/k_1 \text{ (for azirine 14)}] = k_{14}/k_8 = k_{rel} = 9.5 \quad (2)$$

previous work in our laboratory has shown that the relative reactivities of nitrile ylides generated from 2*H*-azirine precursors are very similar toward a given dipolarophile.[22,23] This observation provides strong support for the assumption that the absolute rate constants for bimolecular cycloaddition (i.e., k_2) are extremely similar.

Scheme II

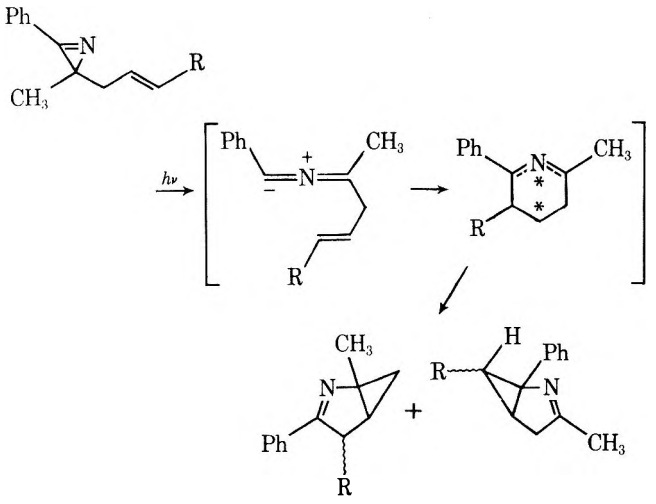


Table I gives a list of the relative rate constants for internal cycloaddition of the seven azirines examined. To facilitate comparison, all of the k_1 values are related to that for 2-methyl-2-(2-methylallyl)-3-phenyl-2*H*-azirine (**26**), which is taken as unity. The data presented in the table show that the rate of cycloaddition is affected by both electronic and steric factors. Attachment of electron-withdrawing substituents to the double bond facilitates the internal cycloaddition reaction relative to the alkyl-substituted olefinic azirines (i.e., **8** or **26**). Interestingly, internal cycloaddition of the (*Z*)-carbomethoxy-substituted 2*H*-azirine **15** is eleven times slower than of the corresponding *E* isomer **14**.

Discussion

Previous papers from this laboratory have established that the irradiation of allyl-substituted 2*H*-azirines produces 2-azabicyclo[3.1.0]hex-2-enes as primary photoproducts.[2-5] The photoreaction has been proposed to proceed via C–C bond cleavage and generation of a bent nitrile ylide intermediate (carbene-like). Attack of the carbene carbon of the dipole onto the terminal position of the neighboring double bond generates a six-membered ring trimethylene intermediate which subsequently collapses to the observed 2-azabicyclohexene ring system. It should be noted that the cycloaddition sequence shown in Scheme II proceeds in a nonconcerted manner and bears a strong resemblance to the stepwise diradical mechanism suggested by Firestone[25,26] to account for bimolecular 1,3-dipolar cycloadditions.

The nonconcerted 1,1-cycloaddition reaction occurs only when the p orbitals of the dipolarophile are constrained to attack perpendicular to the bent[27] nitrile ylide plane. The fact that the irradiation of these electron-deficient allyl-substituted azirines gives rise to azabicyclohexenes and products derived from them (i.e., **21** or **24**) suggests that a similar series of intermediates are involved here. This pathway is distinctly different from that encountered in the bimolecular 1,3-dipolar cycloaddition reactions of nitrile ylides.[14,15,28] The bimolecular path involves a "parallel plane approach of addends" and is an orbital symmetry allowed [3 + 2] concerted process.[7]

As was mentioned earlier, the 1,1-cycloaddition reaction has been suggested to be initiated by interaction of the terminal carbon of the olefin with the second LUMO of the nitrile ylide. Placement of an electron-withdrawing substituent on the π bond will lower both the HOMO and LUMO orbital energies of the olefin, and therefore a diminution in the rate of the intramolecular 1,1-cycloaddition reaction might be expected relative to the unsubstituted olefinic azirine system **8**. Using this rationale, the relative reactivity prediction for the second LUMO controlled intramolecular cycloaddition reaction of these allyl-substituted 2*H*-azirines proves to be incorrect. Thus, the internal cycloaddition of the nitrile ylide derived from the carbomethoxy-substituted 2*H*-azirine **14** proceeds at a faster rate (10-fold) than that derived from azirine **8**. Furthermore, the 2-methylallyl-substituted azirines **26** and **27** undergo internal cycloaddition at a slower rate than azirines **8** and **28** (see Table I). Alkylethylenes generally have ionization potentials 1–2 eV lower than ethylene, depending on the type and number of alkyl substituents. Also, the π–π^* transition energies of alkylethylenes are 0.6–1.0 eV lower in energy than that of ethylene.[29] These findings indicate that alkyl groups should raise both the HOMO and LUMO orbital energies of ethylene and therefore should facilitate the rate of the intramolecular carbene-like 1,1-cycloaddition if the reaction is controlled by the second LUMO of the nitrile ylide. This is clearly not the case.

The relative reactivity pattern exhibited by these allyl-substituted azirines seems more consistent with a HOMO controlled intramolecular cycloaddition reaction. Houk's latest MINDO calculations show that the parent nitrile ylide is definitely bent with an HCN angle of 114–116°.[27] Although the highest occupied molecular orbital of the ylide was found to be heavily localized at C_1, it still resembles the normal three-orbital, four-electron π system present in other 1,3 dipoles. As was pointed out earlier, nitrile ylides will react most rapidly with electron deficient alkenes in bimolecular cycloadditions since such a pair of addends possesses a narrow dipole HOMO–dipolarophile LUMO gap.[14] The same effect seems to be operating in the internal cycloadditions reported here, even though these systems cannot achieve a strictly parallel plane approach of addends. It should be noted, however, that the rate difference for the internal cycloaddition of azirines **8** and **14** is relatively small (i.e., only 10-fold). The rate constants associated with bimolecular dipolar cycloadditions of nitrile ylides generally range over many powers of 10. For example, fumaronitrile undergoes cycloaddition at a rate which is 189 000 times faster than methyl crotonate.[29] Ordinary olefins react so sluggishly that their bimolecular rate constants cannot be measured. Clearly, there has been a marked leveling of the rate profile associated with the above intramolecular cycloadditions.

Bimolecular cycloadditions exhibit large negative entropies of activation[7] since the reactants must be precisely aligned with respect to each other. The interplay of entropy and enthalpy will control the rate-determining activation process. The larger entropy term associated with the intramolecular cycloaddition will tend to compress the rate scale since the smaller the steric requirements of the transition state the less sensitive the system is toward disturbance. Thus, the high degree of order already present in the transition state for these intramolecular nitrile ylide cycloadditions could readily account for the leveling of the rate profile.

Another factor which undoubtedly plays an important role in the intramolecular 1,1-cycloaddition reaction involves the interaction of the secondary orbitals of the dipole and dipolarophile. With nitrile ylides, the in-plane vacant orbital is of lower energy than the vacant π orbital.[10] Consequently, stabilization of the transition state can be enhanced by interaction of this in-plane orbital with the dipolarophile HOMO orbital. For this to occur, a contortion away from the strictly parallel plane approach of the dipole and dipolarophile would be necessary. With these allyl-substituted 2*H*-azirines, the transition state actually involves a geometry where the p orbitals of the olefinic group have been deliberately constrained to attack perpendicular to the nitrile ylide plane. Thus, the 1,1-cycloaddition reaction will involve appreciable interaction of both the in-plane and out-of-plane π-unoccupied orbitals of the dipole with the dipolarophile-filled orbitals. This secondary orbital interaction would be expected to significantly enhance the rate of the intramolecular 1,1-cycloaddition with

unactivated olefins and could readily account for the leveling effect observed. It should be pointed out that while the secondary orbital effect is important, the relative reactivities toward internal 1,1-cycloaddition will still be controlled by the highest occupied molecular orbital of the nitrile ylide.

Experimental Section

All melting points and boiling points are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Ga. The infrared absorption spectra were determined on a Perkin-Elmer Model 137 Infracord spectrophotometer. The ultraviolet absorption spectra were measured with a Cary Model 14 recording spectrophotometer using 1-cm matched cells. The proton magnetic resonance spectra were determined at 100 MHz using a Jeolco-ML-100 and a Varian XL-100 spectrometer. Mass spectra were determined with a Perkin-Elmer RMU6 mass spectrometer at an ionizing voltage of 70 eV.

Preparation and Photolysis of 2-Methyl-2-propargyl-3-phenyl-2*H*-azirine (1). A sample of azirine 1 was prepared by the method previously outlined[2] in 38% yield: NMR ($CDCl_3$, 60 MHz) τ 8.50 (s, 3 H), 7.95 (t, 1 H, J = 3.0 Hz), 7.55 (dd, 1 H, J = 17.5 and 3.0 Hz), 7.27 (dd, 1 H, J = 17.5 and 3.0 Hz), and 2.0–2.6 (m, 5 H); IR (neat) 3300, 2128, 1740, 1600, 1585, 1495, 1450, 1375, 1235, 1200, 1075, 1010, 985, 952, 766, and 690 cm^{-1}; UV (cyclohexane) 241 nm (ϵ 11 500); MS *m/e* 169 (M^+), 128 (base), 105, 104, 103, 102, and 77.

Anal. Calcd for $C_{12}H_{11}N$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.08; H, 6.43; N, 8.31.

A solution containing 75 mg of the above azirine in 200 mL of cyclohexane was purged with an argon stream and irradiated for 15 min using a 450-W Hanovia lamp equipped with a Corex filter sleeve. Removal of the solvent under reduced pressure left a yellow oil which was subjected to preparative thick-layer chromatography using a 25% acetone–hexane mixture as the eluent. The major product was a clear oil (36 mg, 48%) whose structure was assigned as 2-phenyl-6-methylpyridine (3) by comparison with an authentic sample:[30] picrate derivative, mp 131–132 °C (lit.[30] mp 131 °C).

A trapping experiment was also carried out using methyl acrylate as the dipolarophile. A solution containing 50 mg of 1 and 12 mL of methyl acrylate in 175 mL of cyclohexane was irradiated for 15 min using a 450-W Hanovia lamp equipped with a Corex filter sleeve. The polymer which formed was filtered, and the filtrate was evaporated under reduced pressure to give 65 mg of a clear oil which was subjected to preparative thick-layer chromatography using a 15% acetone–hexane mixture as the eluent. The major band contained a 2:3 mixture of *cis*- and *trans*-4-carbomethoxy-5-methyl-2-phenyl-5-propargyl-Δ^1-pyrroline (4) as a clear oil: NMR ($CDCl_3$, 100 MHz) τ 8.74 and 8.34 (singlets, 3 H), 8.05 and 8.02 (t, J = 2.5 Hz, 1 H), 7.49 and 7.24 (t, J = 2.5 Hz, 2 H), 6.30–7.00 (m, 3 H), 6.25 (s, 3 H), 2.50–2.66 (m, 3 H), and 2.10–2.24 (m, 2 H); IR (neat) 3300, 2960, 2140, 1740, 1630, 1585, 1450, 1440, 1345, 1210, 1175, 1125, 1075, 766, and 695 cm^{-1}; MS *m/e* 255 (M^+), 254, 224, 216 (base), 196, 184, 169, 158, 157, 156, 123, 115, 105, 91, and 77.

Irradiation of 2-(2-Butynyl)-2-methyl-3-phenyl-2*H*-azirine (5). A solution containing 165 mg of 5[31] in 150 mL of cyclohexane was irradiated for 15 min using a Corex filter sleeve. The solvent was removed under reduced pressure, and the crude photolysate was subjected to preparative thick-layer chromatography using a 30% acetone–hexane mixture as the eluent. The fastest moving component contained 50 mg (31%) of 2-phenyl-3,6-dimethylpyridine (6): NMR (benzene-d_6, 100 MHz) τ 7.97 (s, 3 H), 7.54 (s, 3 H), 3.35 (1 H, d, J = 8.0 Hz), 2.98 (1 H, d, J = 8.0 Hz), 2.70–2.90 (m, 3 H), and 2.32–2.44 (m, 2 H). The structure of this material was further verified by comparison with an authentic sample;[32] picrate derivative, mp 134–135 °C (lit.[32] mp 134 °C).

The nitrile ylide derived from 5 could be trapped using methyl acrylate as the dipolarophile. A solution containing 200 mg of 5 and 10 mL of methyl acrylate in 150 mL of cyclohexane was irradiated for 15 min using a 450-W Hanovia lamp equipped with a Corex filter sleeve. The solvent was removed under reduced pressure, and the resulting residue was purified by preparative thick-layer chromatography. The major component contained 270 mg (91%) of a 1:2 mixture of the cis and trans isomers of 5-(2-butynyl)-4-carbomethoxy-5-methyl-2-phenyl-Δ^1-pyrroline (7): NMR ($CDCl_3$, 100 MHz) (isomer with methyl and carbomethoxy groups in a cis relationship) τ 8.82 (s, 3 H), 8.32 (t, 3 H, J = 2.5 Hz), 7.38 (q, 2 H, J = 2.5 Hz), 6.40–7.10 (m, 3 H), 6.36 (s, 3 H), 2.60–2.76 (m, 3 H), and 2.18–2.32 (m, 2 H); NMR ($CDCl_3$, 100 MHz) (trans isomer) τ 8.42 (s, 3 H), 8.34 (t, J = 2.5 Hz, 3 H), 7.62 (q, 2 H, J = 2.5 Hz), 6.40–7.10 (m, 3 H), 6.34 (s, 3 H), 2.60–2.76 (m, 3 H), and 2.18–2.32 (m, 2 H); IR (neat) 2940, 1735, 1635, 1585, 1500, 1440, 1330, 1205, 1165, 1125, 1020, 866, 760, and 692 cm^{-1}; MS *m/e* 269 (M^+), 268, 254, 238, 216 (base), 210, 184, 182, 158, 142, 115, 105, 91, and 77.

Irradiation of (*E*)-2-Cinnamyl-2-methyl-3-phenyl-2*H*-azirine (11). A solution containing 100 mg of azirine 11[31] in 150 mL of cyclohexane was irradiated for 8 min using a 450-W Hanovia lamp equipped with a Vycor filter sleeve. Evaporation of the solvent under reduced pressure left a clear oil whose NMR spectrum indicated it to be a mixture of unreacted starting material (50%) and 3,4-diphenyl-1-methyl-2-azabicyclo[3.1.0]hex-2-ene (12): NMR (CCl_4, 60 MHz) τ 9.76 (t, 1 H, J = 4.5 Hz), 9.07 (dd, 1 H, J = 8.0 and 4.5 Hz), 8.31 (s, 3 H), 7.72 (dd, J = 8.0 and 4.5 Hz, 1 H), 5.83 (s, 1 H), and 2.8 (m, 5 H).

Upon standing or on chromatographic workup, the crude photolysate was converted to 2,3-diphenyl-6-methylpyridine (13) in 45% yield: NMR (CF_3CO_2D, 60 MHz) τ 7.02 (s, 3 H), 2.40–2.90 (m, 10 H), 2.16 (d, 1 H, J = 8.0 Hz), and 1.50 (d, 1 H, J = 8.0 Hz); IR (neat) 3010, 2900, 1725, 1680, 1626, 1575, 1490, 1440, 1370, 1070, 756, and 697 cm^{-1}; MS *m/e* 245 (M^+), 244 (base), 202, 86, and 84.

Anal. Calcd for $C_{18}H_{15}N$: C, 88.13; H, 6.16; N, 5.71. Found: C, 88.31; H, 6.03; N, 5.46.

When the irradiation of 11 was carried out for longer periods of time and was allowed to reflux in the presence of 5% palladium on carbon, a quantitative yield of 2,3-diphenyl-6-methylpyridine (13) was obtained.

Preparation and Photolysis of (2-Methyl-3-phenyl-2*H*-azirin-2-yl)acetaldehyde (9). A solution containing 150 mg of 2-allyl-2-methyl-3-phenyl-2*H*-azirine (8)[2] in 200 mL of methanol was ozonized at −78 °C until a blue color persisted. The solution was then flushed with nitrogen, and 20 mL of dimethyl sulfide was added. The mixture was allowed to warm to 0 °C and stirred at this temperature for 4 h. The solvent was removed under reduced pressure, and the residue was extracted with petroleum ether, washed with water, and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure left a clear oil which was distilled at 25 °C (0.05 mm) to give (2-methyl-3-phenyl-2*H*-azirin-2-yl)acetaldehyde (9) in 91% yield: NMR ($CDCl_4$, 100 MHz) τ 8.64 (s, 3 H), 7.72 and 6.94 (AB pattern with J_{AB} = 17.0 Hz; each peak was further coupled into doublets with J = 1.5 and 0.5 Hz, respectively), 2.4–2.6 (m, 3 H), 2.0–2.2 (m, 2 H), and 0.24 (dd, 1 H, J = 1.5 and 0.5 Hz); IR (neat) 3010, 2890, 2820, 2690, 1720, 1680, 1600, 1485, 1447, 1370, 1198, 1115, 938, 763, and 690 cm^{-1}; UV (cyclohexane) 243 nm (ϵ 12 500), 278 (1300), and 288 (1000); MS *m/e* 173 (M^+, base), 158, 144, 130, 115, 105, 104, 91, and 77. This material was extremely sensitive and was immediately used in the next step.

The direct irradiation of 9 afforded intractable material. The irradiation of 9 was also carried out in the presence of methyl acrylate. A solution containing 100 mg of 9 and 30 mL of methyl acrylate in 130 mL of cyclohexane was irradiated for 8 min using a 450-W Hanovia lamp equipped with a Vycor filter sleeve. Removal of the solvent under reduced pressure afforded a 98% yield of (4-carbomethoxy-5-methyl-2-phenyl-Δ^1-pyrrolin-5-yl)acetaldehyde (10) as a 2:3 mixture of cis and trans isomers: NMR ($CDCl_3$, 100 MHz) (cis isomer) τ 8.88 (s, 3 H), 7.40 and 7.16 (AB pattern, J_{AB} = 16.0 Hz, further coupled into doublets with J = 1.5 Hz, 2 H), 6.52–7.10 (m, 3 H), 6.32 (s, 3 H), 2.60–2.90 (m, 3 H), 2.16–2.30 (m, 2 H), and 0.24 (t, 1 H, J = 1.5 Hz); NMR ($CDCl_3$, 100 MHz) (trans isomer) τ 8.44 (s, 3 H), 7.56 and 7.75 (AB pattern, J_{AB} = 16.0 Hz, further coupled into doublets with J = 1.5 Hz, 2 H), 6.52–7.10 (m, 3 H), 6.37 (s, 3 H), 2.60–2.90 (m, 3 H), 2.16–2.30 (m, 2 H), and 0.34 (t, 1 H, J = 1.5 Hz); IR (neat) 3030, 2940, 1736, 1623, 1580, 1450, 1342, 1205, 1170, 1136, 1020, 763, and 692 cm^{-1}; MS *m/e* 259 (M^+), 231, 230, 184, 172 (base), 170, 156, 144, 115, 105, 91, and 77.

Preparation of Methyl 4-(2-Methyl-3-phenyl-2*H*-azirin-2-yl)-2-butenoate. To a solution containing 1.73 g of (2-methyl-3-phenyl-2*H*-azirin-2-yl)acetaldehyde (9) in 20 mL of methyl chloride was added 3.5 g of carbomethoxymethylenetriphenylphosphorane.[33] The mixture was stirred for 24 h at room temperature, and then the solvent was removed under reduced pressure. The resulting oil was triturated with cyclohexane to remove the precipitated triphenylphosphine oxide. After filtration, the solution was concentrated under reduced pressure and the resulting oil was chromatographed on silica gel using a 10% acetone–hexane mixture as the eluent to give the *Z* (0.35 g, 17%; 15) and *E* (1.54 g, 67%; 14) isomers of methyl 4-(2-methyl-3-phenyl-2*H*-azirin-2-yl)-2-butenoate. The *Z* isomer 15 was identified on the basis of its characteristic spectral properties: NMR (CCl_4, 100 MHz) τ 8.64 (s, 3 H), 7.04 (ddt, 1 H, J = 16.0, 7.0, and 1.5 Hz), 6.86 (ddt, 1 H, J = 16.0, 7.0, and 1.5 Hz), 6.42 (s, 3 H), 4.28 (dt, 1 H, J = 11.0 and 1.5 Hz), 3.86 (dt, 1 H, J = 11.0 and 7.0 Hz), and 2.1–2.6 (m, 5 H); IR (neat) 3010, 2940, 1715, 1645, 1430, 1400, 1365, 1175, 1010, 820, 766, and 690 cm^{-1}; UV (cyclohexane) 243 nm (ϵ

16 700); MS *m/e* 229 (M^+), 186, 170 (base), 105, and 77.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.12; H, 6.66; N, 6.03.

The corresponding *E* isomer **14** showed the following spectral properties: NMR (CCl_4, 100 MHz) τ 8.61 (s, 3 H), 7.67 (dd, 1 H, J = 14.0 and 8.0 Hz), 7.38 (dd, 1 H, J = 14.0 and 8.0 Hz), 6.36 (s, 3 H), 4.20 (d, 1 H, J = 16.0 Hz), 3.12 (dt, 1 H, J = 16.0 and 8.0 Hz), 2.48 (m, 3 H), and 2.28 (m, 2 H); IR (neat) 3010, 2940, 1725, 1667, 1490, 1440, 1380, 1330, 1265, 1180, 1075, 1042, 982, 930, 766, and 690 cm^{-1}; UV (cyclohexane) 243 nm (ϵ 14 300); MS *m/e* 229 (M^+), 170 (base), 105, and 77.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.05; H, 6.77; N, 5.77.

Irradiation of Methyl (*E*)-4-(2-Methyl-3-phenyl-2*H*-azirin-2-yl)-2-butenoate (14). A solution containing 170 mg of **14** in 200 mL of cyclohexane was irradiated for 17 min using a 450-W Hanovia lamp equipped with a Vycor filter sleeve. Removal of the solvent left a yellow residue whose NMR spectrum revealed it to be a 1:1 mixture of *exo*- and *endo*-6-carbomethoxy-3-methyl-1-phenyl-2-azabicyclo[3.1.0]hex-2-ene (**16**): NMR ($CDCl_3$, 100 MHz) τ 7.94 and 7.84 (singlets, 3 H), 8.44 (d, 1 H, J = 4.0 Hz), 7.50–7.80 (m, 2 H), 7.24 (d, 1 H, J = 17.5 Hz), 6.60–7.00 (m, 1 H), 6.53 and 6.38 (singlets, 3 H), and 2.4–2.8 (m, 5 H); IR (neat) 1755, 1680, 1625, 1430, and 1160 cm^{-1}.

When the crude photolysate was subjected to preparative thick-layer chromatography, it was not possible to isolate the azabicyclohexenes. Instead, two new compounds were isolated and were derived by an acid-catalyzed rearrangement of **16**. The faster moving component (60%) was identified as 2-phenyl-3-carbomethyoxy-6-methylpyridine (**17**) on the basis of its spectral properties: NMR ($CDCl_3$, 100 MHz) τ 7.34 (s, 3 H), 6.32 (s, 3 H), 2.74 (1 H, d, J = 8.0 Hz), 2.46 (m, 5 H), and 1.90 (1 H, d, J = 8.0 Hz); IR (neat) 3030, 2940, 1715, 1590, 1430, 1380, 1290, 1236, 1217, 1135, 1110, 1055, 818, 803, 769, 743, and 700 cm^{-1}; MS *m/e* 227 (M^+), 212 (base), 196, and 153; UV (cyclohexane) 255 nm (ϵ 22 800).

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.06; H, 5.68; N, 6.04.

The minor component (40%) isolated from the thick-layer plate was assigned the structure of methyl (2-phenyl-5-methylpyrrol-3-yl)-acetate (**18**) on the basis of its characteristic spectra: NMR (CCl_4, 100 MHz) τ 7.80 (s, 3 H), 6.60 (s, 2 H), 6.38 (s, 3 H), 4.24 (s, 1 H), 2.6–2.9 (m, 5 H), and 2.08 (broad s, 1 H, exchanged with D_2O); IR (neat) 3380, 2910, 1755, 1600, 1520, 1430, 1260, 1200, 1015, 795, 765, and 700 cm^{-1}; UV (ethanol) 293 nm (ϵ 5800) and 217 (2700); MS *m/e* 229 (M^+), 217, 170 (base), 155, 129, 105, and 77.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.18; H, 6.46; N, 6.17.

The irradiation of azirine **14** was also carried out in the presence of a trapping agent. A solution containing 100 mg of **14** and 15 mL of methyl acrylate in 150 mL of cyclohexane was irradiated for 20 min using a 450-W Hanovia lamp equipped with a Vycor filter sleeve. Removal of the solvent under reduced pressure left 135 mg (98%) of an oil whose NMR spectrum indicated it to be a 1:1 mixture of the cis and trans isomers of methyl (*E*)-4-(4-carbomethoxy-5-methyl-2-phenyl-Δ^1-pyrrolin-5-yl)-2-butenoate (**19**). The mixture of isomers could not be separated but showed the following properties: NMR (CCl_4, 100 MHz) τ 8.86 and 8.48 (singlets, 3 H), 7.80 (dd, 1 H, J = 16 and 8.0 Hz), 7.28 (dd, 1 H, J = 16.0 and 8.0 Hz), 6.30–7.06 (m, 3 H), 6.30 (s, 3 H), 7.26 and 6.24 (singlets, 3 H), 4.16 (d, 1 H, J = 16.0 Hz), 3.10 (dt, 1 H, J = 16.0 and 8.0 Hz), and 2.10–2.76 (m, 5 H); IR (neat) 2915, 1725, 1655, 1600, 1570, 1430, 1330, 1265, 1198, 1010, 763, and 693 cm^{-1}; UV (cyclohexane) 243 nm (ϵ 17 200); MS *m/e* 315 (M^+), 284, 256, 216, 212, 170, 156, 119, 117, 105 (base), and 77.

Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.90; H, 6.91; N, 4.13.

Irradiation of Methyl (*Z*)-4-(2-Methyl-3-phenyl-2*H*-azirin-2-yl)-2-butenoate (15). A solution containing 80 mg of **15** in 150 mL of cyclohexane was irradiated for 15 min using a 450-W Hanovia lamp equipped with a Vycor filter sleeve. Removal of the solvent afforded a 1:1 mixture of the same *exo*- and *endo*-2-azabicyclo[3.1.0]hex-2-enes **16** as was obtained from the irradiation of the *E* isomer. Preparative thick-layer chromatography of the mixture afforded pyridine **17** and pyrrole **18**.

The irradiation of the (*Z*)-azirine **15** was also carried out in the presence of methyl acrylate. A solution containing 75 mg of **15** and 10 mL of methyl acrylate in 150 mL of cyclohexane was irradiated for 15 min with a 450-W Hanovia lamp equipped with a Vycor filter sleeve. Removal of the solvent under reduced pressure followed by preparative thick-layer chromatography using a 25% acetone–hexane mixture as the eluent gave 95 mg (91%) of a mixture (2:3) of the cis and trans isomers of methyl (*Z*)-4-(4-carbomethoxy-5-methyl-2-phenyl-Δ^1-pyrrolin-5-yl)-2-butenoate (**19**) which could not be separated: NMR ($CDCl_3$, 100 MHz) τ 8.78 and 8.40 (singlets, 3 H), 6.28–7.20 (m, 5 H), 6.28 and 6.24 (s, 3 H), 6.22 and 6.20 (s, 3 H), 4.08 and 3.96 (d, 1 H, J = 12.0 Hz), 3.52 (dt, 1 H, J = 12.0 and 8.0 Hz), and 2.0–2.56 (m, 5 H); IR (neat) 2960, 1730, 1640, 1590, 1445, 1350, 1190, 1045, 831, 769, and 695 cm^{-1}; UV (cyclohexane) 243 nm (ϵ 16 400); MS *m/e* 315 (M^+), 284, 256, 216, 184, 170, 157, 156, 115, 113, 105 (base), and 77.

Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.37; H, 6.64; N, 4.38.

Preparation of (3-Methyl-2-phenyl-2*H*-azirin-2-yl)acetaldehyde. A solution containing 150 mg of 2-allyl-3-methyl-2-phenyl-2*H*-azirine[2] in 200 mL of methanol was ozonized at −78 °C until a blue color persisted. The solution was flushed with nitrogen, and 20 mL of dimethyl sulfide was added. The mixture was allowed to warm to 0 °C and stirred at this temperature for 4 h. The solvent was removed under reduced pressure, and the residue was extracted with ether, washed with water, and dried over sodium sulfate. The remaining oil was quite labile to atmosphere conditions and was immediately used in a Wittig reaction. The crude azirinyl aldehyde exhibited the following spectral properties: NMR ($CDCl_3$, 100 MHz) τ 7.58 (s, 3 H), 7.24 (d, 1 H, J = 18.0 Hz), 6.84 (d, 1 H, J = 18.0 Hz), 2.6–3.0 (m, 5 H), and 0.30 (s, 1 H); IR (neat) 3010, 2950, 2700, 1730, 1590, 1495, 1450, 1370, 1100, 770, and 698 cm^{-1}; MS *m/e* 158 (M^+ and base).

Preparation of Methyl (*E*)-4-(3-Methyl-2-phenyl-2*H*-azirin-2-yl)-2-butenoate (20). Treatment of 175 mg of (2-phenyl-3-methyl-2*H*-azirin-2-yl)acetaldehyde with 400 mg of carbomethoxymethylenetriphenylphosphorane in an analogous fashion to that used to prepare **14** gave 181 mg (79%) of methyl (*E*)-4-(3-methyl-2-phenyl-2*H*-azirin-2-yl)-2-butenoate (**20**): NMR (CCl_4, 100 MHz) τ 7.64 (s, 3 H), 7.24 (ddt, 1 H, J = 15.5, 6.5, and 1.5 Hz), 7.04 (ddt, 1 H, J = 15.5, 6.5, and 1.5 Hz), 6.42 (s, 3 H), 4.22 (dt, 1 H, J = 16.0 and 1.5 Hz), 3.26 (dt, 1 H, J = 16.0 and 6.5 Hz), and 2.7–3.0 (m, 5 H); IR (neat) 3030, 2910, 2800, 1754, 1710, 1650, 1600, 1495, 1430, 1265, 1205, 1160, 1075, 1020, 980, 770, and 693 cm^{-1}; UV (cyclohexane) 253 nm (ϵ 12 600); MS *m/e* 229 (M^+), 214, 170 (base), 157, 130, 115, 91, and 77.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.21; H, 6.46; N, 6.08.

Irradiation of Methyl (*E*)-4-(3-Methyl-2-phenyl-2*H*-azirin-2-yl)-2-butenoate (20). A solution containing 120 mg of azirine **20** in 150 mL of cyclohexane was irradiated for 7.5 min using a 450-W Hanovia lamp equipped with a Vycor filter sleeve. Removal of the solvent under reduced pressure left a yellow oil whose NMR spectrum showed a complex pattern from τ 6.0–9.0. Purification of the crude photolysis mixture by thick-layer chromatography resulted in the isolation of 45 mg of 2-methyl-3-carbomethoxy-6-phenylpyridine (**21**): NMR (CCl_4, 100 MHz) τ 7.16 (s, 3 H), 6.06 (s, 3 H), 2.60–2.74 (m, 3 H), 2.48 (d, 1 H, J = 8.0 Hz), 1.96–2.08 (m, 2 H), and 1.88 (d, 1 H, J = 8.0 Hz); IR (neat) 2900, 1720, 1575, 1430, 1370, 1265, 1190, 1150, 1087, 768, and 694 cm^{-1}; MS *m/e* 227 (M^+, base), 212, 196, 169, 168, 167, 141, 115, 91, and 77. When a mixture of the crude photolysate and 5% palladium on carbon in benzene was heated at reflux, the only product obtained in 74% yield was 2-methyl-3-carbomethoxy-6-phenylpyridine (21).

The structure of this material was further verified by aqueous hydrolysis to the known carboxylic acid.[20] A solution containing 25 mg of the above pyridine in 10 mL of a 50% dioxane-water mixture containing 100 mg of potassium hydroxide was heated at reflux for 4 h. The solution was cooled, acidified with hydrochloric acid, and extracted with chloroform. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give a quantitative yield of 2-methyl-3-carboxy-6-phenylpyridine (**22**): mp 194–196 °C (lit.[20] mp 196 °C); NMR (Me_2SO-d_6, 100 MHz) τ 7.18 (s, 3 H), 2.40–2.52 (m, 3 H), 1.76–1.90 (m, 2 H), and 1.72 and 2.08 (AB doublet, J = 8.0 Hz, 2 H); IR (KBr) 3300–2100, 1680, 1610, 1495, 1395, 1280, 1188, 1149, 1090, 1070, 930, 855, 775, 755, 706, 694, and 687 cm^{-1}; MS *m/e* 213 (M^+, base), 196, 195, 169, 168, 157, 115, 105, and 93.

Preparation of 4-(3-Methyl-2-phenyl-2*H*-azirin-2-yl)-2-butenonitrile (23). The method used to prepare this azirine was essentially identical with that used to prepare **20.** To a solution containing 9 mmol of the aldehyde in 27 mL of methylene chloride was added 3.6 g of cyanomethylenetriphenylphosphorane[34] in 10 mL of methylene chloride. After stirring for 25 h, the solvent was removed and the crude reaction mixture was subjected to silica gel chromatography using a 5% acetone–hexane mixture as the eluent. The major product obtained in 27% yield was identified as (*E*)-4-(3-methyl-2-phenyl-2*H*-azirin-2-yl)-2-butenonitrile (**23**): bp 85 °C (0.02 mm); NMR (CCl_4, 100 MHz) τ 7.64 (s, 3 H), 7.34 (ddd, 1 H, J = 16.5, 6.5, and 1.6 Hz), 7.07 (ddd, 16.5, 6.5, and 1.6 Hz), 4.70 (dt, 1 H, J = 16.0 and 1.6 Hz), 3.52 (dt, 1 H, J = 16.0 and 6.5 Hz), and 2.72–3.16 (m, 5

H); IR (neat) 3010, 2900, 2217, 1755, 1630, 1590, 1490, 1440, 1420, 1360, 1253, 971, 770, and 696 cm^{-1}; UV (cyclohexane) 255 nm (ϵ 2090); MS *m/e* 196 (M^+), 195, 181, 169, 168 (base), 154, 144, 127, 115, 103, and 93.

Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.28. Found: C, 79.34; H, 6.01; N, 14.03.

The minor product (23%) obtained from the column was identified as the *Z* isomer: NMR (CCl_4, 100 MHz) τ 7.62 (s, 3 H), 7.20 (ddd, 1 H, J = 15.5, 7.0, and 1.3 Hz), 4.72 (dt, 1 H, J = 11.0 and 1.3 Hz), 3.67 (dt, 1 H, J = 11.0 and 7.0 Hz), and 2.72–3.04 (m, 5 H); IR (neat) 3030, 2940, 2230, 1779, 1630, 1610, 1505, 1450, 1430, 1355, 1250, 1165, 1075, 760, and 699 cm^{-1}; UV (cyclohexane) 255 nm (ϵ 1750); MS *m/e* 196 (M^+), 181, 169, 168 (base), 154, 144, 103, and 92.

Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.28. Found: C, 79.51; H, 6.19; N, 14.28.

Irradiation of 4-(3-Methyl-2-phenyl-2*H*-azirin-2-yl)-2-butenonitrile (23). A solution containing 50 mg of either the *E* or *Z* isomer of azirine **23** in 150 mL of benzene was irradiated for 15 min using a 450-W Hanovia lamp equipped with a Vycor filter sleeve. Removal of the solvent under reduced pressure left a yellow oil whose NMR spectrum contained a series of bands from τ 7.2 to 9.0. The crude photolysate was dissolved in 5 mL of benzene, 25 mg of 5% palladium on carbon was added, and the mixture was heated at reflux for 4 h. Filtration of the crude reaction mixture and evaporation of the solvent under reduced pressure left a yellow-brown solid which was recrystallized from pentane to give 38 mg (76%) of 2-methyl-3-cyano-6-phenylpyridine (**24**): mp 127–128 °C; NMR ($CDCl_3$, 100 MHz) τ 7.13 (s, 3 H), 2.36–2.48 (m, 3 H), 2.24 (d, 1 H, J = 8.5 Hz). 1.80–1.96 (m, 2 H), and 1.96 (d, 1 H, J = 8.5 Hz); IR (KBr) 2220, 1575, 1550, 1440, 1375, 1300, 1282, 1120, 864, 840, 787, 741, and 693 cm^{-1}; MS *m/e* 194 (M^+, base), 193, 102, and 77.

Anal. Calcd for $C_{13}H_{10}N_2$: C, 80.38; H, 5.19; N, 14.42. Found: C, 80.16; H, 5.50; N, 14.44.

Further support for the structure of pyridine **24** was obtained by its hydrolysis to the known carboxylic acid **22**.[20] A solution containing 70 mg of **24** and 200 mg of potassium hydroxide in 20 mL of a 50% water–dioxane mixture was heated at reflux for 4 h. The solution was then acidified with hydrochloric acid, extracted with chloroform, and dried over magnesium sulfate. Removal of the solvent gave a pure sample of 2-methyl-3-carboxy-6-phenylpyridine (**22**), mp 194–196 °C.

The irradiation of **23** was also carried out in the presence of a trapping agent. A solution containing 35 mg of **23** and 20 mL of methyl acrylate in 50 mL of benzene was irradiated for 15 min using a 450-W Hanovia lamp equipped with a Vycor filter sleeve. Removal of the solvent followed by preparative thick-layer chromatography gave 28 mg of a mixture of the cis and trans (1:1) isomers of 4-(4-carbomethoxy-2-methyl-5-phenyl-Δ^1-pyrrolin-5-yl)-2-butenonitrile (**25**): NMR ($CDCl_3$, 100 MHz) τ 7.84 (s, 3 H), 7.50 (s, 3 H), 6.52–7.40 (m, 5 H), 6.20 (s, cis), 4.84 (dt, 1 H, J = 17.0 and 2.0 Hz), 4.54 (dt, 1 H, J = 17.0 and 2.0 Hz), 3.44 (dd, 1 H, J = 10.0 and 6.5 Hz), 3.28 (dd, 1 H, J = 10.0 and 6.5 Hz), and 2.50–3.00 (m, 5 H); IR (neat) 2935, 2220, 1725, 1665, 1640, 1495, 1430, 1360, 1258, 1175, 966, 770, and 698 cm^{-1}; MS *m/e* 196, 195, 194, 169, 168 (base), 103, 93, and 77.

Quantum Yield Determinations. All quantitative measurements were made on a rotating assembly at room temperature using a Rayonet reactor equipped with 2537-Å lamps. Samples were degassed to 5×10^{-3} mm in three freeze–thaw cycles and then sealed. Cyclopentanone solutions were used as the chemical actinometer, for which a quantum yield of 0.38 was used,[21] giving a reproducible lamp output of 1.73×10^{17} quanta s^{-1}. After irradiation, the degree of reaction was determined by quantitative NMR spectroscopy. The conversions were run to 15% or less.

Competitive studies were carried out photochemically on mixtures of an arylazirine, an internal standard, and methyl acrylate as an external dipolarophile. Since cycloaddition rates varied considerably between systems, tubes were removed periodically and analyzed periodically by NMR spectroscopy until optimum conversion times for analysis had been determined. All measurements were made on a "merry-go-round" assembly at room temperature using a 2437-Å source. Varying quantities of methyl acrylate were added to solutions of the azirine, and the final peak areas of rearranged product were determined by NMR spectroscopy after ca. 30% of the starting material had been consumed.

Acknowledgment. We gratefully acknowledge support of this work by the National Science Foundation and the Hoffmann-La Roche Co. Aid in the purchase of the NMR spectrometer (XL-100) used in this work was provided by the NSF via an equipment grant.

Registry No.—**1**, 66416-62-4; **3**, 46181-30-0; *cis*-**4**, 66416-64-6; *trans*-**4**, 66416-63-5; **5**, 65495-91-2; **6**, 27068-69-5; *cis*-**7**, 66416-66-8; *trans*-**7**, 66416-65-7; **8**, 56434-95-8; **9**, 66416-67-9; *cis*-**10**, 66416-68-0; *trans*-**10**, 66538-26-9; **11**, 65495-83-2; **12**, 66416-42-0; **13**, 66416-43-1; **14**, 66416-61-3; **15**, 66416-60-2; *exo*-**16**, 66416-44-2; *endo*-**16**, 66513-14-2; **17**, 66416-45-3; **18**, 66416-46-4; (*E*)-*cis*-**19**, 66416-47-5; (*E*)-*trans*-**19**, 66416-54-4; (*Z*)-*cis*-**19**, 66416-55-5; (*Z*)-*trans*-**19**, 66416-56-6; **20**, 65495-71-8; **21**, 66416-48-6; **22**, 66416-49-7; (*E*)-**23**, 66416-50-0; (*Z*)-**23**, 66416-51-1; **24**, 66416-52-2; *cis*-**25**, 66416-53-3; *trans*-**25**, 66538-25-8; **26**, 59175-24-5; **27**, 66416-59-9; **28**, 59175-18-7; methyl acrylate, 96-33-3; carbomethoxymethylenetriphenylphosphorane, 2605-67-6; 2-allyl-3-methyl-2-phenyl-2*H*-azirine, 59175-18-7; cyanomethylenetriphenylphosphorane, 16640-68-9.

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Transmission of Substituent Effects across Both Double Bonds of Allenes. Rates and Products of Addition of Arenesulfenyl Chlorides to Allene and Its Methyl-Substituted Derivatives[1]

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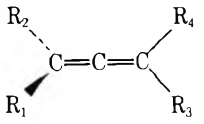
Received May 8, 1978

The rates and products of addition of benzenesulfenyl chloride in methylene chloride and 4-chlorobenzenesulfenyl chloride in 1,1,2,2-tetrachloroethane to allene and its five methyl-substituted derivatives have been determined. Substituting the hydrogens on allene by methyl groups has a large effect upon the rate of addition. The rates of addition to 2,3-pentadiene and 3-methyl-1,2-butadiene are almost identical, indicating that the effect of a methyl group is transmitted across both double bonds. Products are formed by addition to both double bonds. The mechanistic implication of these results is discussed.

The effect of substituents upon molecular properties has been a subject of continuing interest to chemists. Considerable effort has been made to learn how substituents affect the positions of equilibria and the rates of many chemical reactions. Most of what is known about the transmission of substituent effects from one part of a molecule to another has been obtained from studies on aromatic or simple aliphatic compounds. While the reactions of propadiene (allene) and its derivatives have been extensively studied,[3-5] little is known about the ability of the two double bonds in allene to transmit substituent effects. To study this problem, we have examined the effect of progressively substituting the hydrogens on allene by methyl groups on the rates and products of addition of arenesulfenyl chlorides. The results, reported in this paper, support the view that substituent effects are transmitted across both double bonds in electrophilic additions to allenes.

Results

We have measured the rates of addition of benzenesulfenyl chloride (**1**) in methylene chloride and 4-chlorobenzenesulfenyl chloride (**2**) in 1,1,2,2-tetrachlorethane to allene (**3**) and its five methylated derivatives (**4**–**8**) at 25 °C by means of the

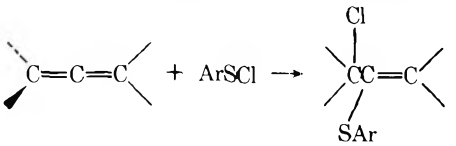


3, $R_1 = H; R_2 = H; R_3 = H; R_4 = H$
4, $R_1 = H; R_2 = H; R_3 = H; R_4 = CH_3$
5, $R_1 = CH_3; R_2 = H; R_3 = CH_3; R_4 = H$
$R_1 = H; R_2 = CH_3; R_3 = H; R_4 = CH_3$
6, $R_1 = H; R_2 = H; R_3 = CH_3; R_4 = CH_3$
7, $R_1 = CH_3; R_2 = H; R_3 = CH_3; R_4 = CH_3$
8, $R_1 = CH_3; R_2 = CH_3; R_3 = CH_3; R_4 = CH_3$

stopped-flow technique using a Durrum–Gibson stopped-flow spectrophotometer. The rates of disappearance of **1** and **2** were followed by measuring the decrease in their absorptions at 392 nm. The additions were found to exhibit second-order kinetics, first order in both allene and arenesulfenyl chloride, to at least 80% completion of the reaction. The observed rate constants which are averages of at least three measurements are given in Table I.

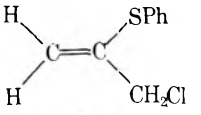
The initially observed products of the addition of arenesulfenyl chlorides to allenes are 1:1 adducts. Their structures were determined by proton and carbon-13 magnetic resonance spectroscopy. The regiochemistry of the adducts was established from the chemical shifts of the protons and carbons α to chlorine. This assignment is based upon the observation that protons and carbons α to chlorine are deshielded relative to those α to sulfur.[7] The proton and carbon-13 data for the adducts and several model compounds are given in Tables II and III.

Several workers have reported that the addition of sulfenyl chlorides to allenes forms products in which the sulfur is bonded to the vinyl carbon (eq 1).[4,8,9] Our results are in



(1)

agreement. Thus, the chemical shifts of the methylene protons of the product of the addition of benzenesulfenyl chloride to allene are similar to those of 2,3-dichloropropene. Furthermore the one-bond C–H coupling constant for the methylene carbon, 152.3 Hz, is in the range expected for a carbon directly bonded to a halogen: e.g., CH_3Cl, J = 148.6 Hz; CH_3Br, J = 150.05 Hz; CH_3I, J = 150.3 Hz. A smaller coupling constant would be expected for a carbon bonded to sulfur; e.g., $(CH_3)_2S$, J = 138 Hz.[10] Thus, the use of both proton and carbon-13 magnetic resonance spectroscopy establishes the structure of the adduct as **9**, in accord with the results of Mueller and



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Butler.[8] The regiochemistry of the other adducts can be established in a similar manner from the data in Tables II and III.

The additions to **4**, **5**, and **7** form E and Z isomeric adducts whose structures were established by carbon-13 magnetic resonance spectroscopy. The assignments are based upon the well-established relationship that the carbon-13 chemical shifts of carbons bonded to a carbon–carbon double bond appear at higher field when the carbons are oriented cis to another functional group than when they are trans to it.[11]

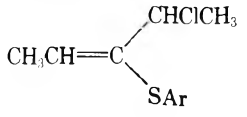
After standing for several hours at 25 °C, the NMR spectrum of the product is observed to change in some cases. For propadiene (**3**), this change is due to formation of the diadduct. When E and Z isomers are formed as products, an increase in the amount of the Z isomer is observed at the expense of the E isomer. The formation of the diadduct can be explained by the well-established reversibility of the additions of arenesulfenyl chlorides to alkenes,[6] while the latter isomerization is due to an allylic rearrangement. These observations suggest that the product composition may change during the addition. We are unable to check this because the rates of addition are too fast. Consequently, we cannot establish conclusively that the observed products are those of kinetic control.

Table I. Second-Order Observed Rates of Addition of Arenesulfenyl Chlorides to a Series of Allenes at 25 °C

compd	benzenesulfenyl chloride in CH_2Cl_2		4-chlorobenzenesulfenyl chloride in TCE[a]	
	k_{obsd}, M^{-1} s^{-1}	k_{rel}	k_{obsd}, M^{-1} s^{-1}	k_{rel}
$CH_2{=}C{=}CH_2$ (3)	0.698	1.0	2.65	1.0
$CH_2{=}C{=}CHCH_3$ (4)	12.9	18.5	115	43
$CH_3CH{=}C{=}CHCH_3$ (5)	171	245	554	213
$CH_2{=}C{=}C(CH_3)_2$ (6)	159	230	512	193
$CH_3CH{=}C{=}C(CH_3)_2$ (7)	1039	1488	3760	1418
$(CH_3)_2C{=}C{=}C(CH_3)_2$ (8)	2360	3400	8605	3309

[a] TCE = 1,1,2,2-tetrachloroethane.

The percentage of each product was determined from the integrated area of nonoverlapping peaks in the proton spectrum (either 60 or 100 MHz) immediately after mixing. The initially observed product distribution for each allene is given in Table IV. These results are in agreement with previous results with one exception. Jacobs has reported that the addition of 2,4-dinitrobenzenesulfenyl chloride to **5** forms the two regioisomers **10** and **11**.[4a] We believe that the NMR data



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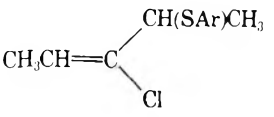

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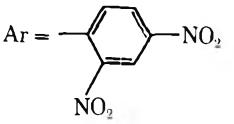
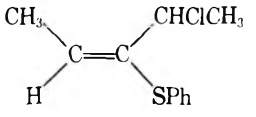


are better explained by a product composition consisting of a mixture of (*E*)- and (*Z*)-4-chloro-2-penten-3-yl phenyl sulfide (**12** and **13**, respectively). This conclusion is based upon



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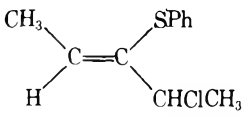

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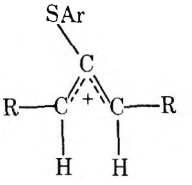
the following facts. Firstly carbon and protons geminal or vicinal to chlorine are considably deshielded relative to sulfur.[7] Therefore, it would be surprising that the chemical shifts of the methyl groups bonded to the saturated carbon are nearly identical for the two isomers.[12] Similarly, the carbon-13 chemical shifts at δ 55.14 and 61.29 are in the region expected for such a carbon bonded to chlorine. If bonded to sulfur, its chemical shift would be at δ 45 based upon the carbon-13 spectra of the model compounds (*E*)-(2*RS*,5*RS*)- and (*E*)-(2*RS*,5*SR*)-5-chloro-3-hexen-2-yl 4′-chlorophenyl sulfide. Finally, the mass spectra of both **12** and **13** give rise to $M^+ - 63$ fragments (*m/e* 149) corresponding to the loss of C_2H_4Cl radicals. In neither case were ions observed at *m/e* 137, which would correspond to the loss of a $C_2H_4SC_6H_5$ fragment. Consequently, we conclude that the regiochemistries of **12** and **13** are identical and that they are *E* and *Z* isomers. A similar result has been observed in the methoxymercuration of **5**.[5a]

Discussion

From the rate data in Table I, it is clear that substituting the hydrogens on allene by methyl groups has a large effect on the observed rate of addition. The effect is almost multiplicative. A plot of log k_2 vs. the number of methyl groups shows a slight curvature, unlike a similar plot for ethylene which is linear.[13] Particularly interesting is the similarity of the observed rates of addition to **5** and **6** in the same solvent, indicating that the polar effect of a methyl group is not restricted to the double bond to which it is bonded.

Rearrangement of the allenes to either isomeric alkynes or dienes does not occur prior to addition. This is evident from the rates of addition to the allenes, which are all faster than the addition to isomeric alkynes[14] or dienes[15] under identical conditions.

Two mechanisms can be proposed to account for the observed effect of the methyl groups. One involves an allylic intermediate **14**, while the other involves a thiiranium ion (or ion pair) intermediate **15**.[16,17] The former mechanism involves



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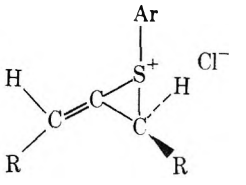

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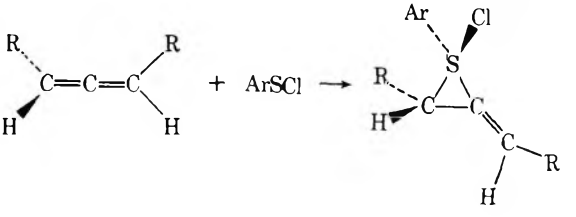
a rate-determining transition state that must resemble the intermediate ion **14**. Rate-determining formation of **14** directly from the allene requires bond rotation in the allene portion while bond formation occurs with the electrophile. Such a concerted process seems unlikely. Alternatively, it is possible that a sulfurane such as **16** may be formed first, which



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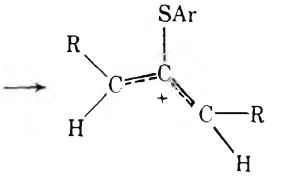
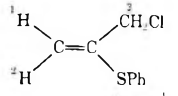
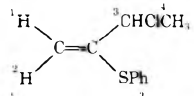
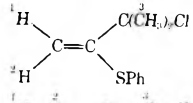
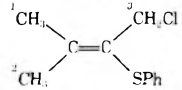
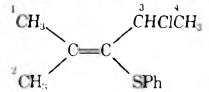
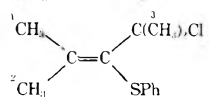


then undergoes a rate-determining ring opening. For the addition to unsymmetrical allenes, such a mechanism would involve at least two sulfuranes and consequently two or more competing paths.

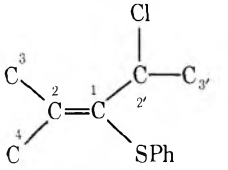
A bridged rate-determining transition state is in accord with the usual mechanism of electrophilic additions of arenesulfenyl chlorides to alkenes and alkynes.[18] For the addition to unsymmetrical allenes, such a mechanism would involve the formation of the two intermediates **17** and **18**. We cannot establish experimentally that the intermediates **17** and **18** are formed irreversibly. Therefore we cannot use the product composition to obtain the ratio k_1/k_1', and consequently we are limited to comparing observed rate constants. Despite this limitation, it is possible to compare the rates of addition of

Table II. Observed Proton Magnetic Resonance Parameters for the Benzenesulfenyl Chloride Adducts

compd	registry no.	chemical shift assignments ($CDCl_3$),[a] δ				coupling constants, Hz						
		H_1	H_2	H_3	H_4	$J^{cis}_{HC=CCH}$	$J^{trans}_{HC=CCH}$	$J^{cis}_{HCC=CCH}$	$J^{trans}_{HCC=CCH}$	$^2J_{H_1H_2}$	$^3J_{H_1H_2}$	$^3J_{H_3H_4}$
	15893-06-8	5.63 dd	5.30 m	4.07 dd		0.9	≤0.4			≤0.4		
	67145-68-0	5.88 dd	5.13 d	4.58 qd	1.73 d	1.0	≤0.3			0.72		6.8
	67145-69-1	5.45 d	4.87 d	1.87 s						1.08		
$CH_3CH{=}C(SPh)CH_2Cl$ (Z)	67145-70-4	1.93 dt	6.43 qt	4.07 q′		1.2			0.9		6.9	
$CH_3CH{=}C(SPh)CH_2Cl$ (E)	67145-71-5	1.88 d	6.19 q	4.15 s			≤0.3	≤0.3			7.0	
	67145-72-6	1.90 s	1.93 t	4.50 q					1.0			
$CH_3CH{=}C(SPh)CHClCH_3$ (Z)	67145-73-7	1.83 dq	6.55 qd	4.80 qqd	1.61 d	0.5					7.25	7.00
$CH_3CH{=}C(SPh)CHClCH_3$ (E)	67145-74-8	1.82 d	5.95 q	5.15 q	1.60 d		≤0.4				6.75	6.60
$CH_3CH{=}C(SPh)C(CH_3)_2Cl$ (Z)	67145-75-9	1.85 d	6.71 q	1.90 s							6.8	
$CH_3CH{=}C(SPh)C(CH_3)_2Cl$ (E)	67145-76-0	1.82 d	6.03 q	1.90 s							6.9	
	67145-77-1	1.93 s	1.91 d	4.96 m	1.66 d				0.86			6.9
	67145-78-2	1.9 bs	1.9 bs	1.88 s								

[a] s = singlet, d = doublet, t = triplet, q = quartet, q′ = quintet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, dqq = doublet of quartets of quartets, bs = broad singlet.

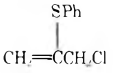
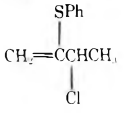
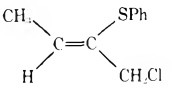
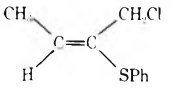
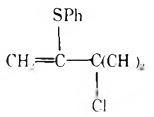
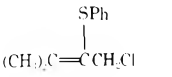
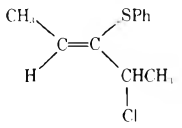
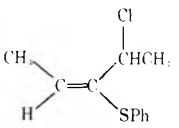
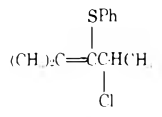
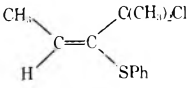
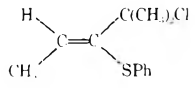
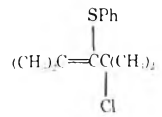
Table III. Observed Carbon-13 Magnetic Resonance Parameters for the Benzenesulfenyl Chloride Adducts



compd	chemical shifts, δ						coupling constants, Hz		
	C_4	C_3	C_2	C_1	$C_{2'}$	$C_{3'}$	$J_{C=CCH}$	$J^{cis}_{CC=CH}$	$J^{trans}_{CC=CH}$
$H_2C{=}C(SPh)CH_2Cl$			119.52	129.29	46.03		4.5	6.3	11.5
$H_2C{=}C(SPh)CHClCH_3$			116.82	146.89	58.47	24.83	4.2	4.8	11.3
$H_2C{=}C(SPh)C(CH_3)_2Cl$			113.61	152.48	70.40	32.66	4.5		
$CH_3CH{=}C(SPh)CH_2Cl$ (*Z*)	15.76		130.04	135.18	48.12			6.5	
$CH_3CH{=}C(SPh)CH_2Cl$ (*E*)		15.10	128.93	136.39	41.33				8.7
$(CH_3)_2C{=}C(SPh)CH_2Cl$	29.78	20.64	125.93	137.83	45.35				
$CH_3CH{=}C(SPh)CHClCH_3$ (*Z*)	15.81				61.29	24.75		4.2	
$CH_3CH{=}C(SPh)CHClCH_3$ (*E*)		14.84			55.14	23.83			11.7
$CH_3CH{=}C(SPh)C(CH_3)_2Cl$ (*Z*)	16.79				67.41	33.28		5.1	
$CH_3CH{=}C(SPh)C(CH_3)_2Cl$ (*E*)		14.99			62.53	33.12			12.3
$(CH_3)_2C{=}C(SPh)CHClCH_3$	29.99	21.36			65.52	25.02			
$CH_3CH(SAr)CH{=}CHCHClCH_3$[a] (*E*)									
(2*RS*,5*RS*)		45.45	132.59	132.94	56.96	25.18			
(2*RS*,5*SR*)		45.30	132.41	132.70	56.82	25.09			

[a] Model compound.

Table IV. Products of the Addition of Benzenesulfenyl Chloride to Allene and Its Methyl-Substituted Derivatives

allene	products		
propadiene			
1,2-butadiene	 71%[a]	 20%[a]	 12%[a]
3-methyl-1,2-butadiene	 74%[a]	 20%[a]	elimination products 6%
2,3-pentadiene	 55%[a]	 45%[a]	
2-methyl-2,3-pentadiene	 15%[a]	 32%[a]	 40%[a] elimination products 13%
2,4-dimethyl-2,3-pentadiene	 25%	elimination products 75%	

[a] New compounds.

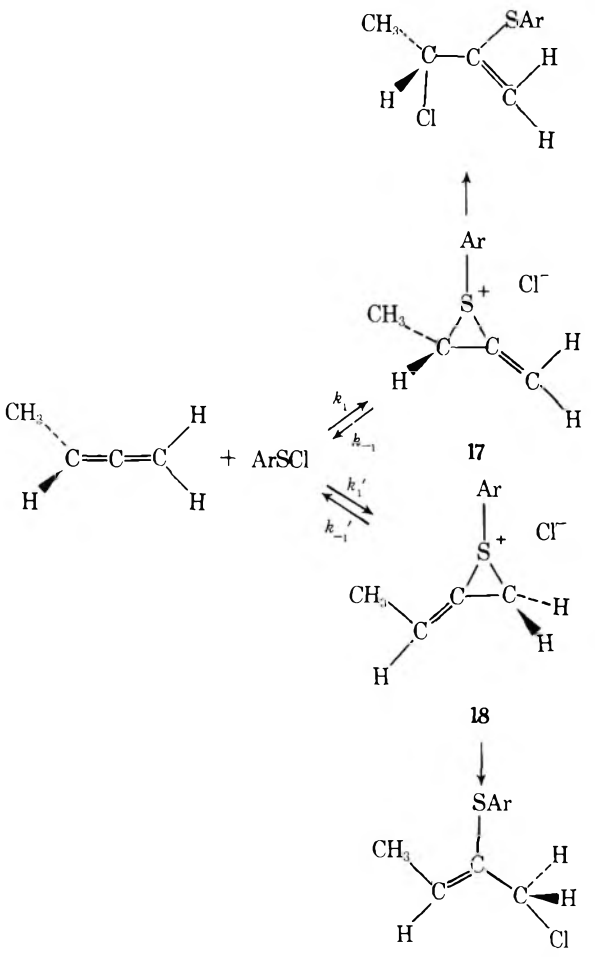
4-chlorobenzenesulfenyl chloride to methyl-substituted ethylenes and allenes. Such a comparison is made in Table V.

Evidence of transmission of substituent effects across both double bonds is found in the relative rates of addition to the symmetrical allenes. If both double bonds were completely independent of each other, it would be expected that the ratio of rates of addition to **3**, **5**, and **8** would parallel those of addition to ethylene, propene, and methylpropene. This is not the case. The ratio of the rates of addition to the ethylene

Table V. Rates of Addition of 4-Chlorobenzenesulfenyl Chloride to a Series of Methyl-Substituted Ethylenes and Allenes in 1,1,2,2-Tetrachloroethane at 25 °C

allenes	k_{obsd} allenes, M^{-1} s^{-1}	k_2 ethylenes, M^{-1} s^{-1}	ethylenes[a]	no. of methyl groups
$CH_2=C=CH_2$ (3)	2.65	65.1	$CH_2=CH_2$	0
$CH_3CH=C=CH_2$ (4)	115	205	$CH_3CH=CH_2$	1
$(CH_3)_2C=C=CH_2$ (6)	512	551	$(CH_3)_2C=CH_2$	2
$CH_3CH=C=CHCH_3$ (5)	554	1340	$CH_3CH=CHCH_3$ (cis)	2
		434	$CH_3CH=CHCH_3$ (trans)	2
$(CH_3)_2C=C=CHCH_3$ (7)	3760	3030	$(CH_3)_2C=CHCH_3$	3
$(CH_3)_2C=C=C(CH_3)_2$ (8)	8605	7760	$(CH_3)_2C=C(CH_3)_2$	4

[a] Data from ref 13.



derivatives is 1:3.2:8.5, while the ratio for the allene derivatives is 1:210:3200.

Furthermore, from the data in Table V it is clear that except for allene, ethylene, and *cis*-2-butene the observed rates of addition are similar for ethylenes and allenes containing the same number of methyl groups. Such a result is surprising when compared to the difference in rates of addition to ethylene and allene. This means that the difference in transition state energies is larger than the difference in ground state energies on addition to ethylene vs. allene. In contrast, the difference in the ground state energies is about the same as the difference in the transition state energies for the addition to 2,3-pentadiene vs. *trans*-2-butene since their rates of addition are almost the same. Thus, the rate-determining transition state is stabilized equally well by a methyl as by an ethylidene (=$CHCH_3$) group. From the data, it seems that the isopropylidene (=$C(CH_3)_2$) group is as good as two methyl groups in stabilizing the rate-determining transition state.

Our data do not permit us to distinguish between the two mechanistic possibilities: one involving an allylic ion intermediate **14** and the other a thiiranium ion **15**. However, the thiiranium ion (or ion pair) mechanism becomes slightly more attractive when the data of previous workers are considered. Caserio[5a] has reported that the bromination of (*R*)-(−)-2,3-pentadiene in CCl_4 or methanol occurs in a highly anti stereoselective manner. In general, the additions of arenesulfenyl chlorides to alkenes and alkynes occur with a higher degree of anti stereoselectivity than does bromination. Thus, it would be expected that the stereochemistry of the addition of 4-chlorobenzenesulfenyl chloride to (*R*)-(−)-2,3-pentadiene would be similar.

In support of this view, Jacobs found that the addition of 2,4-dinitrobenzenesulfenyl chloride to 2,2-dimethyl-3,4-hexadienol, of unspecified absolute configuration, yielded active 3-(2,4-dinitrophenylthio)-1,5,5-trimethyl-Δ^3-dihydropyran.[4c] Unfortunately, neither the optical purities nor the relative configurations of either the product or starting allene were determined. Consequently, it is impossible to establish the stereospecificity of the addition.

While we cannot conclusively establish the mechanism of this addition, it is clear from our data that the effects of substituents are readily transmitted across both double bonds of allene.

Experimental Section

Microanalyses were carried out by A. B. Gygli Microanalysis Laboratory, Toronto, Can. ^1H NMR spectra were obtained on a Varian T-60 or HA-100 spectrometer. ^{13}C NMR spectra were obtained on a Varian CFT-20 spectrometer using a 16K memory. Chloroform-*d* was used as an internal lock and reference. All spectra were referenced to tetramethylsilane as an internal standard.

4-Chlorobenzenesulfenyl chloride was prepared as previously reported.[19] **Benzenesulfenyl chloride** was prepared by the method of Kharasch.[20] **1,1,2,2-Tetrachloroethane** was purified as previously reported.[19] **Methylene chloride** was purified as previously reported.[21] Kinetics and product compositions were carried out as previously described.[14]

Analytical samples were obtained by adding a solution of 0.14 g (0.001 mol) of benzenesulfenyl chloride in 5 mL of CH_2Cl_2 to 0.001 mol of diene in 3 mL of CH_2Cl_2 at room temperature. The solvent was evaporated in a stream of dry nitrogen to a constant weight. Attempts to purify the residue by GLC or distillation led to decomposition. Satisfactory elemental anlayses for C, H, and Cl (±0.4%) were obtained for the adducts of compounds **4** and **5** directly upon removal of the solvent. In each case the analytical samples were mixtures of isomers.

Propadiene, C.P. grade, was obtained from Matheson of Canada Ltd. **1,2-Butadiene, 2,3-pentadiene, and 3-methyl-1,2-butadiene** were obtained from Chemical Samples Co. **2-Methyl-2,3-pentadiene** was prepared by the method of Moore and Ward.[22] **2,4-Dimethyl-2,3-pentadiene** was a gift from Professor J. Powell of this department.

Acknowledgment. The continued financial assistance from the National Research Council of Canada is gratefully acknowledged. A University of Toronto Special Open Fellowship (1973–1974) and a National Research Council of Canada Postgraduate Scholarship (1974–1976) to D.G.G. and

a Government of Iran, Minister of Science and Higher Education Scholarship to S.Y. are also very much appreciated.

Registry No.—**1**, 931-59-9; **2**, 933-01-7; **3**, 463-49-0; **4**, 590-19-2; **5**, 591-96-8; **6**, 598-25-4; **7**, 3043-33-2; **8**, 1000-87-9; (*E*)-(2*RS*,5*RS*)-5-chloro-3-hexen-2-yl 4′-chlorophenyl sulfide, 67145-79-3; (*E*)-(2*RS*,5*SR*)-5-chloro-3-hexen-2-yl 4′-chlorophenyl sulfide, 67145-80-6.

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(3) For reviews, see (a) D. R. Taylor, *Chem. Rev.*, **67**, 317 (1967); (b) M. C. Caserio, *Sel. Org. Transform.*, **1**, 259 (1970).
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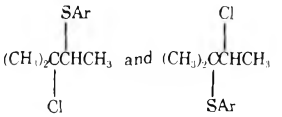
(12) For example, the chemical shifts of the methyl protons of the regioisomers



are δ 1.46 and 1.67, respectively.[13]
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(14) G. H. Schmid, A. Modro, F. Lenz, D. G. Garratt, and K. Yates, *J. Org. Chem.*, **41**, 2331 (1976).
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9-Substituted Fluorenes. Evaluation of Substituent Effects via Carbon-13 Nuclear Magnetic Resonance Spectroscopy

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Received November 28, 1977

The carbon-13 NMR shielding effects for a series of 9-substituted fluorenes and 9-substituted 1-methylfluorenes, where the substituents are OH, Cl, Br, and I, have been determined. Shift data for several other fluorenyl systems are also presented. The substituent effects are discussed in terms of the transmission of electronic interactions. The substituent shifts at the meta and para carbon centers are analyzed using the Swain–Lupton parameters. Qualitatively, this analysis suggests that π-inductive effects are twice as important as hyperconjugative interactions. The first instances of downfield substituent shifts for γ-syn disposed carbons are observed, while upfield shifts are seen for the resonances of γ-anti carbons.

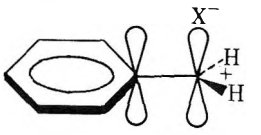
There has been considerable controversy concerning the transmission of the electronic properties of substituents to aromatic systems through potentially insulating centers such as in **1**.[2,3] Three types of substituent effects are generally considered to participate in systems like **1**: (1) σ-inductive

1

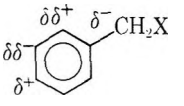
effects; (2) π-inductive effects; and (3) resonance effects, in this case hyperconjugative interactions. Often the discussion of the mechanism for the transmission of the substituent effect is clouded by a lack of understanding or agreement of the terminology involved. So that this is not a problem here, the terms pertinent to the discussion (although available in the literature) will be reviewed.[2g,f,4]

The *σ-inductive effect* requires a net charge transfer between the substituent and the σ framework, resulting in reorganization of the σ charge at various positions leading to *successive* polarization of the σ electrons. This interaction is most probably important only for the α and β carbons in these systems.[5]

Resonance effects result in a net transfer of charge between the aromatic π system and the substituent. In the context of the present discussion, hyperconjugation accounts for the resonance properties. Hyperconjugation requires specific stereochemical orientation and is most favorable when the dihedral angle of the potential hyperconjugative moiety is 0° with the aromatic π bonds.[6] This σ–π bond interaction is shown schematically below.



There are two mechanisms which fall under the heading of *π-inductive effects*:[2,4] (1) a process which causes reorganization of the aromatic π electrons by an *alternating* polarization of the π electrons,



(2) a polarization of the π electrons toward the ipso carbon. This second mechanism is often called a π-polarization effect.

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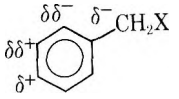
Table I. Chemical Shifts and Substituent Chemical Shifts (ppm) for the 9-Substituted Fluorene Systems (2)[a]

X	$C_{1,8}$	$C_{2,7}$	$C_{3,6}$	$C_{4,5}$	$C_{10(10')}$	$C_{11(11')}$	C_9
H	124.8	126.5	126.5	119.7	143.1	141.6	36.7
I	126.6	127.8	129.0	120.4	145.8	139.9	22.3
	(1.8)	(1.3)	(2.5)	(0.7)	(2.7)	(−1.7)	(−14.4)
Br	126.4	128.1	129.2	120.3	144.2	139.9	46.0
	(1.6)	(1.6)	(2.7)	(0.6)	(1.1)	(−1.7)	(9.3)
Cl	125.7	127.9	129.2	120.0	143.8	140.0	57.5
	(0.9)	(1.4)	(2.7)	(0.3)	(0.7)	(−1.6)	(20.8)
OH	125.1	127.8	129.0	119.9	145.7	140.0	74.9
	(0.3)	(1.3)	(2.5)	(0.2)	(2.6)	(−1.6)	(38.2)

[a] The substituent chemical shifts are in parentheses.

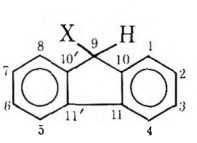
The basic difference between the two π-inductive effects is represented by the magnitude of charge density reorganization at the ortho and meta positions.



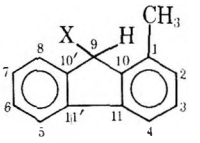
The close relationship between charge density changes and carbon-13 NMR shifts[7] should allow for the dissection of the various mechanisms involved in the transmission of substituent effects. Unfortunately, it is sometimes difficult to distinguish between the π-inductive effects by simple inspection of carbon-13 chemical shift data. This problem arises because ortho carbon shifts are subject to steric and compressional effects, while meta carbon chemical shifts often vary over a very narrow range and thus are marginally influenced by electronic effects.

Separation of inductive–field effects from resonance or hyperconjugative contributions can be readily accomplished by using the dual substituent parameter equation (DSP).[8,9] By confining the study to a closely related series of compounds, the relative importance of the various mechanisms can be determined.

Previous work in this laboratory using the DSP analysis has shown that the transmission of substituent effects in α-substituted toluenes operates via a π-inductive mechanism.[3b] However, the structural features inherent in these molecules, the freely rotating CH_2X moiety, may preclude the availability of hyperconjugative interactions by the CX σ bond. In order to further investigate the transmission of substituent electronic effects through a fully saturated center, a series of stereochemically well-defined systems **2** and **3**, where the α substituent is held rigid, was studied. These compounds are interesting because the X group at the "sp^3" carbon atom is



2



3

constrained with respect to the planar aromatic π system. The incorporation of a methyl moiety in one ring destroys the inherent symmetry of this system and allows comparisons between two slightly different aromatic centers.

Chemical Shift Assignments. The chemical shift (and substituent shift) data for the 9-substituted fluorenyl and 1-methyl-9-substituted fluorenyl compounds are given in Tables I and II, respectively.

Since the discussion of the data depends largely upon correct carbon assignments, substantial care was taken for the parent system. The task of making assignments was facilitated by inspection of the proton-coupled spectrum as well as by consideration of substituent effects observed in some model systems. Using the proton-coupled spectrum "fingerprint",[10] the C_2 and C_3 resonances were readily distinguished from the C_1 and C_4 resonances. Since the chemical shifts for C_2 and C_3 are equivalent, this leaves only C_1 and C_4 to be assigned. The C_4 resonance is expected to be at higher field than C_1 due to steric compression effects. Additional information is derived from the coupled spectrum, where the C_1 resonance is seen to be more highly coupled than is C_4. The C_{10} and C_{11} shift assignments have been made previously by Johnson and Jankowsky.[11] These latter assignments were presumably made by consideration of intensity effects. In the decoupled spectrum the C_{10} resonance is seen to be more intense than the C_{11} resonance owing to the greater number of adjacent hydrogens, and thus a slightly greater NOE effect is obtained.[12] The correctness of these shift assignments can be judged by the good correlation between the observed and calculated chemical shifts in the 1-OH, 1-CH_3, 2-I, and 2-NO_2 fluorenyl systems (Table III).

The shift assignments for the 1-methyl substituted fluorenyl systems were somewhat more difficult to make owing to the increased number of carbon signals. However, this task was facilitated by using the fingerprint method and substituent effects. A reasonable assumption was also employed to make these assignments. That is, the carbon chemical shifts in the unsubstituted ring would remain relatively unchanged. With the aid of the proton-coupled spectrum, the assignments of the protonated carbons will now be described.

By analogy with the unmethylated material, C_4 and C_5 are assigned to the two highest field resonances. The assignment of C_4 to the higher field resonance is consistent with the substituent shift induced by a para methyl group.[7] The coupling

Table II. Chemical Shifts and Substituent Chemical Shifts (ppm) for the 1-Methyl-9-Fluorene Systems (3)

X	H	I	Br	Cl	OH
1	134.1	135.4 (1.3)	136.2 (2.1)	136.4 (2.3)	136.6 (2.5)
2	127.6 (1.1)[a]	128.4 (0.8)	129.0 (1.4)	129.2 (1.6)	129.2 (1.6)
3	127.0	129.4 (2.4)	129.6 (2.6)	129.7 (2.7)	129.7 (2.7)
4	117.4 (−2.3)	118.0 (0.6)	117.8 (0.4)	117.7 (0.3)	117.6 (0.2)
5	120.0	120.5 (0.5)	120.2 (0.2)	120.1 (0.1)	120.2 (0.2)
6	126.5*	129.0 (2.5)	129.6 (3.1)	129.7 (3.2)	129.6 (3.0)
7	126.6*	127.8 (1.2)	127.9 (1.3)	127.9 (1.3)	127.9 (1.3)
8	124.9	126.4 (1.5)	126.1 (1.2)	125.7 (0.8)	125.3 (0.4)
9	35.7	21.7 (−14.0)	46.1 (10.4)	51.4 (21.7)	75.0 (39.3)
10	141.4 (−1.9)	142.9 (1.5)	141.3 (−0.1)	141.1 (−0.3)	143.9 (2.1)
11	142.1* (0.5)	138.7* (−3.4)	139.7 (−2.4)	140.1 (−2.0)	140.3* (−1.8)
10′	143.1 (0.0)	145.4 (2.3)	143.2 (0.1)	143.9 (0.8)	145.9 (2.8)
11′	142.0* (0.4)	139.0* (−3.0)	139.7 (−2.3)	140.1 (−1.9)	140.5* (−1.5)
CH_3	18.7	19.4 (0.7)	18.8 (0.1)	18.6 (−0.1)	18.1 (−0.6)

[a] Substituent shift vs. nonmethylated material; an asterisk indicates that reversal of assignments may be possible.

Table III. Chemical Shifts and Calculated Chemical Shifts (ppm) for Some Fluorenyl Derivatives[a]

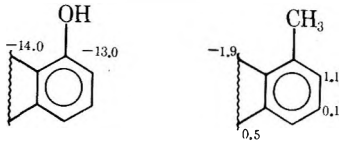
	1-OH	1-CH_3	2-I	2-NO_2
1	152.1 (152.0)[b]	134.1 (133.8)	134.1 (133.9)	121.2 (119.8)
2	113.5 (113.4)	127.6 (127.0)	91.8 (91.8)	146.8 (144.5)
3	126.9 (127.4)	127.0 (126.2)	135.7 (135.6)	123.0 (121.6)
4	113.0 (112.1)	117.4 (116.5)	121.4 (119.0)	120.4 (120.7)
5	120.2	120.0 (119.7)	119.9 (119.9)	119.8 (120.1)
6	126.7	126.5 (126.5)	127.3 (127.0)	127.4 (126.9)
7	128.5	126.6 (126.5)	126.9 (126.7)	128.8 (128.2)
8	125.1	124.9 (124.8)	124.9 (125.0)	125.3 (125.2)
9	33.5	35.7	36.5	36.9
10	128.5 (130.0)	141.4 (143.6)	145.4 (145.3)	144.8 (144.1)
10′	141.6	143.1	142.6 (142.9)	139.4 (139.6)
11	142.8 (142.7)	142.1 (142.1)	140.7 (141.0)	148.0 (148.0)
11′	144.0	142.0	141.2 (141.2)	143.9 (144.0)

[a] Registry No.: 1-OH, 6344-62-2; 2-I, 2523-42-4; 2-NO_2, 607-57-8. [b] Calculated values are in parentheses.

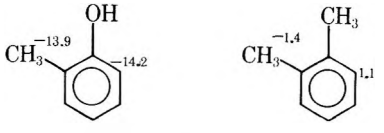
pattern of the next resonance indicates that this carbon is an ortho-type carbon, and therefore it is assigned to C_8. The fingerprint method was also used to assign the next three signals, all being meta-type carbons.[10] These must arise from C_2, C_6, and C_7. Assuming a minimal effect of the methyl at C_6 and C_7, the assignments were made as shown in the table. The assignment of C_3 is obvious from the coupled spectrum because of its lack of long range couplings.

The assignments of the nonprotonated carbons were based primarily upon substituent shifts as well as on peak intensity considerations. Thus, C_1 is assigned to the highest field nonprotonated carbon shift. Intensity considerations separate the C_{10},$C_{10'}$ signals from the C_{11},$C_{11'}$ signals. This is also consistent with the upfield shift of the C_{11},$C_{11'}$ signals observed by comparison with the parent compound. The C_{10} assignment is made by consideration of substituent effects.

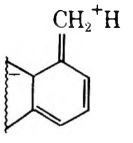
Substituent Effects. Before proceeding with the discussion of substituent effects in the 9-substituted fluorenyl systems, it may prove worthwhile to look at the unusual substituent effects observed for the 1-OH and 1-CH_3 systems. The substituent shifts are shown below.



Similar effects are observed in the substituent shifts in *o*-cresol and *o*-xylene,[13] as well as in some 1-substituted naphthalenes.[14]



Possible explanations for the observed shifts include participation of canonical forms such as shown.



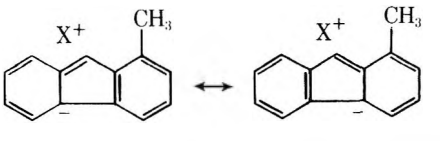
An alternative explanation involves deformation of the C_1–C_{10}–C_9 bond angle to diminish steric interactions. In analogy with the 1-substituted naphthalenes, this would lead to shielding of C_{10} and deshielding of the C_2 resonances.[14] The actual picture is probably a blend of these two situations. In any case, the incorporation of the methyl group at C_1 should affect the ease and nature of the transmission of substituent effects to the substituted ring.

The substituent shifts at C_9 in both systems compare well with the analogous values obtained for the α-substituted toluenes.[3b] The substituent shifts at $C_{10(10')}$ do not correlate with the toluene data, and in **3** it is apparent that the shifts are not symmetric with respect to the substituent. The $C_{10'}$ substituent shifts in **3** compare well with those in **2**, but the C_{10} shifts are somewhat smaller in magnitude. This may be a consequence of the opening of the C_9–C_{10}–C_1 bond angle mentioned earlier. If the bond angle opening mechanism is important, then the substituent shift of the methyl group should be to higher field as X becomes larger. The substituent shifts observed at C_{10} obtained by comparing **2** and **3** are −1.9 (H), −2.2 (OH), −2.7 (Cl), −2.8 (Br), and −2.9 (I) ppm, and thus they are in agreement with the proposed mechanism.

The substituent shifts observed at the carbons in the γ position are interesting owing to the inherent assymmetry in these compounds. In **2** there are two different γ carbons, and in **3** there are four different γ carbons. Because of this assymmetry, these systems should prove useful in assessing the mechanism by which the γ shift is transmitted to aromatic centers. Since the γ carbons are virtually equidistant, albiet differently disposed geometrically from the substituent, as measured from molecular models, the differences in the γ shifts should reflect electronic interactions. In 1-substituted naphthalenes the γ shift of the peri carbon to higher field was interpreted as a steric interaction.[15] In the present instance, C_1 and C_8 are seen to be in a somewhat similar orientation to the substituent. However, these carbon resonances are invariably shifted to low field while the resonances for the anti carbons C_{11} and $C_{11'}$ are shifted to higher field. It was found that in α-substituted toluenes the ortho carbon (to the CH_2X moiety) resonances were shifted to higher fields.

A simplistic approach to explain the fluorene shift trends would be to consider that in the toluene system the methylene moiety is freely rotating and on a time averaged basis one ortho carbon will be syn and the other anti to the substituent. The observed shift would reflect the sum of the syn and anti interactions. Based on this notion, the sum of the substituent shifts for $C_{1(8)}$ and $C_{11(11')}$ observed in the fluorene systems **2** and **3** should be equal to that found in the α-substituted toluenes. In the instance of **2** the values compare favorably with the toluene data given in parentheses: X = Br, −0.1 (−0.3); X = Cl, −0.7 (−0.7); and X = OH, −1.3 (−2.0) ppm. For system **3**, the correlation is poor.

In **3** the substituent shifts for the $C_{11(11')}$ resonances are generally much larger than those found in **2** and seem to indicate a greater degree of negative charge on this carbon in **3**. A possible explanation which would account for the upfield shift involves a hyperconjugative electron release mechanism.



For system **3**, the hyperconjugative electron release is favored to a greater degree owing to relief of steric interactions between the methyl and the 9 substituent. The parallelism between substituent shift and substituent size is in accord with this possibility. A similar hyperconjugative electron release in aliphatic systems has been invoked to explain the upfield substituent shifts of γ-anti carbons.[16]

There are other interesting trends observed for the γ carbons C_1 and C_8. In **2** and **3**, the substituent shifts are to lower field. This is somewhat surprising since these carbons are

γ-syn to the substituent. In 1-substituted naphthalenes, a somewhat similar system at least as far as steric interactions are concerned, upfield shifts are observed. These upfield shifts were purposed to be due to steric interactions. The observations here suggest that the shifts in the fluorenes, as well as in the naphthalenes, are electronic in nature. It is also noticed for C_8 in **2** and **3** that the magnitude of the substituent shift follows an inverse order with respect to substituent electronegativity. However, for the C_1 resonance in **3** the opposite trend prevails. This appears to be due to the interaction of the substituent and the methyl group at C_1. As the substituent shift at the methyl becomes more negative, the substituent shift at C_1 becomes more positive. It is interesting that the sum of the C_1 and C_8 substituent effects stays relatively constant.

The analysis of the substituent shifts at δ carbons $C_{2,7}$ and $C_{4,5}$ also indicates differences in the electronic transmission of charge density as a function of relative position to the substituent. The anti carbons C_4 and C_5 are less affected by the substituent than are C_2 and C_7. The $C_{2,7}$ shifts are also larger than those observed in the α-substituted toluene series. The methyl carbon is also δ disposed to the substituent, and it is believed that these shifts are through space in origin.[17] The substituent effects observed at $C_{2,7}$ in **2** and at C_7 in **3** were analyzed by the DSP equation (C_2 in **3** did not give good correlation, presumably due to the ortho effect of the methyl group). The results are as follows.[18] For **2** $C_{2,7}$: $\rho F = 1.77$, $\rho R = -0.82$, $\bar{r}$ 0.985. For **3** C_7: $\rho F = 1.62$, $\rho R = -0.79$, $\bar{r}$ 0.997. This observation suggests that inductive-type interactions are twice as important for the substituent shifts as are resonance effects.

The remaining substituent effects to be discussed are those observed at C_3 and C_6. In all instances downfield shifts are observed, and they indicate a decrease of electron density at these carbons. The DSP analysis of these shifts indicates that the inductive term F is about twice as important as the resonance term R. For **2** $C_{3,6}$: $\rho F = 3.16$, $\rho R = -1.65$, $\bar{r} = 0.991$. For **3** C_3: $\rho F = 3.78$, $\rho R = -1.78$, $\bar{r} = 0.983$. For **3** C_6: $\rho F = 3.49$, $\rho R = -0.76$, $\bar{r} = 0.996$.

The shifts observed at the para position here are about twice as large as those observed at the meta position (C_2, C_7). This result is consistent with the observations made on para-substituted benzenes.[19]

Conclusions

It has been shown that substitution at the 9 position of a fluorenyl ring induces substantial changes in the chemical shifts of the aryl ring system. It is clear that the magnitude of the substituent shift is very dependent upon the relative orientation of the interacting nuclei. From the DSP treatment of the data at C_2, C_3, C_6, and C_7, both resonance (hyperconjugative) and π-inductive effects are important. Judging from the pattern of the substituent shifts, π-bond polarization toward the ipso carbon is the dominant π-inductive mechanism.

Experimental Section

Fluorene, 9-chlorofluorene, 9-hydroxyfluorene, 9-bromofluorene, 1-methylfluorene, 1-hydroxyfluorene, 2-iodofluorene, and 2-nitrofluorene were commercially available and were used as received. 1-Methyl-9-fluorenone was received from Professor P. D. Bartlett, Texas Christian University. The proton NMR spectra were recorded on a Jeol MH100 spectrometer system. The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a Jeol FX-60 spectrometer system equipped with a Texas Instruments computer with a 24K memory. The spectra were obtained at an observing frequency of 15.03 MHz. Sample concentrations were ca. 10% w/v in deuteriochloroform of the proton-decoupled spectra and ca. 50% w/v for the proton-coupled spectra in 10 mm o.d. sample tubes. General NMR spectral and instrumental parameters that were employed are the following: internal deuterium lock to the solvent; spectral width of 2500 Hz (166.6 ppm); a pulse width of 5 μs, corresponding to a 45° pulse angle; and a pulse repetition time of 1.8 s. For all spectra, 8K time-domain data points were used. All shifts reported are referenced to internal Me_4Si and are estimated to be accurate to ±0.05 ppm.

High-resolution mass spectra were recorded by Mr. G. Gabel of the Biochemistry Department at Texas A&M University, College Station, Tex., on a Consolidated Electronics mass spectrometer system.

9-Iodofluorene. A methylene chloride solution of 1.8 g (0.01 mol) of 9-fluorenol and 48% hydroiodic acid was stirred at room temperature for 1 h. The organic layer was separated, neutralized by a saturated solution of sodium bicarbonate, and washed three times with 50-mL portions of water. After removing the solvent at reduced pressure, the crude material was dissolved in petroleum ether and placed in the freezer. After about 1 h, 1.6 g (53% yield) of light yellow crystals was deposited: mp 148–149 °C dec; NMR ($CDCl_3$) δ 6.42 (1 H), 7.40 (m, 4 H), 7.70 (m, 4 H). This compound was found to be quite unstable, liberating iodine readily. An accurate analysis therefore could not be obtained.

9-Hydroxy-1-methylfluorene. This compound was prepared by the addition of an excess of sodium borohydride to an ethanol solution containing 4.0 g (0.022 mol) of 1-methylfluorenone. The reaction mixture was stirred for 0.5 h and quenched with water, and the organic material was extracted into methylene chloride. After drying the organic layer with magnesium sulfate, removing the solvent in vacuo, and recrystallization from hexane, 3.9 g (91% yield) of colorless cotton-like crystals was isolated: mp 162–162.5 °C; NMR ($CDCl_3$) δ 2.56 (3 H), 5.54 (1 H), 7.20–7.70 (m, 7 H). Anal. Calcd for $C_{14}H_{12}O$: 196.0888. Found: 196.0883.

9-Bromo-1-methylfluorene. To a cooled methylene chloride solution (0 °C) containing 2.0 g (10 mmol) of 9-hydroxy-1-methylfluorene was added 5.4 g (20 mmol) of phosphorus tribromide. The reaction mixture immediately turned brown. After careful quenching of the reaction mixture with 100 mL of ice water and neutralization by a saturated aqueous solution of bicarbonate, the organic layer was collected. After drying the solvent and removal in vacuo, 2.1 g (86%) of light brown crystals was deposited. Recrystallization from hexane afforded colorless crystals: mp 98–99.5 °C; NMR ($CDCl_3$) δ 2.50 (3 H), 5.92 (1 H), 7.12–7.68 (m, 7 H). Anal. Calcd for $C_{14}H_{11}Br$: 258.0044. Found: 258.0031.

9-Chloro-1-methylfluorene. A procedure similar to that used to prepare the bromo derivative was used here, starting with 2.0 g (10 mmol) of the alcohol and 7.5 g of phosphorus pentachloride. Recrystallization from hexane yielded 1.7 g (85%) of slightly yellow crystals: mp 78–80 °C; NMR ($CDCl_3$) δ 2.58 (3 H), 5.82 (1 H), 7.20–7.23 (m, 7 H). Anal. Calcd for $C_{14}H_{11}Cl$: 216.0510. Found: 216.0526.

9-IodO-1-methylfluorene. This compound was prepared by the same method used to prepare 9-iodofluorene: 35% yield of pale brown crystals; mp 104–105 °C dec; NMR ($CDCl_3$) δ 2.42 (3 H), 6.36 (1 H), 7.16–7.75 (m, 7 H). This compound liberated iodine readily and thus did not analyze properly.

Acknowledgment. The author would like to thank the Robert A. Welch Foundation for their generous financial support and the National Institutes of Health and the National Science Foundation for their grants to Professor P. D. Bartlett which allowed the purchase of Jeol FX-60 spectrometer. The author would also like to express his gratitude to Professor Bartlett for his encouragement during the course of this and other research.

Registry No.—**2** (X = H), 86-73-7; **2** (X = I), 64421-01-8; **2** (X = Br), 1940-57-4; **2** (X = Cl), 6630-65-5; **2** (X = OH), 1689-64-1; **3** (X = H), 1730-37-6; **3** (X = I), 67145-88-4; **3** (X = Br), 36804-48-5; **3** (X = Cl), 67145-89-5; **3** (X = OH), 36804-47-4; hydroiodic acid, 10034-85-2; sodium borohydride, 16940-66-2; 1-methylfluorenone, 5501-37-1; phosphorus tribromide, 7789-60-8; phosphorus pentachloride, 10026-13-8.

References and Notes

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$$\delta = \rho_F F + \rho_R R + \delta o$$

δo is the intercept of the equation, and ρ_F and ρ_R are the regression coefficients. *F* and *R* are contributions arising from field and inductive effects, taken together, and resonance effects, respectively.[9]
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Notes

Thallium in Organic Synthesis. 51. Oxidation of Enolizable Ketones to α-Nitrato Ketones by Thallium(III) Nitrate in Acetonitrile[1]

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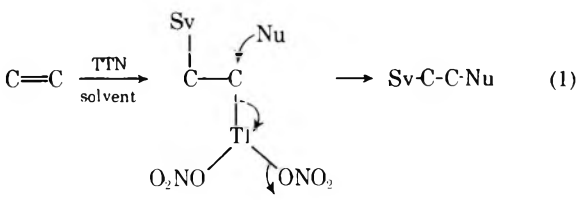
Received November 25, 1977

Thallium(III) nitrate (TTN) is a versatile reagent for the oxidation of a wide variety of olefinic and enolic groups, and in almost all cases the exclusive or predominant reaction pathway is oxidative rearrangement.[2] Occasionally, however, nucleophilic displacement of the thallium substituent in the intermediate oxythallation adduct leads to unrearranged products (eq 1). This latter type of reaction appears to occur



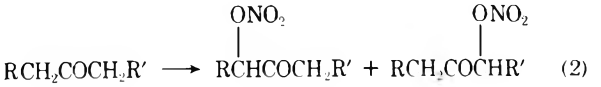
(1)

most frequently when water or methanol is used as solvent (i.e., Nu = H_2O or CH_3OH), but we[3] and others[4-7] have noted instances where nitrate ion participates as the nucleophile to give nitrate esters, usually in low yield. Recently, however, Ouellette and Bertsch have shown that certain olefins and cyclopropanes can be converted into diol dinitrates in moderate to excellent yield by treatment with TTN in pentane,[8] and this report prompts us to describe some related studies.

In the course of our systematic study of the utility of TTN as an oxidant, we have examined the reactions of various types of functional groups with TTN in aprotic, poorly or nonnucleophilic solvents. We describe now one aspect of these studies, namely the smooth conversion of enolizable ketones into the corresponding α-nitrato ketones[9] by treatment with TTN in either dimethyl or diethyl carbonate or, preferably, acetonitrile.

Addition of TTN to an equimolar amount of acetophenone dissolved in dimethyl or diethyl carbonate resulted in the immediate formation of a dark brown color as the TTN dissolved. When the mixture was heated to 60–80 °C, however, the brown color rapidly discharged and thallium(I) nitrate precipitated. NMR spectroscopic examination of the product obtained after workup showed that it consisted of approximately equal amounts of unreacted acetophenone and its α-nitrato derivative, $C_6H_5COCH_2ONO_2$. Similar results were obtained with a variety of substituted acetophenones and with propiophenone. When 2 equiv of TTN[10] were used, however, acetophenone was converted into the α-nitrato ketone in 84–87% yield; propiophenone was similarly converted into $C_6H_5COCH(ONO_2)CH_3$ in 86–89% yield.

Use of dimethyl and diethyl carbonate for the oxidation of substituted acetophenones was not entirely satisfactory. In certain cases, most notably with 3-methoxyacetophenone, the α-nitrato ketone was obtained in poor yield (10–15%); in other cases the reactions proceeded exothermically, and NMR examination of the crude products revealed the presence of variable amounts of decomposition products. Fortunately, these problems were readily eliminated by the use of acetonitrile as solvent; 2 equiv of TTN were again necessary.[10] Oxidations were carried out at 60–80 °C for 12 h and led to excellent yields of the α-nitrato ketones. Yield data for the various conversions are listed in Table I. Unsymmetrical dialkyl ketones of the type $RCH_2COCH_2R^1$ (butan-2-one, pentan-2-one) were also smoothly oxidized in high yield, but as anticipated, approximately equal amounts of isomeric α-nitrato ketones were obtained (eq 2).



(2)

It is now well established[11] that oxidation of acetophenones by TTN in methanol results in initial methoxythallation of the enol C=C bond and that a subsequent 1,2-aryl migration

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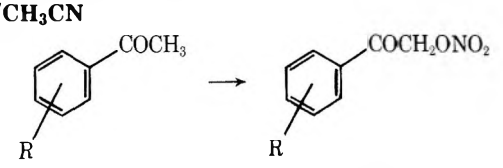
Table I. Oxidation of Ketones to α-Nitrato Ketones with TTN/CH_3CN



R	registry no.	mp, °C	yield, %[a]	registry no.
H	98-86-2	*b*	97	66702-75-8
4-CH_3	122-00-9	60	89	66702-76-9
3-CH_3O	586-37-8	*b*	90	66702-77-0
4-CH_3O	100-06-1	97	89	66702-78-1
4-Cl	99-91-2	82	91	66702-79-2
4-Br	99-90-1	79 (dec)	90	66702-80-5
4-NO_2	100-19-6	100	84	66702-81-6

$RCH_2COCH_2R \rightarrow RCH(ONO_2)COCH_2R$

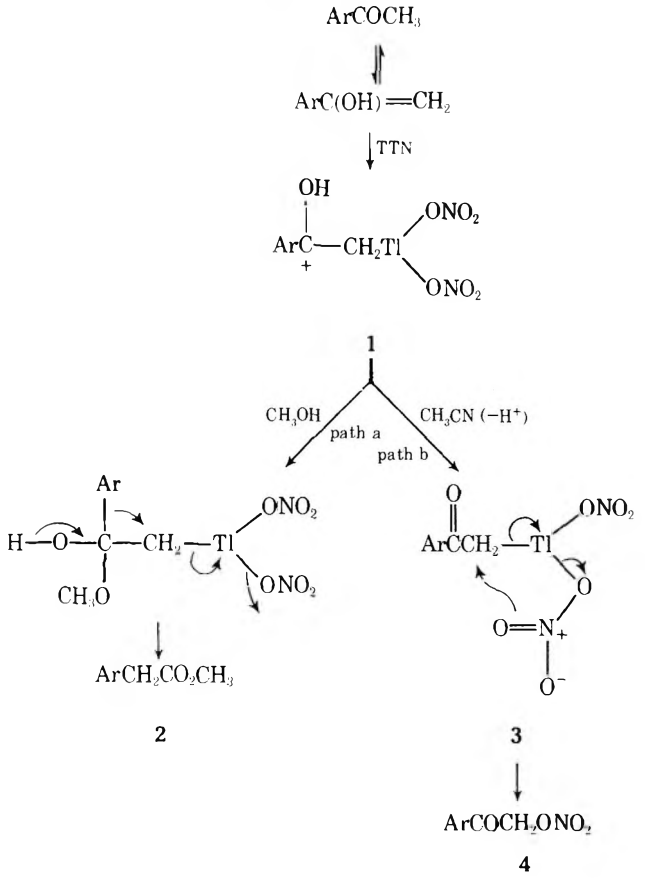
R	registry no.	mp, °C	yield, %[a]	registry no.
H	67-64-1	*b*	78	6745-71-7
CH_3CH_2	123-19-3	*b*	85	66702-82-7
$CH_3(CH_2)_2$	502-56-7	*b*	88	66702-83-8
C_6H_5	102-04-5	*b*	90	66702-84-9

$RCOCH_2R' \rightarrow RCOCH(ONO_2)R'$

R	registry no.	R′	mp, °C	yield, %[a]	registry no.
t-C_4H_9	75-97-8	H	*b*	87	66702-85-0
C_6H_5	93-55-0	CH_3	*b*	90	60434-74-4
2-$C_{10}H_7$	93-08-3	H	89	81	66702-86-1

[a] Estimated by NMR. [b] Liquid; no attempt was made to purify liquid α-nitrato ketones, as these are known to be thermally unstable.[12,13] The spectroscopic data (IR, NMR) for all products were consistent with the assigned structures.

Scheme I



gives methyl arylacetates (**2**) (Scheme I, path a). In a nonnucleophilic solvent such as diethyl carbonate or acetonitrile, however, reaction of the electrophilic Tl(III) salt with the enol C=C bond can proceed only as far as **1**, which would be expected to undergo rapid deprotonation to **3**. Reductive displacement of the weak C–Tl bond by nitrate anion (an intramolecular route is shown in Scheme I, path b) then leads to the α-nitrato ketone (**4**).

Experimental Section[14]

General Procedure for the Preparation of α-Nitrato Ketones. A solution of the ketone (10 mmol) in acetonitrile (5 mL) was added in one portion to a solution of TTN (20 mmol) in acetonitrile (25 mL) and the mixture was heated at 60–80 °C for 12 h. It was then cooled and the precipitated thallium(I) nitrate was collected by filtration and washed well with ether (3 × 100 mL). The filtrate was washed with water (2 × 150 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude α-nitrato ketone; yields were determined by NMR.

No attempt was made to purify liquid α-nitrato ketones as these are known to be thermally unstable. Solid products (Table I) were recrystallized from aqueous methanol for microanalysis.

4-$CH_3C_6H_4COCH_2ONO_2$. Anal. Calcd for $C_9H_9NO_4$: C, 55.39; H, 4.65; N, 7.18. Found: C, 54.95; H, 4.73; N, 6.97.

4-$CH_3OC_6H_4COCH_2ONO_2$. Anal. Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 50.93; H, 4.31; N, 6.66.

4-$ClC_6H_4COCH_2ONO_2$. Anal. Calcd for $C_8H_6ClNO_4$: C, 44.57; H, 2.80; Cl, 16.44; N, 6.49. Found: C, 45.71; H, 3.10; Cl, 16.81; N, 5.95.

4-$BrC_6H_4COCH_2ONO_2$. Anal. Calcd for $C_8H_6BrNO_4$: C, 36.95; H, 2.33; Br, 30.73; N, 5.38. Found: C, 37.01; H, 2.18; Br, 31.15; N, 5.15.

4-$O_2NC_6H_4COCH_2ONO_2$. Anal. Calcd for $C_8H_6N_2O_6$: C, 42.11; H, 3.53; N, 12.28. Found; c, 42.34; H, 2.69; N, 12.46.

2-$C_{10}H_7COCH_2ONO_2$. Anal. Calcd for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.42; H, 4.21; N, 6.27.

Acknowledgments. D.W.Y. acknowledges the receipt of a Science Research Council Research Studentship and R.P.H. is grateful for financial support from the Stiftung für Stipendien auf dem Gebiete der Chemie (Basel).

Registry No.—TTN, 13746-98-0; acetonitrile, 75-05-8.

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(9) α-Nitrato ketones have received little attention; the only previously reported method of preparation involves treatment of an α-bromo ketone with silver nitrate (W. D. Emmons and J. P. Freeman, *J. Am. Chem. Soc.*, **77**, 4415 (1955); N. Kornblum and H. W. Frazier, *J. Am. Chem. Soc.*, **88**, 865 (1966)).
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Acid Catalysis of the Claisen Rearrangement. 1. Formation of 4,4′-Bis(2*H*-chromenyl)mercury Derivatives from Aryl 2-Propynyl Ethers

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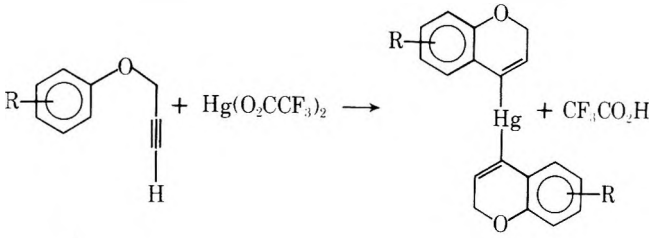
Received February 14, 1978

Schmid[1] has reported that phenyl propynyl ether when refluxed with silver tetrafluoroborate in chloroform gives 2*H*-chromene via a charge-induced Claisen rearrangement. Extending this reaction to 1,4-bis(aryloxy)-2-butynes we found[2] that the product may be a 4-substituted-2*H*-chromene or a 6*H*-benzofuro[3,2-*c*]-1,6a-dihydro-11a-methylbenzopyran depending on the aryl group and the reaction time. We felt that soft Lewis acids[3] other than Ag^+ ion might also induce such rearrangements and therefore undertook a survey of the interaction of various soft Lewis acids with aryl 2-propynyl ethers (1). The initial phase of this study revealed a very novel reaction of mercury(II) trifluoroacetate[4] with **1**, which we now report.

Treatment of a series of **1** in dichloromethane solution with an equimolar amount of $Hg(O_2CCF_3)_2$ at room temperature followed by quenching with alkaline sodium borohydride[5] produced good to excellent yields of crystalline products. Elemental analysis of these products, listed in Table I, indicated the incorporation of a mercury atom. The fact that these compounds survived $NaBH_4$ treatment indicates the mercury atom is covalently bound. The NMR spectra are very similar to that reported[6] for 2*H*-chromene except the coupling due to H-4 is absent. Based on these data the 4,4′-bis(2*H*-chromenyl)mercury structure (**2**) is assigned to these compounds.



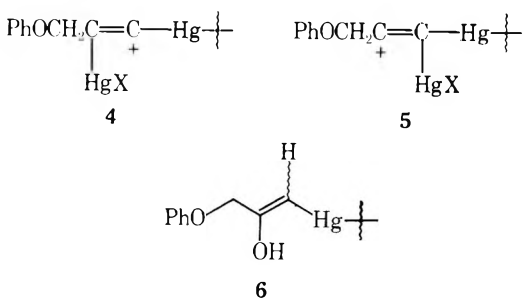
1 **2**

Organomercurials of this type have not been previously reported.[7]

Additional support for this assignment comes from the mass spectral fragmentation[8] of **2**, e.g., for **2a**: *m/e* 464 (14%, M^+, $C_{18}H_{14}Hg^{202}O_2$), 262 (10%, M − Hg), and 131 (100%, $C_9H_7O^+$).

Since terminal alkynes are known[9] to yield mercury bis(acetylides) on treatment with certain mercuric salts, it is reasonable to postulate the intermediacy of **3** in the formation of **2**. Indeed compound **3a**, prepared via standard procedures, produces **2a** smoothly under the rearrangement conditions. The mechanism of conversion of **3** into **2** could involve two quite different mechanisms depending upon whether the mercuric ion triggers rearrangement via a σ or a π complex with the triple bond. After formation of **3** a π complex between **3** and remaining mercuric ion could effect a charge-induced Claisen rearrangement analogous to the process proposed[1] for rearrangement of **1** in the presence of silver(I) ion. Unlike silver ion, however, mercuric ion may form strong σ complexes as well as π complexes. Conversion of the initial π complex into a σ complex capable of cyclization via intramolecular electrophilic aromatic substitution, a process which may be viewed as a metal ion promoted Friedel–Crafts alkenylation of an aromatic ring by an alkyne,[11,12] is therefore an additional possibility.

Two different σ complexes **4** and **5**, differing by the site of charge localization, may form. The preferred site of charge localization was determined by hydration (mercuric acetate, methanol, trace of sulfuric acid or methanol, sulfuric acid) of **3a**. Under these conditions the only product isolated was phenoxypropanone. That this product arises directly from **3a** and not from prior decomposition of **3a** to **1a** is evidenced by the fact that **1a** does not produce the ketone nearly as quickly as **3a** under identical conditions. Phenoxypropanone would be expected to readily form from compounds such as **6**, as the facile protonolysis of vinylic C–Hg bonds is well known.[13] Intermediate **6** in turn would arise from nucleophilic attack



on **5**. Thus hydration of **3a** implicates **5** as the more favorable σ complex. Since **5** can form only a five-membered ring on cyclization with the adjacent aromatic ring (under aprotic conditions), we favor an electrocyclic mechanism initiated by a π complex for 2*H*-chromene formation as shown in Scheme I.[14]

Results of the interaction of **1** with other soft Lewis acids

Table I. Physical and Spectral Data for 4,4′-Bis(2*H*-chromenyl)mercury Derivatives

	R (1)	registry no.	Yield,[c] %	mp, °C (corr)	NMR[b] ($CDCl_3$), δ
a	H[a]	66901-46-0	75	141–142	6.03 (2 H, t, J = 3.4 Hz), 4.90 (4 H, d, J = 3.4 Hz)
b	4-CH_3[a]	66901-45-9	83	177–178.5	6.07 (2 H, t, J = 3.6 Hz), 4.88 (4 H, d, J = 3.6 Hz)
c	4-OCH_3	66901-44-8	97	172–173	6.17 (2 H, t, J = 3.6 Hz), 4.88 (4 H, d, J = 3.6 Hz)
d	4-Cl		83[d]		
e	2-Cl	66901-43-7	54	196.5–197	6.13 (2 H, t, J = 3.8 Hz), 5.08 (4 H, d, J = 3.8 Hz)
f	2,4-Cl_2		72[e]		

[a] IR (KBr) **2a**: 1470 (s), 1220 (s), 1080 (s), 750 (s) cm^{-1}. IR (KBr) **2b**: 1480 (s), 1220 (s), 820 (s) cm^{-1}. [b] Compare 2*H*-chromene (ref 6): (CCl_4) δ 6.30 (1 H, d with t-like fine structure, H-4), 5.60 (1 H, d × t, $J_{3,4}$ = 10 Hz, H-3), 4.72 (2 H, d × d, $J_{2,3}$ = 3.5 Hz, $J_{2,4}$ = 1.7 Hz, H-2). The resemblance of the spectrum of **2b** to that of 4,4′-bis(6-methyl-2*H*-chromene) is even more striking: mp 115–116 °C; NMR δ 6.8 (3 H, m), 5.8 (1 H, t, J = 4 Hz), 4.7 (2 H, d, J = 4 Hz), 2.3 (3 H, s). [c] Isolated product. Correct elemental analysis (±0.4%) was obtained for all new compounds. Purification consisted of filtration through alumina followed by recrystallization from hexane–chloroform. [d] The product isolated was 1-(4-chlorophenoxy)-2-propanone characterized by NMR and by conversion to the semicarbazone; mp 189.5–190.5 °C (lit.[10] mp 181–182 °C). An authentic sample gave a semicarbazone, mp 189.5–190.5 °C. [e] The product isolated was 1-(2,4-dichlorophenoxy)-2-propanone characterized by comparison with an authentic sample.

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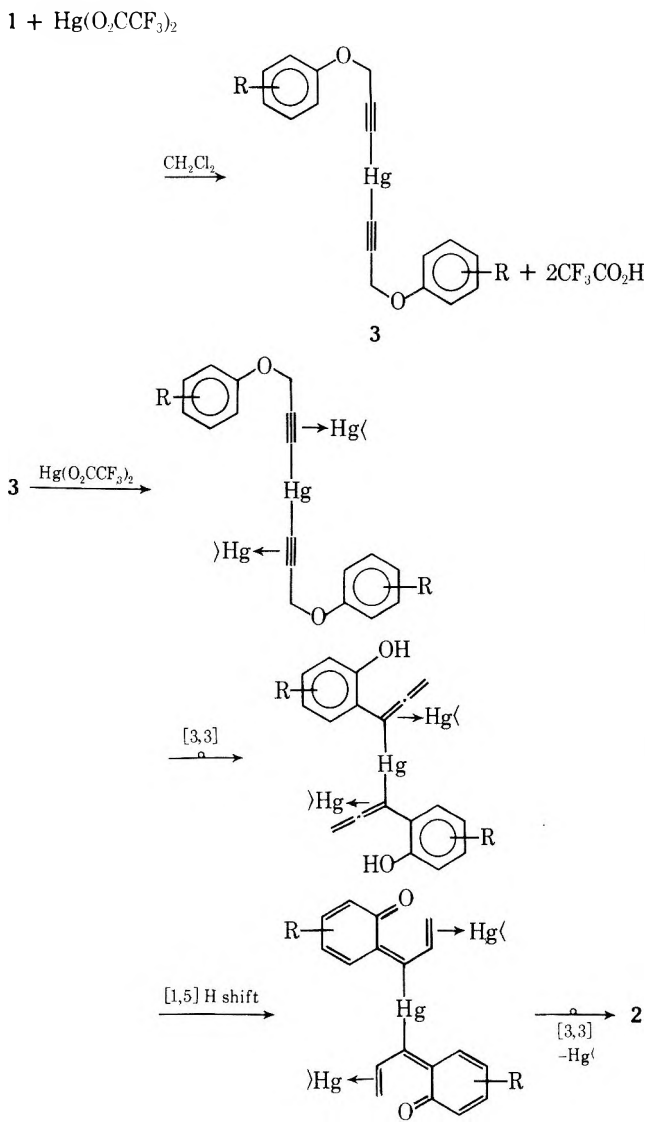
Scheme I



will be reported in due course as will the utility of **2** in organic synthesis.

Experimental Section

Melting points were determined on a Fischer–Johns melting point apparatus and are corrected. Spectral data was collected as follows: IR, Perkin-Elmer 435B (KBr); NMR, $CDCl_3$; Me_4Si reference (δ 0.00), Varian T-60; mass spectra, Hitachi Perkin-Elmer RMU-6E. The mass spectra were kindly provided by Dr. J. D. Willett of the University of Idaho, Moscow, Idaho. Microanalyses were performed under the supervision of Mr. Mike Gilles in the Michigan Technological University microanalytical laboratory.

General Procedure for the Preparation of 2. Equimolar amounts of **1a** and mercuric trifluoroacetate were mixed, under N_2, in dichloromethane (5 mL/mmol) and stirred at room temperature for 2 h. The reaction was then quenched slowly (frothing) with excess alkaline (2 M NaOH) 2 M $NaBH_4$ solution. The mixture was filtered and the organic phase was washed with water. The dried ($MgSO_4$) organic layer was rotary evaporated to yield the products listed in Table I as colorless crystalline solids.

Acknowledgment. We wish to thank Dr. K. K. Balasubramanian for supplying spectral data for 4,4′-bis(6-methyl-2*H*-chromene). This research was supported by the Research Corp.

Registry No.—Phenyl 2-propynyl ether, 13610-02-1; *p*-tolyl 2-propynyl ether, 5651-90-1; *p*-anisyl 2-propynyl ether, 17061-86-8; *p*-chlorophenyl 2-propynyl ether, 19130-39-3; *o*-chlorophenyl 2-propynyl ether, 17061-92-6; 2,4-dichlorophenyl 2-propynyl ether, 17061-90-4; mercuric trifluoroacetate, 13257-51-7; 1-(4-chlorophenoxy)-2-propanone, 18859-35-3; 1-(2,4-dichlorophenoxy)-2-propanone, 17199-30-3.

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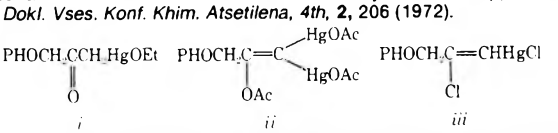
(7) The reaction of **1** with other mercuric salts has been described. Compounds such as **3** have been observed only under alkaline conditions with HgI_2 and $Hg(CN)_2$ (see also ref 9). Under neutral conditions **1** reacts with mercuric oxide (in aqueous ethanol) to give i and with mercuric acetate to give ii. Under acidic conditions mercuric chloride and **1** yield iii: A. Filippova, et al., *Dokl. Vses. Konf. Khim. Atsetilena, 4th*, **2**, 206 (1972).



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(14) This paper is dedicated to the memory of Professor H. Schmid.

Photocyclodimerization of Bicyclo[6.3.0]undec-1(8)-en-9-one. Synthesis of Highly Congested Pentacyclopropellanones

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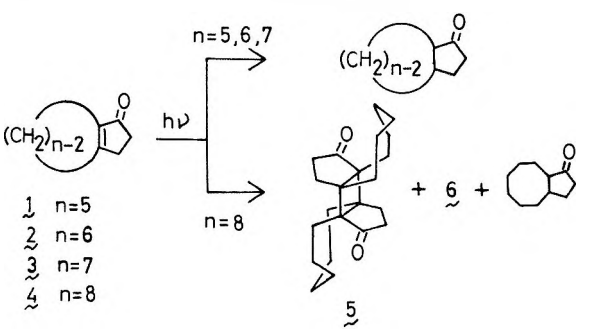
Received May 4, 1978

There has been considerable interest recently in pentacyclopropellanes wherein two propellane units share a common cyclobutane ring from theoretical and synthetic viewpoints.[1] Within this class of highly strained compounds, those constituted of large carbocyclic rings fused to the cyclobutane ring are expected to show unusual chemical and physical properties as a consequence of significantly repulsive nonbonded interaction of hydrogens between two kinds of carbocyclic rings facing each other. In this connection, we present here the synthesis of highly congested pentacyclopropellanes as a part of studies on the synthesis of sterically crowded polycyclic propellanes.[2]

For the purpose of building up such pentacyclic skeleton, photocyclodimerization of bicyclic cyclopentenones **1**–**4** was



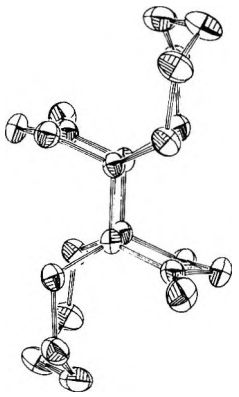


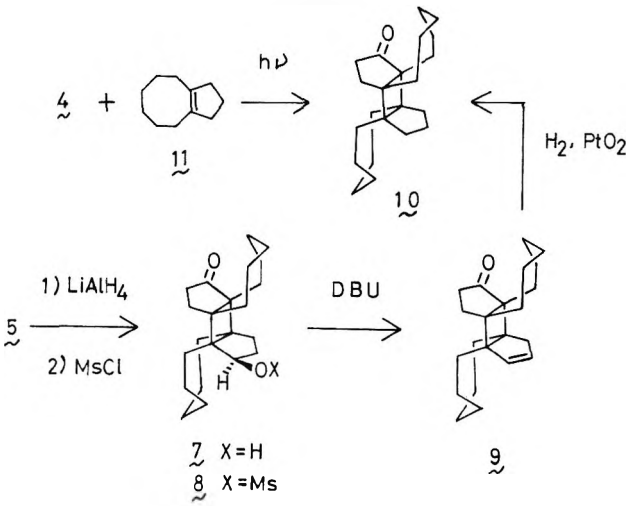
Figure 1. Molecular structure of **5**.

attempted, because we have already found that these enones are very reactive toward photocycloaddition to monocyclic olefins.[2] When a 0.5 M solution of enone **4** in ethyl ether was irradiated, crystalline cyclodimer (**5**) (mp 271–272 °C) was obtained in 42% yield (Φ = 0.041) along with small amounts of its isomer (**6**) (5.3%, mp 253–254 °C) and bicyclo[6.3.0]-undecan-9-one (9.6%). Absence of olefinic absorption in ^{1}H NMR, ^{13}C NMR, and IR spectra of **5** and **6** suggests that these are cyclodimers of **4**. Configuration around cyclobutane of the major cyclodimer **5** was established to be anti-head-to-tail by X-ray crystallographic study (Figure 1).[3] On the other hand, in the cases of enones **1–3**, consumption of enones was very slow and small amounts (15–19%) of the corresponding saturated ketones were obtained as the only product identified without any formation of cyclodimers.

It is significant that reactivity of bicyclic cyclopentenones toward photocyclodimerization is principally governed by the degree of flexibility of alicyclic rings fused to the double bond of cyclopentenone.[4] We have already found on the basis of the spectroscopic data of **1–4** that flexibility of the fused alicyclic rings has no significant effect on the nature of their excited triplet states,[2b] which are the reactive species for photocyclodimerization.[5] Consequently, the observed distinction in reactivity between **1–3** and **4** is interpreted in terms of the steric effects of alicyclic rings fused to the double bond of cyclopentenone in 1,4-diradical intermediates derived from one-bond formation between excited and ground state enones as well as the case of photocycloaddition of **1–4** to cyclohexene.[2b] Namely, in the cases of **1–3**, having cyclopentene, cyclohexene, and cycloheptene ring, respectively, second bond formation by radical coupling in the 1,4-diradical intermediates is markedly depressed owing to large nonbonded interaction of hydrogens facing each other between alicyclic ring methylenes. On the other hand, such nonbonded interaction in the case of **4** is smaller than those in the above cases because of large flexibility of cyclooctene ring, and, therefore, second bond formation occurs readily to afford the cyclodimers effectively. But in the cases of higher bicyclic cyclopentenones, containing more flexible rings than cyclooctene such as cyclononene and cyclodecene, intramolecular hydrogen abstraction took place exclusively and, as a result, cyclodimer was not formed.[6]

Pentacyclopropellanone (**10**) was, moreover, synthesized by cross photocycloaddition of enone **4** to bicyclo[6.3.0]-undec-1(8)-ene (**11**). Irradiation of **4** with twofold excess of **11** in ethyl ether gave **10** in 65% yield (Φ = 0.085) as a sole cycloadduct. Configuration around cyclobutane of **10** was confirmed by its identity with the compound prepared by the stepwise reduction of **5** as shown in Scheme I. Treatment of **5** with a large excess of lithium aluminum hydride gave monoalcohol (**7**) in 94% yield.[7] **7** was treated with methanesulfonyl chloride in pyridine to afford methane sulfonate (**8**)

Scheme I



in 95% yield, which was heated with 1,8-diazabicyclo[5.4.0]-undec-7-ene in dimethyl sulfoxide to give olefin (**9**) in 17% yield. Hydrogenation of **9** over platinum dioxide catalyst afforded **10** in 94% yield. High reactivity of **4** toward cross cycloaddition to **11** is similarly interpreted in terms of large flexibility of cyclooctene ring in **4** and **11**.

Unlike a variety of tetracyclopropellanones reported previously,[2] the present highly congested compounds, **5** and **10**, and their derivatives might be expected to show unusual chemical and physical properties owing to the nonbonded interaction of hydrogens between rings facing each other. Work on this subject is now being undertaken.

Experimental Section[8]

Irradiation of Enones 1, 2, and 3 in Ether. Enones **1**,[9] **2**,[10] and **3**[11] in ether (0.4–0.5 M) were irradiated for 30–100 h. During irradiation no precipitate was formed and the color of the solution gradually turned brown. After removal of the ether, the brown residue was distilled under reduced pressure and the distillate was analyzed by GLC to show the presence of unreacted enones (conversion ~30%) and the corresponding saturated ketones (15–19% yields).

Irradiation of Enone 4 in Ether. Enone **4** (9.6 g, 58.5 mmol) in 100 mL of ether was irradiated for 150 h. During irradiation white precipitate formed was collected at appropriate intervals to afford 3.1 g of a mixture of dimer **5** and **6**. The ether was removed from the filtrate and the residue was distilled under reduced pressure. GLC analysis of the distillate showed the presence of **4** (conversion 65%) and bicyclo[6.3.0]undecan-9-one (9.6%). Cyclodimers **5** and **6** were isolated by chromatography on silica gel and elution with benzene first gave 2.6 g (42%) of **5** and then 0.32 g (5.3%) of **6**. **5**: mp 271–272 °C from dioxane; IR (KBr) 1700 cm^{-1}; MS *m/e* 165 ($M^+/2$ + 1); ^{1}H NMR ($CDCl_3$) δ 0.65–2.65 (m); ^{13}C NMR ($CDCl_3$) δ 21.90 (t), 24.95, 25.21, 26.12, 30.54 (t), 39.31 (t), 49.25 (s), 59.58 (s), 222.34 (s);[12] UV ($CHCl_3$) λ_{max} 304 nm (ϵ 72.7). Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.55; H, 10.10. The structure of **5** was determined by the X-ray analysis. **6**: mp 253–254 °C from THF; IR (KBr) 1710 cm^{-1}; MS *m/e* 165 ($M^+/2$ + 1); ^{1}H NMR ($CDCl_3$) δ 0.60–2.60 (m); ^{13}C NMR ($CDCl_3$) δ 22.55, 24.30, 24.62, 24.95, 25.73, 26.05, 31.38 (t), 39.24 (t), 49.83 (s), 56.40 (s), 219.74 (s); UV ($CHCl_3$) λ_{max} 320 nm (ϵ 154). Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.19; H, 9.88.

Pentacyclopropellanone (10). (a) By Photocycloaddition of Enone 4 to Olefin 11. Enone **4** (0.820 g, 5.00 mmol) and 1.50 g (10.0 mmol) of olefin **11** in 10 mL of ether was irradiated for 25 h. The white solid formed was filtered (0.667 g) and the filtrate was concentrated and chromatographed on silica gel. Elution with petroleum ether afforded unreacted **11**, petroleum ether–benzene (1:1) additional **10** (0.17 g, total yield 65%), petroleum ether–benzene (1:4) bicyclo[6.3.0]undecan-9-one (0.029 g, 4.2%), and benzene–ether (9:1) unreacted **4** (0.144 g, conversion; 82.4%). An analytical sample of **10** was obtained by recrystallization from THF–methanol: mp 223–225 °C; IR (KBr) 1700 cm^{-1}; MS *m/e* 314 (M^+), 165, 150; ^{1}H NMR ($CDCl_3$) δ 0.60–2.75 (m); UV ($CHCl_3$) λ_{max} 304 nm (ϵ 49.8). Anal. Calcd for $C_{22}H_{34}O$: C, 84.01; H, 10.90. Found: C, 83.81; H, 11.02.

(b) By Reduction of 5. **5** (0.656 g, 2.00 mmol) in 100 mL of THF was added dropwise to a suspension of 0.76 g (20 mmol) of $LiAlH_4$ in

100 mL of THF, and the reaction mixture was refluxed for 20 h. The excess hydride was decomposed by water and the organic layer was washed with dilute hydrochloric acid and saturated sodium chloride solution and then dried (Na_2SO_4). Evaporation of the solvent gave 0.62 g (94%) of white solid which was recrystallized from THF–methanol to give **7**: mp 237–238 °C; IR (KBr) 3550, 1700, 1075 cm^{-1}; MS *m/e* 330 (M^+), 165, 149; ^1H NMR (pyridine-d_5) δ 0.70–2.80 (m, 32 H), 4.72 (q, 1 H), 6.05 (broad s, 1 H). Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.89; H, 10.40.

To a solution of 0.360 g (1.09 mmol) of **7** in 20 mL of pyridine was added dropwise 0.57 g (5.0 mmol) of methanesulfonyl chloride and the solution was stirred at room temperature for 20 h. The solution was diluted with 150 mL of water and extracted with THF. The organic layer was washed with saturated sodium chloride solution and dried (Na_2SO_4). Evaporation of the solvent and trituration with ether gave 0.42 g (95%) of pale yellow solid which was recrystallized from THF–petroleum ether to give **8**: mp 155–156 °C with decomposition; IR (KBr) 1700, 1320, 1160 cm^{-1}. Anal. Calcd for $C_{23}H_{36}O_4S$: C, 67.61; H, 8.88; S, 7.85. Found: C, 67.23; H, 9.01; S, 7.85.

To a solution of 0.427 g (1.05 mmol) of **8** in 40 mL of dimethyl sulfoxide was added dropwise 0.38 g (2.5 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene and the solution was heated with stirring at 100–110 °C for 45 h. The solution was diluted with 200 mL of water and extracted with THF. The organic layer was washed with dilute hydrochloric acid and saturated sodium chloride solution and then dried (Na_2SO_4). Evaporation of the solvent gave brown residue, which was chromatographed on silica gel. Elution with petroleum ether–benzene (1:1) gave 0.052 g (17%) of **9**: mp 191–193 °C from THF–methanol; IR (KBr) 3030, 1700, 720 cm^{-1}; MS *m/e* 165 ($M^+ - C_{11}H_{17}$); ^1H NMR ($CDCl_3$) δ 0.80–2.60 (m, 30 H), 5.50–5.80 (m, 2 H); UV ($CHCl_3$) λ_{max} 304 nm (ϵ 43.6). Anal. Calcd for $C_{22}H_{32}O$: C, 84.56; H, 10.32. Found: C, 84.34; H, 10.51.

9 (0.102 g, 0.33 mmol) in 80 mL of acetic acid was hydrogenated with PtO_2 in the presence of hydrogen under atmospheric pressure. The catalyst was filtered off and the filtrate was diluted with 150 mL of water and extracted with chloroform. The organic layer was washed with dilute sodium carbonate solution and water. Evaporation of the solvent gave 0.098 g (94%) of white solid which was recrystallized from THF–methanol to give **10**. This material was identical with the sample synthesized by cross photocycloaddition of **4** to **11** (IR and melting point).

Bicyclo[6.3.0]undec-1(8)-ene (11). Olefin **11** was prepared according to the method of Ohloff et al.,[13] namely hydrogenation of enone **4** with Raney nickel in the presence of hydrogen at atmospheric pressure in 1% methanolic sodium hydroxide gave a mixture of saturated alcohols (90%), which was dehydroxylated with *p*-toluenesulfonic acid in boiling toluene to afford a mixture of olefins (78%). This mixture contains ~5% of undesired bicyclo[6.3.0]undec-1(2)-ene. Purification of **11** was carried out through hydroboration–oxidation (60%) according to the procedure of Benkeser et al.[14] GLC and NMR analysis showed **11** thus prepared was >99% pure. **11**: bp 88–90 °C (15 mmHg); IR (neat) 2900, 1440 cm^{-1}; MS *m/e* 150 (M^+); ^1H NMR (CCl_4) δ 1.30–2.45 (m). Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 87.55; H, 12.03.

Registry No.—**1**, 10515-92-1; **2**, 22118-00-9; **3**, 769-32-4; **4**, 38262-50-9; **5**, 66921-98-0; **6**, 67009-06-7; **7**, 66922-00-7; **8**, 66922-01-8; **9**, 66921-99-1; **10**, 66922-02-9; **11**, 25107-10-2; bicyclo[6.3.0]undecan-9-one, 40696-12-6; bicyclo[6.3.0]undec-1(2)-ene, 66922-03-0.

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(12) ^{13}C NMR of **5** shows nine signals because two pairs of the methylene carbon have nearly the same shifts most likely at 25.21 and 26.12 ppm which have almost twice the intensity of the other methylene signals.

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A Facile Synthesis of (3-Methoxyisoquinol-7-yl)acetic Acids

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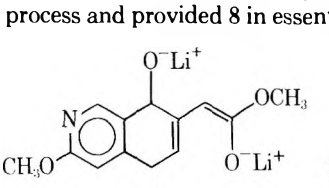
Our work on the total synthesis of 2-azasteroids necessitated the development of a synthesis of 7-aza-6-methoxy-1-tetralone (**1**).[1] While this compound has been successfully utilized for the preparation of 2-azaestrone derivatives, its potential as a precursor for the preparation of other biologically interesting molecules was apparent. We would now like to report on the use of this material for the facile preparation of (3-methoxyisoquinol-7-yl)acetic acids.[2] Previous syntheses of the carbocyclic analogues of this system have employed the Wilgerodt–Kindler reaction[3] on the appropriately substituted 2-acylnaphthalene,[2] or high temperature catalytic dehrogenation of the dihydro derivatives produced from tetralones.[4] In contrast to the rather severe conditions of these methods, the approach described herein proceeds under mild conditions and provides a method of general utility for the synthesis of a variety of systems related to **6**.

Treatment of the azatetralone **1** with glyoxylic acid monohydrate in aqueous alcoholic hydroxide solution[5] afforded the unsaturated acid **2**.[6] Following esterification to the methyl ester, sodium borohydride reduction of the ketone **3** provided the conjugated hydroxyester **4**. This ester **4** could then be conveniently converted to the isoquinoline system (**6**) by deconjugation with 2 equiv of lithium diisopropylamide (LDA)[7] and subsequent dehydration of the allylic alcohol **5** with acetic acid at room temperature. It was originally thought that the intermediate **7** generated from LDA treatment might be susceptible to side-chain alkylation during the isomerization process and provided **8** in essentially a single-pot process from



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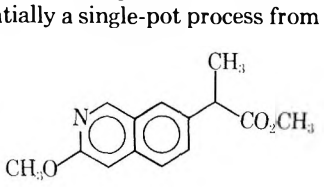

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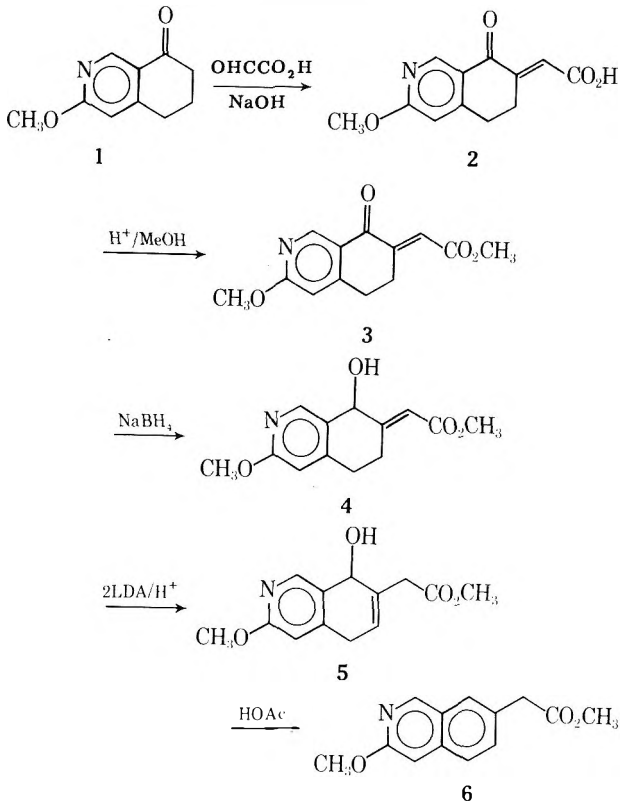
Scheme I



5.[8] Unfortunately, alkylation of **7** was not observed when methyl iodide was added to the LDA reaction mixture and **8** was ultimately prepared by LDA/MeI alkylation of **6** in a separate step.

Experimental Section

NMR spectra were obtained on a Varian A-60A or T-60 spectrometer with tetramethylsilane as the internal standard. UV spectra were obtained in MeOH on a Beckman DK-2A. TLC was on 7.6-cm microscope slides covered with Woelm F silica with a magnesium silicate binder using 5% phosphomolybdic acid–EtOH (wt/v) followed by heat for visualization. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

(3-Methoxy-8-oxo-5,6,7,8-tetrahydroisoquinol-7-ylidene)-acetic Acid (2). To 15.0 g (0.085 mol) of **1** in 100 mL of methanol was added 9.0 g (0.12 mol) of glyoxylic acid hydrate followed by 100 mL of 5% sodium hydroxide solution (0.125 mol) and the purple reaction mixture was stirred overnight at room temperature, then refluxed for 3 h. Addition of 200 mL of water was followed by extraction of the aqueous basic solution three times with chloroform. The aqueous solution was then acidified with formic acid to pH 4 whereupon the precipitate which formed was collected providing 11.2 g of product. Extraction of the filtrate three times with ethyl acetate followed by drying the extracts over sodium sulfate and solvent removal in vacuo gave 2 g of oil which upon trituration with ethyl acetate afforded an additional 0.45 g of **2** (58% total). Recrystallization from ethanol gave the pure acid: mp 221–222 °C dec; UV 297 (ϵ 12 600), 255 nm (ϵ 10 700), 235 nm (ϵ 11 300); NMR (C_5D_5N) δ 2.82 (2 H, m, CH_2), 3.55 (2 H, m, CH_2), 3.97 (3 H, s, OCH_3), 6.59 (1 H, brd s, 4-H), 7.38 (1 H, t, J = 1.5 Hz, vinyl-H), 9.10 (1 H, s, 1-H).

Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.70; H, 4.82; N, 5.93.

(3-Methoxy-8-oxo-5,6,7,8-tetrahydroisoquinol-7-ylidene)-acetic Acid Methyl Ester (3). To 16.6 g (0.071 mol) of **2** in 150 mL of methanol was added 4 mL of concentrated sulfuric acid and the reaction mixture was refluxed for 3 h. After cooling, water was added followed by sufficient ammonium hydroxide solution to raise the pH of the solution to 8. The precipitate which formed was collected affording 14.1 g (80%) of ester. Recrystallization from methanol gave **3**: mp 111–112 °C; UV (MeOH) 301 (ϵ 12 400), 252 (ϵ 13 300), 241 nm (ϵ 13 600); NMR ($CDCl_3$) δ 2.93 (2 H, brd m, CH_2), 3.42 (2 H, brd m, CH_2), 3.80 (3 H, s, CO_2CH_3), 4.00 (3 H, s, OCH_3), 6.60 (1 H, brd s, 4-H), 6.90 (1 H, t, J = 1.5 Hz, vinyl H), 8.93 (1 H, brd s, 1-H).

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 62.85; H, 5.40; N, 5.83.

(8-Hydroxy-3-methoxy-5,6,7,8-tetrahydroisoquinol-7-ylidene)acetic Acid Methyl Ester (4). To 4.15 g (0.0167 mol) of **3** suspended in 100 mL of methanol cooled to −5 °C was added 0.4 g of sodium borohydride in portions over a 5-min period. The cooling bath was then removed and the now homogeneous reaction mixture was stirred at room temperature for 20 min after which time product began separating from the solution. Water was added and the precipitate collected providing 2.6 g of analytically pure **4**. The aqueous filtrate was extracted three times with chloroform and these extracts provided an additional 1.2 g of product (91% total): mp 141–142 °C; UV (MeOH) 220 (ϵ 22 900), 272 nm (ϵ 3600); NMR ($CDCl_3$) δ 3.72 (3 H, s, CO_2CH_3), 3.90 (3 H, s, OCH_3), 5.17 (1 H, brd s, 8-H), 6.17 (1 H, brd s, vinyl H), 6.52 (1 H, brd s, 4-H), 8.18 (1 H, brd s, 1-H).

Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.27; H, 5.87; N, 5.56.

(3-Methoxyisoquinol-7-yl)acetic Acid Methyl Ester (6). To 2.5 g (25 mmol) of diisopropylamine in 35 mL of tetrahydrofuran under a nitrogen atmosphere at room temperature was added 14 mL of 1.7 M methyllithium in ether solution (24 mmol) and the solution was then cooled to −70 °C. After addition of 2.3 g (9.25 mmol) of **4** in 25 mL of tetrahydrofuran over a 15-min period, the deep red solution was stirred at the above temperature for 90 min before a solution of 5 mL of acetic acid in 5 mL of ether was added and the cooling bath was removed. After the reaction mixture had warmed to room temperature, additional ether and saturated salt solution were added and the two phases were separated. The aqueous phase was extracted with an additional portion of ether and the combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal gave an oil which by thin layer chromatography (silica; 50% ethyl acetate/50% benzene) showed two components with the more polar **5** in preponderance. The oil was taken up into 5 mL of acetic acid and let stand at room temperature overnight. Water was added to the reaction mixture followed by sufficient concentrated ammonium hydroxide solution to basify the solution (pH 8). After extracting the solution several times with pentane, the combined extracts (ca. 250 mL in volume) were washed with saturated salt solution, dried over sodium sulfate, treated with activated charcoal, and filtered through a cake of diatomaceous earth. Solvent removal in vacuo gave 1.6 g (75%) of fluffy white solid. Recrystallization from pentane gave pure **6**: mp 49.5–51 °C; UV 226 nm (ϵ 70 000); NMR ($CDCl_3$) δ 3.70 (3 H, s, CO_2CH_3), 3.73 (2 H, s, CH_2), 4.00 (3 H, s, OCH_3), 6.95 (1 H, brd s, 4-H), 7.50–7.70 (3 H, aromatic H's), 8.87 (1 H, brd s, 1-H).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.72; H, 5.74; N, 5.79.

(3-Methoxyisoquinol-7-yl)-2-propionic Acid Methyl Ester (8). To 0.75 g (0.0075 mol) of diisopropylamine in 30 mL of tetrahydrofuran at room temperature under an atmosphere of nitrogen was added 4.3 mL of a 1.7 M methyllithium in ether solution. The reaction mixture was then cooled to −70 °C before the dropwise addition of 1.6 g (0.007 mol) of **6** in 10 mL of tetrahydrofuran over a 5-min period. After stirring the above for 20 min at −70 °C 1.15 g (0.081 mol) of methyl iodide in an equivalent volume of tetrahydrofuran was added and stirring was continued at the above temperature for 3 h. The reaction mixture was allowed to warm to −25 °C before addition of saturated ammonium chloride solution then ether and the layers were separated. The aqueous phase was extracted with two additional portions of ether and the combined extracts were washed with saturated salt solution and dried over sodium sulfate. Solvent removal gave 1.6 g of oil (95%). The analytically pure material was obtained by extracting the crude oil with pentane and subsequent removal of the hydrocarbon solvent to give a clear oil which crystallized upon standing: mp 35–36 °C; UV 227 nm (ϵ 71 500); NMR ($CDCl_3$) δ 1.63 (3 H, d, J = 7 Hz, CH_3), 3.68 (3 H, s, CO_2CH_3), 4.01 (3 H, s, OCH_3), 6.96 (1 H, brd s, 4-H), 7.60 (2 H, brd s, aromatic H's), 7.77 (1 H, brd s, aromatic H), 8.92 (1 H, brd s, 1-H).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.30; H, 6.38; N, 5.73.

Acknowledgments. We would like to thank Ms. M. A. Oram for technical assistance, Mr. E. Zielinski and associates for microanalyses, and Mr. A. J. Damascus and associates for obtaining the spectral data.

Registry No.—**1**, 56053-58-8; **2**, 66967-20-2; **3**, 66967-21-3; **4**, 66967-22-4; **5**, 66967-23-5; **6**, 61714-84-9; **8**, 61714-85-0; glyoxylic acid, 298-12-4.

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A Direct Synthesis and Carbon-13 Nuclear Magnetic Resonance Spectral Analysis of 4-Substituted Isoquinolines[1]

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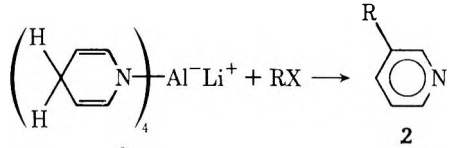
Received March 28, 1978

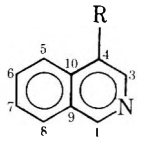
We have shown[2] that the reaction of lithium tetrakis(*N*-dihydropyridyl)aluminate (LDPA, **1**; from pyridine and lithium aluminum hydride ($LiAlH_4$))[3] with electrophilic reagents leads directly to 3-substituted pyridines, **2**, in high



1 **2**

yields. It was demonstrated[4] that the optimum yields of 3-substituted pyridines were obtained when 1 molar equiv of the appropriate alkyl halide was added per mol of LDPA. The addition of larger amounts of electrophilic reagent did not increase the yield of 3-substituted products. These results suggest that only one "dihydropyridyl" moiety per molecule of LDPA is reactive.

We now report the extension of this reaction to the synthesis of 4-substituted isoquinolines **3** from isoquinoline, $LiAlH_4$,



3

and electrophilic reagents. Isoquinoline compounds with substitution in the 4 position have been shown to possess significant antispasmodic and vasodilatory properties,[5] and a tetrahydro derivative exhibited selective β_2-adrenergic agonist activity.[6] A number of synthetic studies have been directed toward these substances.[7]

Initially, the reaction of isoquinoline, $LiAlH_4$, and benzyl chloride was investigated. We first wished to ascertain if the desired reaction would occur at all and then to determine the reaction stoichiometry which is necessary for optimum yields.

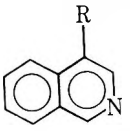
A series of reactions was carried out in tetrahydrofuran (THF) in which the molar ratio of isoquinoline to $LiAlH_4$ was kept constant at 4:1, but the number of molar equivalents of benzyl chloride was varied in increments of 1, from 1 to 4. The results of these experiments are shown in Table I and illustrate that the most efficient conversion of alkyl halide to 4-benzylisoquinoline occurs when 1 molar equiv is present (yield ≃ 90%). In contrast to the pyridine series,[4] the yield of 4-benzylisoquinoline increases as the amount of benzyl chloride increases (column 3, Table I); therefore, more than 1 of the 4 molar equiv of isoquinoline is rendered reactive by treatment with a single molar equiv of $LiAlH_4$. Since the yield increased in an irregular manner, we are as yet unable to speculate on the exact nature of the reactive species.

Table I. Effect of Various Molar Ratios of Reagents on the Yield[a] of 4-Benzylisoquinoline[b]

$PhCH_2Cl$/ $LiAlH_4$	% yield based on $PhCH_2Cl$	% yield based on $LiAlH_4$
1:1	91 (88)[c]	91 (88)[c]
2:1	59 (45)	118 (91)
3:1	46 (45)	134 (128)
4:1	39 (35)	158 (142)

[a] The percent yields in this table were obtained by GLC analysis. [b] Isoquinoline (4 molar equiv) was present in THF solvent in each reaction. [c] Values in parentheses were obtained in a duplicate experiment.

Table II. Yields of 4-Substituted Isoquinolines



R	registry no.	% yield (isolated)	% yield (GLC)[a]	% yield (lit)
$PhCH_2$	10166-05-9	43[a] (56)[b]	90	34[c]
$H_2C{=}CHCH_2$	66967-18-8	24 (9)	80	
CH_3CH_2	41219-10-7	2 (13)[d]	35	<4[e]

[a] Molar ratio of isoquinoline/$LiAlH_4$/RX, 4:1:1. [b] Molar ratio of isoquinoline/$LiAlH_4$/RX, 4:1:4. [c] Reference 9. [d] Based on recovered isoquinoline. [e] Reference 10.

Subsequent reactions have been carried out using both a 4:1:1 molar ratio and a 4:1:4 molar ratio of isoquinoline/$LiAlH_4$/alkyl halide. The yields of 4-benzyl- (**4**), 4-allyl- (**5**), and 4-ethylisoquinolines (**6**) are listed in Table II. In each instance the isolated yield of purified material is less than the GLC yield, owing to nonoptimal isolation procedures. In spite of the modest isolated yields, we feel that this method is a useful one due to its simplicity and the ready availability of the inexpensive starting materials. In addition, the alkylation may be carried out using a simple aliphatic alkyl halide, which has not always been possible using other methodologies.[7,8] Work is in progress in our laboratories to optimize the yields of this process and to extend it to the preparation of more complex substances.

^{13}C NMR Spectral Analysis. As part of a thorough characterization of the 4-substituted isoquinolines prepared in this study, their ^{13}C NMR spectra were recorded. Most of the carbon resonances were readily assigned using standard chemical shift theory[11] and by comparison to a previous rigorous assignment of the spectrum of isoquinoline itself.[12] Using these data, however, it was not possible to unambiguously assign the C-7 and C-8 resonances, which are separated by about 1.5 ppm in the 4-substituted isoquinolines and by only 0.4 ppm in the parent heterocycle.

A straightforward solution to this problem results from recognition that the nonnitrogenous ring of isoquinolines can be viewed as an unsymmetrically ortho-disubstituted benzene

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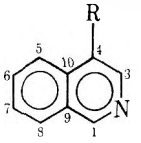
Table III. ^{13}C NMR Chemical Shifts of Isoquinolines[a]



carbon no.	R = H[b]	R = $PhCH_2$	R = CH_2=$CHCH_2$	R = CH_3CH_2
1	152.5	151.8	151.9	151.1
3	143.0	143.8	143.0	141.8
4	120.4	129.6	129.2	132.9
5	126.4	123.4	123.3	122.7
6	130.2	130.2	130.1	130.0
7	127.2	126.8	126.8	126.6
8	127.6	128.1	128.3	128.2
9	128.6	127.2	126.1	127.5
10	135.7	134.8	134.7	134.5

[a] The δ values are in ppm downfield from Me_4Si. The spectra were taken in $CDCl_3$ solutions where $\delta(Me_4Si) = \delta(CDCl_3) + 77.1$ ppm. [b] Reference 12; the numbers reported here were obtained in our laboratory.

and is therefore amenable to spectral analysis using the "fingerprint" technique described by Günther and his coworkers.[13,14]

In the ^1H-coupled spectra of the 4-alkylisoquinolines, the resonances of C-6 and C-7 were predictably observed as clean doublets of doublets and that of C-8 appeared as a doublet of multiplets. It was thus possible to easily differentiate the C-7 and C-8 resonances, thereby completing the chemical shift assignments of the 4-substituted isoquinolines, which are catalogued in Table III. Chemical shifts of the exocyclic carbons are shown in Chart I.

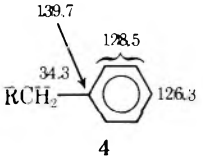
A potentially useful phenomenon was observed for the signal arising from C-5, which in the ^1H-coupled ^{13}C NMR spectrum of each 4-substituted isoquinoline is simplified to a distinct doublet of doublets. This may be ascribed to the absence of a hydrogen at the 4 position and should prove useful in spectral analysis of more complex isoquinolines.

The data in Table III reveal that the major chemical shift perturbations resulting from the introduction of a 4 substituent to an isoquinoline skeleton occur at C-4 and C-5, the former position being deshielded and the latter shielded with respect to analogous centers in isoquinoline itself. This observation is reminiscent of perturbations produced upon the introduction of an alkyl group at the 1 position of naphthalene[15] and may be attributed in part to steric interactions between the alkyl group and the peri hydrogen (at C-5 in the isoquinolines).

Experimental Section.

Boiling points and melting points are uncorrected. Infrared spectra of neat liquids were recorded on a Perkin-Elmer 227B spectrophotometer, and mass spectra were obtained on a Hewlett-Packard 5982A spectrometer. ^1H and ^{13}C NMR spectra were run on $CDCl_3$ solutions with Me_4Si as an internal standard (δ = 0 ppm) on a Varian T-60 spectrometer and a Jeol JNM-PS-100 spectrometer operating at 25.034 Hz in the Fourier transform mode, respectively. GLC analyses were performed on a 6 ft × 0.25 in 3% OV-1 on 100–120 mesh Gas Chrom Q column in a Varian Aerograph Series 1520 chromatograph. 4-Benzylisoquinoline was analyzed at a column temperature programmed from 125–250 °C at 20 °C/min, while other analyses were run isothermally at 168 °C. Peak height comparisons were made to a five point calibration curve obtained by injecting a standard solution of the appropriate pure isoquinoline. Preparative TLC utilized Merck silica gel 60 PF-254 as adsorbent. Tetrahydrofuran (THF) was freshly distilled from $LiAlH_4$ before each reaction. Solutions of reaction mixtures were dried over anhydrous sodium sulfate. A representative procedure appears below. Similar reactions were carried out using this procedure with modified quantities and types of reagents where appropriate.

Chart I. ^{13}C NMR Chemical Shifts (δ) of Exocyclic Carbons (R = 4-Substituted Isoquinoline)



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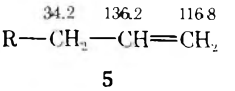

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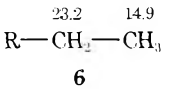

6

4-Allylisoquinoline (5). A solution of 7.250 g (0.056 mol) of isoquinoline in 10 mL of dry THF was added over 0.5 h under nitrogen to a stirring mixture of 0.551 g (0.015 mol) of lithium aluminum hydride in 20 mL of THF at room temperature. After 24 h a solution of 1.755 g (0.0145 mol) of allyl bromide in 5 mL of THF was added over 15 min. The mixture was stirred and refluxed for 1 h, quenched cautiously with 10 mL of water, and diluted with 50 mL of acetone. The mixture was filtered over Celite, and most of the acetone and THF was removed in vacuo. The residue was diluted with 100 mL of dichloromethane and dried. Evaporation of the solvent provided 8.482 g of orange liquid which was fractionally distilled twice to provide, after a forerun of isoquinoline, 788 mg of a colorless liquid, bp 133–160 °C (5–6 Torr), which was primarily 4-allylisoquinoline (80% pure by GLC). This could be further purified (with some sacrifice of material) by repeated distillation to give a colorless liquid: bp 86 °C (0.25 Torr); IR 1645, 1630, 1590, 1520 cm^{-1}; ^1H NMR δ 3.69 (d, 2, J = 6 Hz, CH_2), 4.83–5.09 (m, 1, olefinic H), 5.11–5.29 (m, 1, olefinic H), 5.50–6.42 (m, 1, olefinic H), 6.95–8.12 (m, 4, C-5, C-6, C-7, and C-8 H's), 8.38 (s, 1, C-3 H), 9.11 (s, 1, C-1 H); mass spectrum, m/e 169 (M^+), 168 (base), 167, 157, 141, 115; picrate mp 157 °C (from aqueous ethanol).

Anal. Calcd for $C_{18}H_{14}N_4O_7$: C, 54.27; H, 3.55; N, 14.07. Found: C, 54.48; H, 3.57; N, 14.06.

Acknowledgment. The authors are grateful to the Robert A. Welch Foundation for the financial support of this work and to members of our laboratory for their comments and assistance.[16]

Registry No.—5 picrate, 66967-19-9; isoquinoline, 119-65-3; allyl bromide, 106-95-6; benzyl chloride, 100-44-7.

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Stereoselective Oxidation by Thionyl Chloride Leading to the Indeno[1,2-*c*]isoquinoline System

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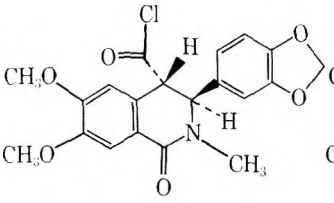
Received February 28, 1978

Thionyl chloride is commonly used for the conversion of carboxylic acids to acid chlorides and alcohols to alkyl chlorides. Several transformations are also known in which this

reagent acts as an oxidant.[1-8] The trans acid chloride **1** is formed smoothly on treatment of the corresponding acid with thionyl chloride and it recently served as an intermediate in a total synthesis of nitidine chloride.[9] However, subjection of the cis acid **2** to thionyl chloride at room temperature resulted



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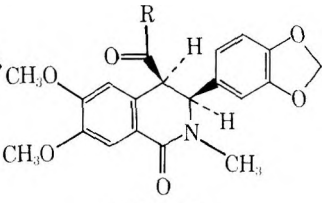
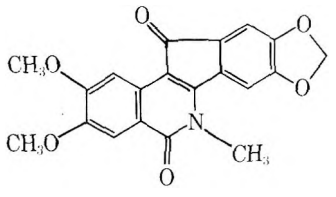


2, R = OH
7, R = OCH_3
9. R = Cl

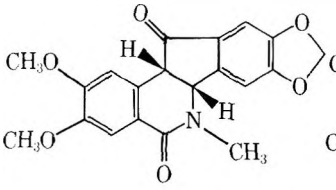
in the formation of a dark red, crystalline compound which was not the expected acid chloride. The elucidation of its structure and studies concerning the mechanism of its formation are presented herein.

The insolubility of the dark red compound in common organic solvents necessitated a Fourier transform proton magnetic resonance study, which indicated the disappearance of the two methine protons from the starting material **2**[9] as well as one aromatic proton from the methylenedioxyphenyl ring and the acidic proton. The transformation was also accompanied by a downfield shift of the *N*-methyl protons by ca. 0.9 ppm, suggesting the indeno[1,2-*c*]isoquinoline system **3**. The infrared spectrum of the new compound showed the disappearance of the carboxylic acid carbonyl of the starting material (1740 cm^{-1}) and its replacement by a new carbonyl (1690 cm^{-1}) expected for 11-ketoindeno[1,2-*c*]isocarbostyrils.[10] The molecular ion (*m/e* 365) observed in the mass spectrum also supported structure **3**.



3

The conversion of **2** to **3** obviously involves a two-electron oxidation and an intramolecular Friedel–Crafts reaction, offering the indeno[1,2-*c*]isoquinoline **4** and the dehydro acid chloride **5** for consideration as intermediates. Compound **4** was prepared by heating the cis acid **2** with phosphorus pentoxide in refluxing chloroform, while the ester **6** was obtained by DDQ oxidation of the methyl ester **7**. Heating the ester **6** with potassium hydroxide in Me_2SO gave the desired acid **8**. The hypothetical intermediate **4** was recovered largely unchanged even after stirring in thionyl chloride for 72 h, although several minor peaks in the NMR spectrum of the crude material could be attributed to **3** (conversion <15%). The oxidation of **4** to **3** did occur smoothly with DDQ. In contrast, the acid **8** was completely converted into **3** by thionyl chloride within 4 h. Since **3** can be isolated in 80% yield after reacting **2** with thionyl chloride for 4 h, the oxidation step probably precedes the intramolecular Friedel–Crafts reaction.



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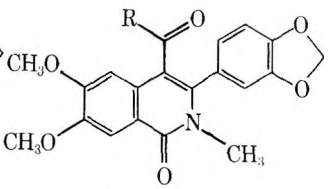
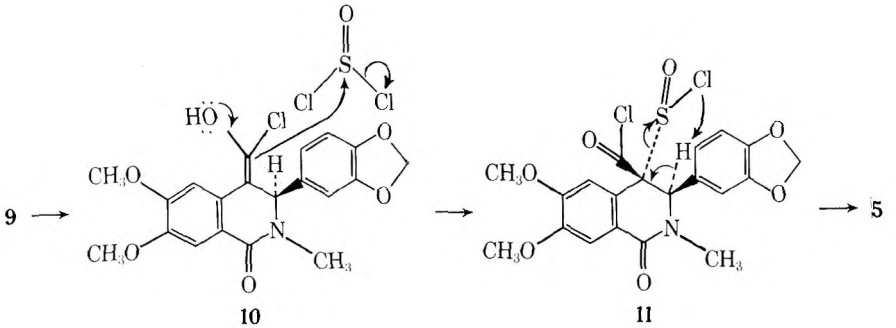
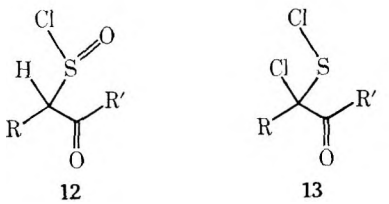


5, R = Cl
6, R = OCH_3
8, R = OH

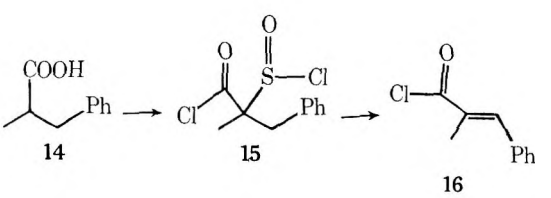
We assume that the initial step in the oxidation of the acid chloride **9** is enolization to **10**, followed by Hell–Volhard–Zelinsky-type addition of thionyl chloride from the less sterically hindered side to afford the α-sulfinyl chloride **11**. This hypothesis is supported by the observation that a variety of carboxylic acid chlorides and ketones react with thionyl chloride in the presence of catalytic amounts of pyridine to form unstable α-sulfinyl chlorides **12** which are converted to the α-chloro-α-sulfenyl chlorides **13** by the Pummerer rearrangement.[4] The latter compounds have served as intermediates in the formation of 3-thietanones[5,11] and benzo[*b*]-thiophenes.[7,12,13] The dehydro acid chloride **5** may then arise from **11** by a concerted elimination of HCl and sulfur monoxide, which is in equilibrium with sulfur dioxide and elemental sulfur.[14] This step finds analogy in the thionyl chloride oxidations of benzil[2] and certain tetramic acids,[3] as well as the decomposition of α-phenylsulfinyl lactones to α,β-unsaturated lactones.[15] Further support for this mechanism is provided by the detection of the α-sulfinyl chloride **15** in the previously reported thionyl chloride oxidation of 2-methyl-3-phenylpropanoic acid **14** to the dehydro acid chloride **16**.[12] An HCl-catalyzed intramolecular Friedel–Crafts reaction[16] of the



10 **11**



12 **13**



14 **15** **16**

acid chloride **5** then completes the formation of **3**. This reaction is expected to occur with greater facility in the oxidized system **5** as opposed to **9** due to resonance stabilization of the intermediate acylium ion.

The difference in reactivity of the diastereomeric acid chlorides **1** and **9** may be ascribed to a stereoelectronic effect.[17] In both compounds the aromatic substituent is expected to be pseudoaxial in order to avoid a severe nonbonded interaction with the *N*-methyl group (A strain).[9,18,19] Therefore the enolizable proton of the cis diastereomer **9** is pseudoaxial and inspection of Dreiding models reveals that the C–H bond is parallel with the adjacent p orbitals of the aromatic π system. The resulting orbital overlap should facilitate enolization.[17] In contrast, the corresponding C–H bond of the trans diastereomer and the p orbitals of the adjacent aromatic π system are nearly orthogonal.

The cis acid **2** is readily available from the condensation of 4,5-dimethoxyhomophthalic anhydride and 3,4-methylenedioxybenzylidenemethylamine.[9] Our two-step synthesis of indenoisoquinoline **3** therefore compares favorably with other approaches to this system.[10,20]

Experimental Section

All reactions were performed under a nitrogen atmosphere. Melting points were determined on a Thomas-Hoover Unimelt or a Meltemp apparatus and are uncorrected. NMR spectra were recorded on a Varian EM-360 60 MHz or an FT-80 spectrometer and except where noted in $CDCl_3$ solvent. Chemical shifts are reported in ppm relative to Me_4Si as internal standard. IR spectra were recorded on a Beckman IR-33 spectrophotometer. Mass spectra were determined on a Dupont 21-492 B double-focusing spectrometer using an ion source temperature of 230–270 °C, an ionization potential of 70 eV, and an ionizing current of 100 μA.

2,3-Dimethoxy-5,6-dihydro-5,11-diketo-6-methyl-8,9-methylenedioxy-11*H*-indeno[1,2-*c*]isoquinoline (3). A. Thionyl chloride (1 mL, freshly distilled from triphenyl phosphite) was added with stirring to the cis acid **2**[9] (100 mg, 0.26 mmol) to give a pale yellow heterogeneous mixture. The system became homogeneous and turned red within 10 min but returned heterogeneous shortly thereafter. After 4 h the reaction mixture was diluted with benzene (5 mL) and evaporated to dryness. The brownish-red residue thus obtained was passed through a short column of silica gel (1 g), eluting with chloroform, to afford dark red needles (75 mg, 79%): mp 295–299 °C dec; IR (KBr) 1690, 1642 cm^{-1}; NMR δ 7.98 (s, 1 H), 7.65 (s, 1 H), 7.12 (s, 1 H), 7.06 (s, 1 H), 6.08 (s, 2 H), 4.04 (s, 3 H), 3.98 (s, 3 H), 3.97 (s, 3 H); mass spectrum *m/e* (rel intensity) 365 (M^+, 100), 351 (9), 350 (42), 322 (9), 320 (11), 182 (15), 83 (8), 71 (8), 69 (10), 57 (16), 55 (11), 43 (14).

B. A mixture of the dehydro acid **8** (15 mg, 0.039 mmol) and thionyl chloride (0.3 mL) was allowed to stir for 4 h during which the system remained heterogeneous. Removal of thionyl chloride gave a dark red residue which upon preparative TLC (silica gel, 1 mm, CH_3OH–$CHCl_3$, 1:9) afforded a crystalline solid (12 mg, 84%). The mp, NMR, and IR spectra were identical with the above.

C. A solution of ketolactam **4** (150 mg, 0.408 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (98%, 150 mg, 0.648 mmol) in distilled dioxane (10 mL) was heated at reflux for 43 h. After cooling and addition of $CHCl_3$ (100 mL) the red organic phase was washed with 5% aqueous $NaHCO_3$ (150 mL) and then water (200 mL). The organic phase was dried ($MgSO_4$) and evaporated to dryness to yield dark red crystals (104 mg, 70%). The mp, IR, and NMR spectra were identical with those above.

***cis*-2,3-Dimethoxy-5,6,12,13-tetrahydro-5,11-diketo-6-methyl-8,9-methylenedioxy-11*H*-indeno[1,2-*c*]isoquinolone (4).** A stirred mixture of the cis acid **2** (200 mg, 0.52 mmol) and phosphorus pentoxide (2 g) in $CHCl_3$ (20 mL) was heated at reflux. After 2 h ice water (100 mL) was added and the aqueous phase was extracted with $CHCl_3$ (75 mL). The combined $CHCl_3$ extracts were washed with 5% aqueous $NaHCO_3$ (40 mL) and then water (200 mL). After drying ($MgSO_4$), the $CHCl_3$ was removed to give a yellow powder (130 mg, 68%): mp 270–272 °C (dec); IR (KBr) 1695, 1645, 1595 cm^{-1}; NMR δ 7.60 (s, 1 H), 7.18 (s, 1 H), 7.08 (s, 1 H), 7.05 (s, 1 H), 6.10 (d, 1 H, J = 1 Hz), 6.06 (d, 1 H, J = 1 Hz), 5.14 (d, 1 H, J = 8 Hz), 4.21, (d, 1 H= J = 8 Hz), 3.95 (s, 3 H), 3.88 (s, 3 H), 3.51 (s, 3 H); mass spectrum *m/e* (rel intensity) 367 (M^+, 100), 365 (19), 337 (35), 211 (16), 193 (22), 189 (13), 163 (48).

***cis*-*N*-Methyl-3-(3′,4′-methylenedioxyphenyl)-4-methoxycarbonyl-6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (7).** The cis acid **2** (400 mg, 1.04 mmol) was added to an ethereal solution of diazomethane (ca. 30 mmol) at 0 °C. After stirring at 0 °C for 50 min the reaction mixture was evaporated to dryness to give a white solid (402 mg, 97%): mp 156–158 °C; IR (KBr) 1740, 1635, 1595 cm^{-1}; NMR δ 7.82 (s, 1 H), 7.06 (s, 1 H), 6.86–6.43 (m, 3 H), 5.93 (s. 2 H), 4.93 (d, 1 H, J = 7 Hz), 4.70 (d, 1 H, J = 7 Hz), 4.03 (s, 3 H), 3.93 (s, 3 H), 3.73 (s, 3 H), 3.05 (s, 3 H).

***N*-Methyl-3-(3′,4′-methylenedioxyphenyl)-4-carboxy-6,7-dimethoxy-1(2*H*)-isoquinolone (8).** A solution of the cis ester **7** (400 mg, 1.0 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (98%, 340 mg, 1.47 mmol) in distilled dioxane (25 mL) was heated at reflux for 24 h. After cooling and addition of $CHCl_3$ (75 mL), the organic phase was washed with 5% aqueous $NaHCO_3$ (150 mL) and then water (200 mL). The organic phase was dried ($MgSO_4$) and evaporated to dryness. The light orange residue, after chromatography on silica gel (10 g, $CHCl_3$ as eluent), gave the crude dehydro ester **6** as a white glassy solid (276 mg, 69%): mp 172–178 °C; IR (KBr) 1710, 1645, 1605 cm^{-1}; NMR δ 7.93 (s, 1 H), 7.20 (s, 1 H), 7.05–6.83 (m, 3 H), 6.12 (s, 2 H), 4.06 (s, 3 H), 4.01 (s, 3 H), 3.57 (s, 3 H), 3.40 (s, 3 H). A solution of **6** (233 mg, 0.586 mmol) and KOH (85%, 501 mg, 7.6 mmol) in Me_2SO (6.5 mL) was heated at 72–75 °C for 16 h. The reaction mixture was diluted with water (200 mL), acidified with concentrated HCl, and extracted with $CHCl_3$ (150 mL). The organic phase was backwashed with 5% aqueous $NaHCO_3$ (75 mL). The combined aqueous extracts were acidified and extracted with $CHCl_3$ (150 mL). After washing with water (300 mL), the $CHCl_3$ was evaporated to afford **8** as a white solid (172 mg, 45% overall): mp 256–258 °C; IR (KBr) 3600–2200, 1710, 1635, 1600 cm^{-1}; NMR ($CDCl_3$ + 2 drops of Me_2SO-d_6) δ 7.83 (s, 1 H), 7.24 (s, 1 H), 6.87 (s, 3 H), 6.04 (s, 2 H), 4.01 (s, 3 H), 3.96 (s, 3 H), 3.33 (s, 3 H), 3.50–2.70 (broad s, exchangeable with D_2O); mass spectrum *m/e* (rel intensity) 383 (M^+, 100), 382 (32), 369 (16), 340 (9), 339 (8), 192 (6), 162 (10), 83 (10), 71 (12), 69 (12), 47 (22), 45 (14).

Acknowledgment. This investigation was supported by Grant 1 RO1 CA19204-02, awarded by the National Cancer Institute, DHEW.

Registry No.—**2**, 64036-07-3; **3**, 66358-49-4; **4**, 66358-50-7; **6**, 66358-51-8; **7**, 66358-52-9; **8**, 66358-53-0; thionyl chloride, 7719-09-7.

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Dienone Intermediates in the Pummerer Rearrangement of 4-Methylsulfinyl-3,5-xylenol

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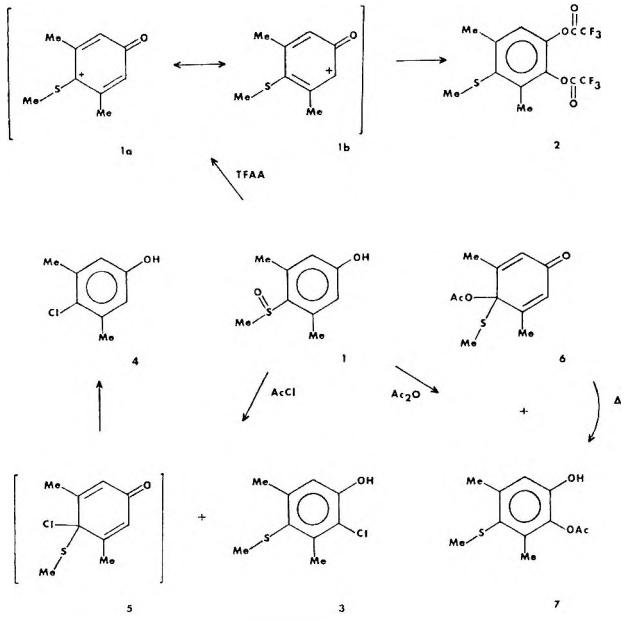
Received May 2, 1978

The rearrangement of sulfoxides to α-substituted derivatives of the corresponding sulfides is well documented[1,2] and is widely known as the Pummerer reaction. The number of interesting variations on this reaction reported recently[3] suggests that its synthetic utility has been relatively underdeveloped.

We have previously described[4] (for gas–liquid chromatography characterization purposes) the rapid transformation of 4-methylsulfinyl-3,5-xylenol (1) to the bis(trifluoroacetyl)catechol analogue **2** after reaction with trifluoroacetic anhydride at room temperature. Mechanistically it was inferred that upon initial trifluoroacetylation of the sulfoxide oxygen, the trifluoroacyl anion removed a proton from the phenolic OH moiety rather than from the S–CH_3 group. This could result in production of the intermediate 2,4-dienone cation **1b,** which if trapped by attack of trifluoroacetate ion at C-2 would (after trifluoroacetylation of the phenol group) yield the observed bistrifluoroacetate **2.** Alternately, trapping of the intermediate 2,5-dienone cation **1a** with a subsequent 1,3 trifluoroacetyl migration to C-2 is also a potential pathway. This consideration, plus the knowledge that an intermediate monotrifluoroacetate was not isolated previously, encouraged us to examine the reaction of **1** with two less active acylating agents, namely acetyl chloride and acetic anhydride.



Results and Discussion

Although prolonged mixing of 4-methylsulfinyl-3,5-xylenol (1) in benzene at room temperature with an excess of acetic anhydride did not initiate any reaction, similar treatment with acetyl chloride eventually brought about complete conversion to two new compounds. The minor compound (18%) was tentatively identified as the 2-chloro analogue **3** on the basis of its spectral data; i.e., NMR studies showed the loss of an aromatic proton, and the mass spectrum indicated incorporation of a chloride atom and a parent ion of *m/e* 202. The major compound (57%) was readily identified by comparison with a known sample as 4-chloro-3,5-xylenol (4).[5] A preponderance of this latter product strongly supports the existence of a 2,5-dienone precursor **5** with subsequent aromatization by elimination of $-SCH_3$ as the major pathway. Failure to isolate such an intermediate and determine its conversion products negated any speculation as to a related reaction sequence culminating in production of the 2-chloro compound **3.**

Since acetic anhydride is a less reactive acylating agent than acetyl chloride, refluxing a mixture of 4-methylsulfinyl-3,5-xylenol (1) in benzene with an excess of acetic anhydride was investigated. Periodic TLC examination indicated that some reaction was taking place, and after 48 h approximately 20% of the sulfoxide (1) had reacted. Preparative TLC of the reaction mixture yielded two new products which could be separated and fully characterized. The major product from this reaction was assigned the structure **6** and would arise from trapping of the 2,5-dienone cation **1a.** The identity of **6** followed from its spectroscopic properties, the infrared spectrum of which showed the absence of hydroxyl functions and the presence of strong carbonyl adsorptions at 1745 (acetate) and 1660 cm^{-1} (cross-conjugated dienone). In accordance with its formulation as a dienone structure, the NMR spectrum of **6** showed that absorption of the two previously aromatic protons (H-2 and H-6) was now shifted upfield from δ 6.60 to δ 6.20. Introduction of an acetate group was also confirmed by NMR spectroscopy. Identification of the minor reaction product as the 2-acetoxy compound **7** (spectroscopic data indicated the presence of a hydroxyl function and just one aromatic proton) suggested a sequential relationship proceeding via a 1,3 acetyl migration in the dienone **6.** Demonstration of this supposition was readily achieved by refluxing a sample of **6** in benzene. This treatment yielded a compound identical in all respects with the previously isolated 2-acetoxy analogue **7.** It was later discovered that in contrast to its sluggish reaction in acetic anhydride–benzene the sulfoxide readily rearranged in a 2:1 mixture of acetic anhydride–acetic acid at 100 °C, but the major product was the 2-acetoxy compound **7.**

The evidence obtained, specifically the transformations effected by acetic anhydride, leads us to conclude that a 2,5-dienone intermediate pathway followed by a 1,3 trifluoroacyl migration most probably accounts for the previously observed reaction of 4-methylsulfinyl-3,5-xylenol (1) with trifluoroacetic anhydride.

Experimental Section

Melting points are uncorrected and were determined on a Kofler hot stage microscope. NMR spectra were recorded on a Varian T-60 NMR spectrometer with Me_4Si as an internal standard. IR spectra were determined as Nujol mulls using a Beckman IR-20A spectrophotometer. Mass spectra were determined on a Perkin-Elmer Hitachi mass spectrometer. Thin-layer chromatograms were run on glass plates coated with silica gel GF. Separated components were detected by UV fluorescence and iodine vapor.

Preparation of 4-Methylsulfinyl-3,5-xylenol. 4-Methylsulfinyl-3,5-xylenol (1) was prepared by oxidation of 4-methylthio-3,5-xylenol with hydrogen peroxide in aqueous acetone at room temperature overnight. The product was purified by recrystallization from ethyl acetate and its identity confirmed by comparison with an authentic specimen.[6]

Reaction of 4-Methylsulfinyl-3,5-xylenol with Acetyl Chloride. A suspension of 4-methylsulfinyl-3,5-xylenol (1; 430 mg) in benzene (10 mL) was treated with an excess of acetyl chloride (0.5 mL) and stirred until thin-layer chromatography studies indicated that the reaction was complete (approximately 1 h). The reaction mixture was then neutralized by decantation into a cold saturated solution of sodium bicarbonate (40 mL). After extraction of the neutral solution with chloroform (2 × 50 mL), the chloroform extracts were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was subsequently purified by preparative thin-layer chromatography (ethyl acetate–hexane, 1:3). Crystallization of the major component (R_f 0.56) from hexane gave 4-chloro-3,5-xylenol (**4;** 183 mg), which had identical NMR, IR, and mass spectra and melting point with an authentic sample.[5] The minor compound (R_f 0.85), 2-chloro-4-methylthio-3,5-xylenol (**3;** 58 mg), was a yellowish oil:

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NMR ($CDCl_3$) δ 6.78 (1 H, s, aromatic H), 2.60 (3 H, s, CCH_3), 2.34 (3 H, s, CCH_3), and 2.17 (3 H, s, SCH_3); MS *m/e* 202 (M^+).

Reaction of 4-Methylsulfinyl-3,5-xylenol with Acetic Anhydride. A suspension of 4-methylsulfinyl-3,5-xylenol (**1**; 410 mg) in benzene (10 mL) was treated with an excess of acetic anhydride (0.5 mL) and refluxed with stirring for 48 h. Workup and purification as outlined for the acetyl chloride reaction afforded one major compound (R_f 0.33) which crystallized from hexane to give the 2,5-dienone **6** (41 mg): mp 110–112 °C; IR (Nujol) 1745, 1660, 1620 cm^{-1}; NMR ($CDCl_3$) δ 6.20 (2 H, s, dienone H), 2.18 (3 H, s, SCH_3), 2.04 (6 H, s, CCH_3), and 1.84 (3 H, s, OAc); MS *m/e* 226 (M^+). Crystallization of the minor compound (R_f 0.76) from hexane gave 2-acetoxy-4-methylthio-3,5-xylenol (**7**; 17 mg): mp 84–85 °C; IR (Nujol) 3310, 1738, and 1565 cm^{-1}; NMR ($CDCl_3$) δ 6.78 (1 H, s, aromatic H), 2.36 (3 H, s, CCH_3), 2.34 (3 H, s, OAc), 2.22 (3 H, s, CCH_3), and 2.16 (3 H, s, SCH_3); MS *m/e* 226 (M^+).

Reaction of 4-methylsulfinyl-3,5-xylenol (1) in a 2:1 mixture of acetic anhydride–acetic acid at 100 °C went to completion within an hour. The predominant product was the 2-acetoxy compound **7**, and a trace of the dienone **6** was also isolated.

Acknowledgment. The author wishes to thank G. Lonergan and M. T. Austria, Chemistry Department, University of New Brunswick, Fredericton, New Brunswick, for the NMR determinations and the mass spectral data, respectively.

Registry No.—**1**, 22454-92-8; **3**, 67030-99-3; **4**, 88-04-0; **6**, 67031-00-9; **7**, 67031-01-0; 4-methylthio-3,5-xylenol, 7379-51-3.

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Model Studies of Thiamin Catalysis. Inductive Effects of Nitrogen-Bonded Substituents and Influence of Steric Inhibition of Resonance on Kinetic Carbon Acidities of Thiazolium Ions

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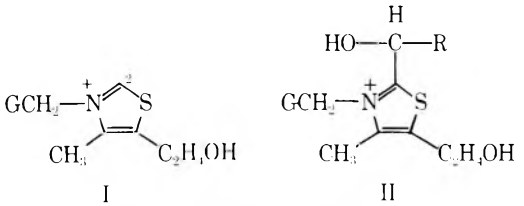
Received March 24, 1978

Thiazolium ions are important catalysts both in biological[1] and in chemical systems.[2] Thiamin or vitamin B_1 (I), for example, is involved in a number of transformations involving carbonyl compounds, such as the conversion of acetaldehyde to acetoin.[3] Similarly, other thiazolium salts are useful catalysts in the synthesis of acyloins.[2]



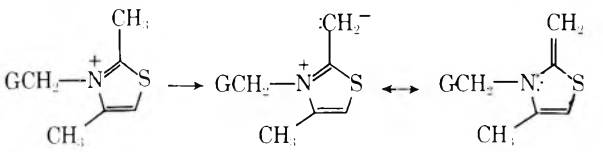
I II

I, IIa, G = 4-amino-2-methylpyrimidinyl
IIb, G = H; R = CH_3

Key steps in the mechanism of acyloin formation include deprotonation of a thiazolium ion at position 2 to give an ylide which then adds to a carbonyl electrophile. Resultant intermediate II then is deprotonated at the newly formed side chain to give a second nucleophile, often called an "enamine". Reaction of this enamine with additional carbonyl compound followed by expulsion of ylide gives rise to acyloin product.

On a more detailed level, our current knowledge is very limited. Consideration of the reactivity of a series of substituted thiazolium ions at each step of the multistep sequences reveals that much remains to be learned.

We report results designed to clarify some aspects of this complex mechanism. We have measured the influence of substituents at an annular nitrogen atom on the rates of deprotonation of simple thiazolium ions (III) to produce an enamine (eq. 1). Our results provide an indication of how



III, G = H, C_6H_5, p-$O_2NC_6H_4$, CN (1)

sensitive side-chain deprotonation is to inductive effects of nitrogen-bonded substituents. A second aspects of our study deals with the magnitude of steric inhibition of resonance found when IIb (G = H, R = CH_3) is deprotonated at the 1-hydroxyethyl position.

Results and Discussion

Inductive Effects. Rates of deprotonation of 2,4-dimethylthiazolium ions (III) having groups G = H, C_6H_5, p-$O_2NC_6H_4$, and CN were obtained by studying hydrogen isotope exchange. Loss of a proton from the 2-methyl group to give a resonance stabilized conjugate base, eq 1, was catalyzed by acetate ion buffers in D_2O. Neither water nor deuterioxide compete significantly with acetate ion general base; pseudo-first-order rate constants for deprotonation, k_ψ, can be converted to second-order rate constants k_B reflecting acetate ion catalysis according to the equation

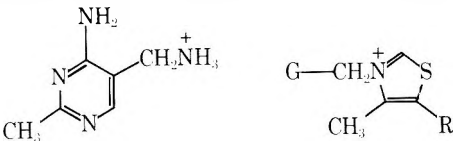
$$k_\psi = k_B[CH_3CO_2^-] \quad (2)$$

Examination of the results in Table I shows that k_B obtained in this way is essentially constant as the concentration of catalyst is varied by as much as tenfold.

Comparison of the four k_B values reveals that substituents G, in spite of being removed from the thiazolium ring by a saturated carbon atom, have a significant influence on kinetic acidity. Comparing k_B values and using the value for G = H as a reference gives rise to relative rate constants of 1.0, 9.1, 27, and 187 for substituents G = H, C_6H_5, p-$O_2NC_6H_4$, and CN, respectively.

A linear free-energy correlation can be constructed between the logarithm of k_{rel} and pK_a values for substituted methylammonium ions, $GCH_2NH_3^+$,[4,5,8] having the same substituents. The slope of this correlation (correlation coefficient r = 0.962) is −0.40. Electron-withdrawing substituents promote the acidity of both the carbon and nitrogen acids. Naturally, effects are smaller in the case of the carbon acids where proton transfer is less complete. Although electron-withdrawing substituents destabilize both the positively charged carbon acid and the transition state, effects on transition-state energies are smaller because of extensive charge neutralization.

Using the pK_a (8.01) of methylammonium ion IV substituted with a pyrimidine ring as in thiamin and the free-energy



IV V

Table I. Kinetic Results for Hydrogen–Deuterium Exchange at the 2-Methyl Group of 3-Substituted 2,4-Dimethylthiazolium Ions in Acetate-Buffered D_2O at 75.0 °C and 1.0 M Ionic Strength

substituent	registry no.	pD[a]	total buffer, M[b]	$10^4 k_\psi$, s^{-1}	$10^3 k_B$ M^{-1} s^{-1}	k_{rel}
CH_3	29488-88-8	5.45	0.030	0.030	0.150	
		5.84	0.240	0.290	0.124	
					av 0.137 ± 0.013	1.0
$C_6H_5CH_2$	67145-81-7	5.10	0.500	2.76	1.13	
		5.13	0.080	0.49	1.23	
		5.20	0.350	2.22	1.16	
		5.79	0.120	1.43	1.44	
					av 1.24 ± 0.10	9.1
p-$O_2NC_6H_4CH_2$	67145-82-8	5.11	0.400	6.80	3.43	
		5.14	0.040	0.78	3.71	
		5.20	0.350	6.94	3.63	
		5.79	0.120	3.73	3.77	
					av 3.64 ± 0.11	27
$NCCH_2$	67145-83-9	4.33	0.060	0.246	29.4	
		5.09	0.100	12.7	25.9	
		5.09	0.154	18.7	24.9	
		5.09	0.200	21.4	22.1	
					av 25.6 ± 2.1	187

[a] Measured at 25 °C. [b] $pK_a = 5.12$.

Table II. Kinetic Results of Hydrogen–Deuterium Exchange at the 2 Position of 2,3,4-Trimethylthiazolium and 2-(1-Hydroxyethyl)-3,4-dimethyl-5-(2-hydroxyethyl)thiazolium Ions in Phosphate Buffered D_2O at 75.0 °C and 1 M Ionic Strength

compd	pD[a]	total buffer, M[b]	$10^6 k_\psi$, s^{-1}	k, M^{-1} s^{-1}
III (G = H)	6.09	0.220	101	5.81×10^{-3} (DPO_4^{2-})
	7.17	0.040	162	(45) (OD^-)
	7.24	0.240	794	
	8.16	0.058	525	
IIb[c]	6.74	0.420	4.68	3.34×10^{-5} (DPO_4^{2-})
(G = H; R = CH_3)				
	7.03	0.203	3.22	2.4 (OD^-)
	7.12	0.300	5.56	
	7.17	0.403	8.86	
	7.72	0.360	14.7	
	8.19	0.320	20.9	

[a] At 25 °C. [b] pK_a 7.10. [c] Registry no.: 67145-84-0.

correlation ($\log k_{rel} = -0.40\ pK_a + 4.55$), it is possible to estimate that this substituent will increase reactivity by about a factor of 20 over that for G = H. The effect is similar to that produced by a nitrophenyl group. We expect that a similar correlation will apply to the kinetic acidities of thiazolium ions having hydroxyalkyl side chains (II).

Unfortunately, it is not possible to make an unequivocal comparison between the effects of substituents on ylide and on enamine formation. Two different values for the slope of a $\log k_{rel}$ vs. pK_a correlation for ylide formation can be derived from published data; both are the result of two point correlations. Thus, data for the lyate ion catalyzed dedeuteration of thiazolium ions V, where G is H and C_6H_5 (R = H), give a slope of −0.37,[12] while data for the detritiation of I and of V having phenyl as group G (R = CH_3) yield −0.80.[13] However on the assumption that both pairs belong to a single correlation, a three-point plot may be constructed using G = C_6H_5[14] as a common reference. The slope is −0.60 (r = 0.986). It would seem that ylide rather than enamine formation is more sensitive to substituent effects. Such a conclusion would be understandable in terms of a more product like transition state for the ylide reaction[15] with its associated greater amount of negative charge.

Inhibition of Resonance. By examining the reactivity of a series of 2-substituted-3-methylbenzothiazolium ions we demonstrated earlier that the rate of deprotonation of a 1-hydroxyethyl group is retarded due to steric inhibition of resonance in the transition state. Relative to a methyl group a 1-hydroxyethyl substituent is about 35 times less reactive toward either water or formate ion base.[16] In order to establish the magnitude of such inhibition in thiazolium ions having structures more like those of thiamin and its derivatives, the following experiments were performed.

The reactivity of III, G = H, was determined at 75.0 °C toward phosphate base. Under these more basic conditions deuterioxide ion provides a contribution to the rate of deprotonation along with buffer base. Pseudo-first-order rate constants are represented by the equation

$$k_\psi = k_B[DPO_4^{2-}] + k_{OD}[OD^-] \quad (3)$$

where a second term is present to reflect additional catalysis, k_{OD} being the second-order rate constant for lyate ion. However, the relative contribution of lyate ion to the rate is large only in the last run in Table II, where it is 44%. Consequently, the reported k_{OD} value should be regarded as approximate.

Similarly, deprotonation of IIb (G = H; R = CH_3), a structurally close relative of the biologically important thiamin derivative IIa,[1] was investigated using the same buffer. Kinetic data again may be dissected into component parts representing buffer and lyate ion catalysis (eq 3). This time the k_{OD} rate constant is likely to be estimated more closely because lyate ion catalysis is present at a significant

level in more runs, being 46% in the run at the highest pD.

Using the second-order rate constants given in Table II for both substrates and the appropriate concentrations of bases, it is possible with the aid of eq 3 to calculate a value for k_ψ. The calculated value differs from the observed value on the average by 4.2 and 8.7% in the case III and IIb, respectively.

Comparison of the second-order rate constants associated with phosphate ion general base for III and IIb (Table II) reveals that the thiazolium ion with the acidic methyl group is 174 times more reactive than the 1-hydroxyethyl ion. This value is five times larger (174 vs. 35)[16] than that we reported for benzothizolium ions reacting with water and formate ion bases.[16] The larger ratio found in the present study is due in part to the presence of the 5-(2-hydroxyethyl) group of IIb, which is absent from III. This electron-donating group decreases the reactivity of IIb, thereby increasing the magnitude of the rate constant ratio. A similar reactivity pattern is found for the two carbon acids toward lyate ion. But due to the uncertain value of k_{OD} for III, an accurate ratio cannot be calculated.

As is the case for benzothiazolium ions,[16] the primary reason for the diminished reactivity of the 1-hydroxyethyl chain is steric inhibition of resonance. Interaction between the hydroxy group of this chain with the substituent bonded to nitrogen prevents maximum orbital overlap, resulting in effective delocalization of the electrons from the reactive CH bond into the positively charged ring in the transition state. The unfavorable interaction leads to an increase in the energy barrier and a reduced rate.

Clearly a start has been made, but much yet remains to be done to develop our understanding of reactions catalyzed by thiazolium ions.

Experimental Section

Rates of hydrogen–deuterium exchange were determined by a previously employed NMR method on buffered solutions in D_2O.[16] Ionic strength was maintained at 1.0 M using KCl. In the case of fast runs on the cyanomethyl substrate, the NMR probe was cooled to about 5 °C before analysis in order to minimize continuing isotope exchange. Kinetic plots were constructed using the 2:4 group area ratio. The pD of solutions was measured at room temperature; owing to the slight temperature dependence of the dissociation constant of the buffers,[17] values are expected to be very similar to those at 75 °C, the reaction temperature. The pD was measured before and after each run; changes were <0.1 except in the slowest run for the cyanomethyl substrate, where a decrease of 0.16 was recorded. The initial value was used.

Equation 3 contains two unknowns, second-order rate constants k_B and k_{OD}, whose values are determined by treating the four (III) or six (IIb) values of k_ψ in Table II as a series of overdetermined simultaneous equations. Lyate ion concentration is calculated from a measured pD and $pK_w = 13.53$ (D_2O, 75 °C), while the concentration of DPO_4^{2-} is given by the product of the total phosphate buffer concentration and the term $K_a/([D] + K_a)$.

3-Methyl-[18] and 3-benzyl-2,4-dimethylthiazolium[18] salts were prepared by quaternization. 3-(4-Nitrobenzyl)-2,4-dimethylthiazolium bromide, mp 203–205 °C, was made by the method used to synthesize the chloride.[19] Anal. Calcd for $C_{11}H_{11}BrN_2O_2S$: C, 43.78; H, 3.98; H, 8.51. Found: C, 43.84; H, 3.99; N, 8.45. Similarly, the 3-cyanomethyl salt was prepared from 2,4-dimethylthiazole and cyanomethyl chloride; it was isolated as the perchlorate; mp 225–227 °C dec. Anal. Calcd for $C_7H_9ClN_2O_4S$: C, 33.27; H, 3.59; N, 11.09. Found: C, 33.47; H, 3.63; N, 10.95. 2-(1-Hydroxyethyl)-3,4-dimethyl-5-(2-hydroxyethyl)thiazolium iodide was made from acetaldehyde and the 2-unsubstituted thiazolium iodide[20] by the method used to prepare 2-(1-hydroxyethyl)thiamin.[21] The yield of crude product was 64%; repeated recrystallization from methanol–ethyl acetate gave pure product, mp 106–107 °C (lit.[22] mp 109°).

pK_a of 2-Methyl-4-amino-5-(aminomethyl)pyrimidine Dihydrochloride. A 2.00×10^{-3} M solution of the title compound (Aldrich) was titrated potentiometrically with 0.0467 M KOH at 25.7 °C using a radiometer TTT-1C titrator. Data were treated according to the method of Albert Serjeant;[23] although overlap is minor, the data were analyzed on the assumption that the two ionization steps do overlap. No correction was applied to reflect changing ionic strength; corrections would modify pK_a values by ≤0.1. Five determinations gave pK_1 (ring) 4.85 and pK_2 (side chain) 8.01. Literature values include 7.1,[24] 8.4,[6] and 8.6.[7]

Control Runs. In order to determine whether D_2O might catalyze hydrogen exchange the 3-methyl and 3-benzyl substrates were heated for 127 h in 0.1 M DCl (ionic strength 1.0 M) at 75 °C. Approximately 2.5 and 7.7% deuteration took place at the 2-methyl group of each, respectively. This sets as upper limits to the rate constants values of 5.6×10^{-8} and 1.8×10^{-7} s^{-1}, respectively. Hence, catalysis by D_2O does not compete significantly with that by acetate ion.

Control runs on the 3-(*p*-nitrobenzyl) and 3-(cyanomethyl) substrates using acetate buffer in H_2O showed no evidence (NMR) of degradation after 12 half-lives for the former and after 3 half-lives for the latter. Some decomposition of the cyanomethyl compound was evident after heating for a period corresponding to 8 half-lives; new peaks appeared at higher field.

Samples of IIb (G = H; R = CH_3) degrade on heating in phosphate buffer. Early studies using low concentrations of buffer showed that the pD of reaction mixtures decreased substantially with time; therefore, kinetic runs were discarded. The use of higher buffer concentrations minimized the drift in pD. A sample in phosphate-buffered H_2O gave some evidence (NMR) of substrate decomposition after a period of heating at 75 °C, which corresponds to about 2.3 half-lives for isotope exchange; considerable starting material remained after about 6 half-lives. Some of the NMR signals which appear in the sample in H_2O are not observed in D_2O, suggesting H–D exchange. Decomposition products were not identified.

Acknowledgment. This work was supported by Grant AM-17442 from the National Institutes of Arthritis, Metabolism and Digestive Diseases. Dr. L. S. Helmick kindly carried out three kinetic runs on IIb, Table II.

Registry No.—3-(4-Nitrobenzyl)-2,4-dimethylthiazolium bromide, 67145-85-1; 3-cyanomethyl-2,4-dimethylthiazolium perchlorate, 67145-86-2; 2-(1-hydroxyethyl)-3,4-dimethyl-5-(2-hydroxyethyl)-thiazolium iodide, 52084-19-2; 2-methyl-4-amino-5-(aminomethyl)-pyrimidine dihydrochloride, 874-43-1; 2,4-dimethylthiazole, 541-58-2; cyanomethyl chloride, 107-14-2; acetaldehyde, 75-07-0; 3,4-dimethyl-5-(2-hydroxyethyl)thiazolium iodide, 16311-69-6; deuterium, 7782-39-0; thiamin, 59-43-8.

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Novel 7-Pyrrolocephalosporins

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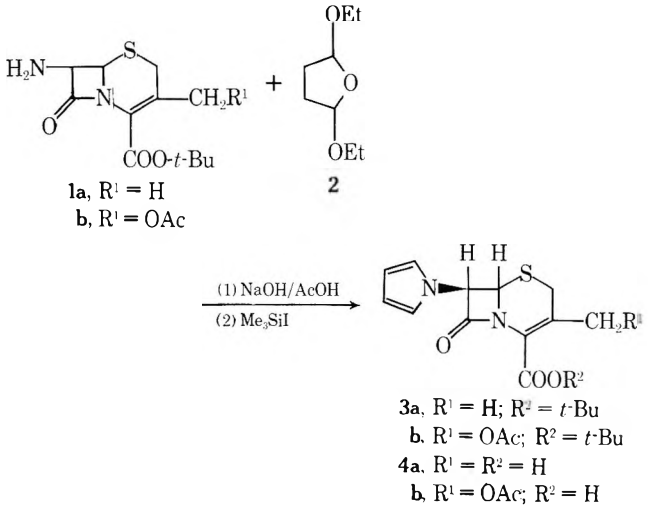
Received January 13, 1978

In the search for novel analogues of the naturally occurring β-lactam antibiotics, a large number of modifications have been carried out at positions 6 of the penicillins and 7 of the cephalosporins.[1] With the discovery of a family of the cephamycins, a renewed effort has been directed at the development of methods for the introduction of substituents at positions 6 and 7 of penicillins and cephalosporins, respectively.[2]

The modifications carried out have reported the introduction of alkyl, halogen, alkoxy, hydroxy, and azido groups. The naturally occurring amide function has, in turn, been converted into amino, amido, imino, and imido groups. We report here the first 7-heteroaromatic-substituted cephalosporins.

When the *tert*-butyl esters[3] of 7-aminocephalosporanic and 7-aminodesacetoxycephalosporanic acids (**1**) are treated with 2,5-diethoxytetrahydrofuran[4] (**2**) novel 7-pyrrolocephalosporins (**3**) are obtained.

In order to test compounds **3** for antibacterial properties, it was necessary to remove the *tert*-butyl ester group. The standard procedure for *tert*-butyl ester hydrolysis required acid catalysis. The instability of pyrroles to strongly acidic conditions brought about the decomposition of the compounds when subjected to trifluoroacetic acid. Even 1 equiv of trifluoroacetic acid in chloroform caused immediate and extensive decomposition. The *tert*-butyl ester groups of **3** were



1a, $R^1 = H$
b, $R^1 = OAc$

2

3a, $R^1 = H$; $R^2 = t$-Bu
b, $R^1 = OAc$; $R^2 = t$-Bu
4a, $R^1 = R^2 = H$
b, $R^1 = OAc$; $R^2 = H$

successfully removed upon treatment with trimethylsilyl iodide by the recently reported method of Jung and Lyster.[5] The great selectivity of this reagent was witnessed by the removal of the *tert*-butyl group of **3a**, leaving the acetate group intact. The acids **4a,b** showed weak antibacterial properties with MIC of ≥100 μg/mL against Streptococcus pneumoniae D137 and Streptococcus pyogenes ST 139.

Experimental Section

All new compounds gave satisfactory elemental analyses.

1,1-Dimethylethyl 3[(Acetyloxy)methyl]-8-oxo-7-(1*H*-pyrrol-1-yl)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (3b). To a boiling solution of sodium acetate (0.25 g, 3 mmol) in acetic acid (10 mL) was added 7-ACA *tert*-butyl ester (**1a**) (1.64 g, 5 mmol) followed by 2,5-diethoxytetrahydrofuran (**2**) (0.8 g, 5 mmol). The solution was further boiled for about 1 min and was then poured into ice. A yellow solid was obtained which was chromatographed on 15 g of silica gel eluted with ether to give 250 mg (15%) of **3b**: mp 150–153 °C; IR (KBr) 1765 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 1.58 (s, 9), 2.10 (s, 3), 3.45 (q, 2), 4.7–5.3 (superimposed q and d, 3), 5.91 (d, 1, J = 5 Hz), 6.78 (t, 2), and 6.80 (t, 2).

1,1-Dimethylethyl 3-Methyl-8-oxo-7-(1*H*-pyrrol-1-yl)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (3a). The title compound was obtained in 46% yield, as described for **3b** using the appropriate 7-ADCA *tert*-butyl ester **1b**: mp 160–161 °C; IR (KBr) 1765 cm^{-1} (β-lactam); NMR ($CDCl_3$) δ 1.60 (s, 9), 2.10 (s, 3), 3.27 (q, 2), 5.0 (d, 1), 5.79 (d, 1, J_{AB} = 5 Hz), 6.14 (t, 2), and 6.66 (t, 2).

3-Methyl-8-oxo-7-(1*H*-pyrrol-1-yl)-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic Acid (4a). To a solution of **3a** (0.8 g, 2.5 mmol) in 10 mL of dry chloroform was added trimethylsilyl iodide[5] (1 g, 5 mmol). The solution was stirred at room temperature for 40 min while protected from light and was then poured into 5% aqueous sodium bicarbonate. The aqueous phase was washed with ethyl acetate, cooled, acidified to pH 3 with dilute hydrochloric acid, and extracted with ethyl acetate. The organic phase was dried and evaporated to give **4a**, 0.3 g (45%), as a yellow powder: IR (KBr) 1750 cm^{-1} (β-lactam); NMR (Me_2SO) δ 2.02 (s, 3), 3.44 (q, 2), 5.13 (d, 1), 6.0 (t, 2), 6.18 (d, 1, J_{AB} = 5.5 Hz), and 6.64 (t, 2).

3-(Acetyloxy)methyl-8-oxo-7(*H*-pyrrol-1-yl)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic Acid (4b). The title compound was obtained in 50% yield as described for **4a** from the corresponding **3b**: IR (KBr) 1760 cm^{-1} (β-lactam); NMR (Me_2SO) δ 2.02 (s, 3), 3.52 (q, 2), 4.8 (q, 2), 5.22 (d, 1), 6.06 (t, 2), 6.36 (d, 1), and 6.69 (t, 2)

Registry No.—**1a**, 33610-06-9; **1b**, 6187-87-7; **2**, 3320-90-9; **3a**, 66967-02-0; **3b**, 66967-03-1; **4a**, 66967-04-2; **4b**, 66967-05-3.

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Convenient Preparation of α,β-Unsaturated Aldehydes

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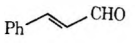
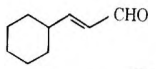
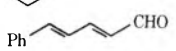
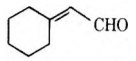
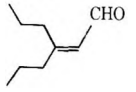
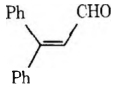
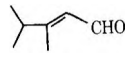
Received April 3, 1978

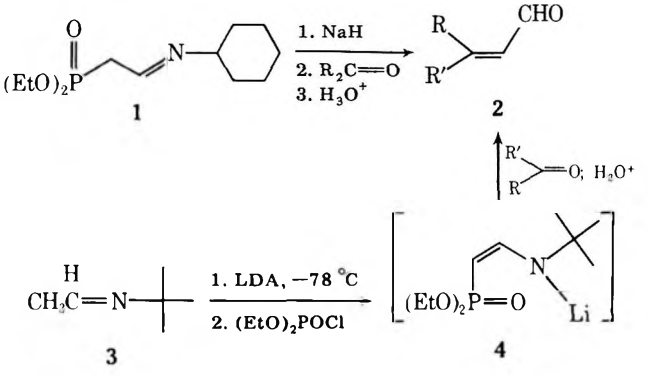
A number of methods designed to convert carbonyl compounds into homologated α,β-unsaturated aldehydes have been reported.[1] All of these techniques possess variable degrees of utility and indeed have found widespread use. In 1969, Nagata[2] described the preparation of the phosphonate imine **1** and its ability to convert carbonyl compounds into α,β-unsaturated aldehydes **2**. This process is in effect a combination of the Wadsworth–Emmons[1d] olefination and the Wittig directed aldol condensation.[1g] We wish to describe in this report a simple and efficient procedure, beginning with the *N-tert*-butylimine of acetaldehyde **3**, leading to **2** without isolation of any of the intermediates. This method precludes the preparation of Nagata's reagent **1**,[2] which required three

0022-3263/78/1943-3788$01.00/0

Table I. α,β-Unsaturated Aldehydes 2

carbonyl R	carbonyl R′	registry no.	product	registry no.	% yield[a,b]
Ph	H	100-52-7			70[c]
$Ph(CH_2)_2$	H	104-53-0		33046-84-3	73[d]
	H	2043-61-0		935-03-5	76[e]
PhCH=CH−	H	104-55-2		13466-40-5	67[c]
		108-94-1		1713-63-9	94[c]
		123-19-3		34626-45-4	53[c]
$Ph_2C=O$		119-61-9		1210-39-5	71[c]
		563-80-4		57398-52-4	72[f,g]

[a] Isolated yields by distillation or PTLC. [b] All compounds gave satisfactory spectral data and were identical with authentic samples. [c] A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973). [d] K. Hirai and Y. Kishida, *Tetrahedron Lett.*, 2743 (1972). [e] J. H. van Boon, P. P. Montijn, L. Brandsma, and J. F. Arens, *Recl. Trav. Chim. Pays Bas*, **84**, 31 (1965). [f] M. Julia and B. Badet, *Bull. Soc. Chim. Fr.*, 1363 (1975). [g] *E*/*Z* ratio, as determined by NMR, is 6:4.



steps from commercial materials. Metalation of **3** with excess lithium diisopropylamide followed by introduction of diethyl chlorophosphate furnished in situ the lithioenaminophosphonate **4**. Addition of the carbonyl components and then an aqueous oxalic acid solution afforded, after workup, the α,β-unsaturated aldehydes **2** in satisfactory yields (Table I). Thus, in a single reaction vessel, starting with the imine **3**, the entire sequence is carried out to the final product.

Experimental Section

Cinnamaldehyde, General Procedure for all Aldehydes, 2. To a cooled solution (−78 °C) of lithium diisopropylamide [from 0.84 mL (6.0 mmol) of diisopropylamine and 2.73 mL (6.0 mmol) of butyllithium in hexane] in 8 mL of tetrahydrofuran was added acetaldehyde *N*-*tert*-butylimine[3] (0.4 mL, 3.0 mmol) and the mixture was stirred for 30 min. Diethyl chlorophosphate (518 mg, 3.0 mmol) was added and the solution was stirred at −78 °C for 2 h, allowed to warm to −10 °C over a period of 3 h, and recooled to −78 °C. Benzaldehyde (0.2 mL, 2.0 mmol) was added to the yellow solution and the mixture was stirred for 30 min and allowed to warm to ambient (usually overnight). The mixture was then treated with oxalic acid (6 mmol in 20 mL of water) and then 20 mL of benzene was added. The two phase system was stirred overnight at room temperature and the layers separated. The aqueous layer was extracted with ether (2 × 30 mL) and the organic layers were combined and washed successively with 5% oxalic acid, 15% sodium bicarbonate, and brine. Drying (K_2CO_3) and concentration of the organic phase followed by purification of the residue (distillation or preparative TLC, silica gel, 30% ethyl acetate–hexane) gave 185 mg of cinnamaldehyde, 70%.

Acknowledgment. Support of this work by the National Institutes of Health (CA-16051) is gratefully acknowledged. An NIH Postdoctoral Fellowship (National Service Award, IF32CA05946-01) to M. P. Fleming is likewise acknowledged.

Registry No.—**3**, 7020-80-6.

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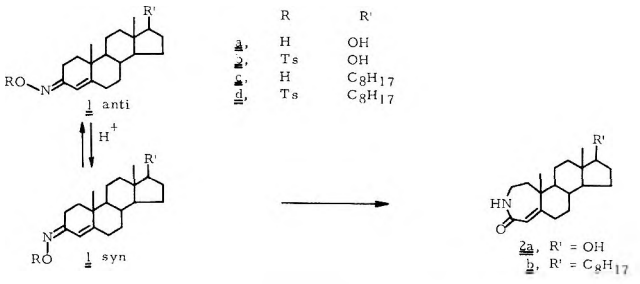
Communications

Regiospecific Beckmann Rearrangement of 3-Oxo-4-ene Steroid Oximes

Summary: Improved regiospecific Beckmann rearrangement of oxime *p*-toluenesulfonates of testosterone, cholestenone, 4-cholestene-3,6-dione, and 17,17-ethylenedioxy-19-hydroxy-4-androsten-3-one to afford 3-aza-*A*-homo steroids is described.

Sir: In the field of steroids, there is a serious drawback to using the Beckmann rearrangement and the Schmidt reaction in that they produce a mixture of both possible regioisomers.[1-3] Many Beckmann rearrangements of 3-oxo-4-ene steroid oximes (isomeric mixtures) have been carried out using thionyl chloride in nonpolar solvents with the yields of 3-aza lactams being slightly higher than might be expected from the percentage of syn isomer in the starting material.[4] Oximes which consist predominantly of the anti isomer seem to resist rearrangement under these reaction conditions.[5,6] Some other experimental approaches have been reported,[7-9] but none of them are entirely satisfactory. Our present paper deals with a new method which involves fast geometrical isomerization between syn and anti oxime *p*-toluenesulfonates in polar solvents and preferential rearrangement of the syn isomers to 3-aza lactams.

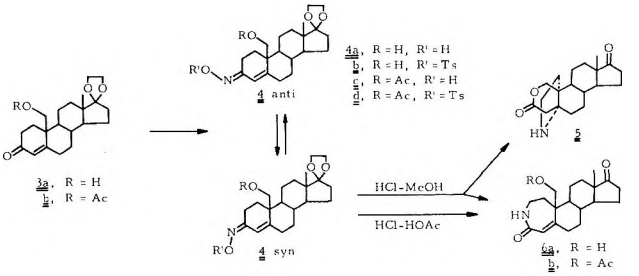
Testosterone oxime (**1a**) prepared in the usual manner consists of 33% syn isomer and 67% anti isomer.[10] The pure,



isolated isomers are stable in nonpolar solvents, but undergo rapid isomerization to the equilibrium mixture when exposed to polar solvents containing hydrogen chloride. When the oxime mixture was dissolved in chloroform containing 2 molar equiv of *p*-toluenesulfonyl chloride and treated with 15% sodium hydroxide solution, the hydroxyimino group was sulfonylated specifically while the 17-hydroxyl was not attacked. The ratio of geometrical isomers of **1b** was the same as that of starting oxime **1a**. This material was dissolved in methanol and then treated with concentrated hydrochloric acid at 50 °C for 30 min to give the 3-aza lactam **2a** in high yield, mp 293–295 °C (lit.[9] 282–285 °C). In one experiment where the pure geometrical isomers were used, we observed that the syn isomer rearranged smoothly at room temperature while the anti isomer required higher temperatures to complete the rearrangement, each isomer affording **2a** in 85–90% yields. These results clearly show the efficiency of the isomerization where the rate of vinyl migration of the anti isomer is very slow compared with alkyl migration of the syn isomer.

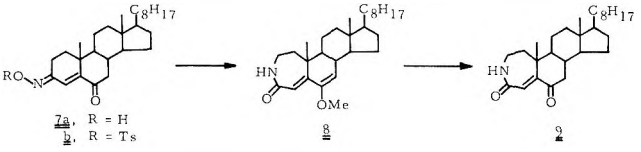
Almost the same results were obtained with the cholestenone oxime mixture **1c** (25% syn and 75% anti), which yielded **2b** in 87% yield, mp 251–253 °C (lit.[4e] 250–254 °C).

In the case of 19-hydroxy analogue **4**, the reaction is somewhat more complex. The *p*-toluenesulfonate **4b**, prepared from oxime mixture **4a** (mp 208–210 °C; 25% syn and 75% anti), on treatment with hydrogen chloride in methanol at 50 °C for 2 h gave the amino lactone **5** in 65% yield, mp 171–172 °C, and the desired 3-aza lactam **6a** in 18% yield, mp 115–118 °C. The formation of **5** can be explained in terms of an intramolecular rearrangement induced by 19-hydroxyl participation. When the tosylate mixture **4d** was treated with 1% hy-



drogen chloride in acetic acid at 60 °C for 30 min, the acetoxy lactam **6b** was obtained in 85% yield, mp 202–203 °C. Hydrolysis of this compound in methanol with potassium hydroxide at room temperature gave the hydroxy lactam **6a** and acetylation of **6a** gave the acetoxy lactam **6b**. The hydroxy tosylate mixture **4b** gave similar results when the reaction was carried out in acetic acid; apparently acetylation of the 19-hydroxy group precedes the Beckmann rearrangement.

4-Cholestene-3,6-dione was also subjected to the specific rearrangement. Monooxime **7a**, prepared from the dione by



treatment with 1 molar equiv of hydroxylamine, consists predominantly of the anti isomer (100% after one recrystallization to remove a small amount of 6-oxime). It has been reported that this oxime did not undergo Beckmann rearrangement by the known method.[5] However, exposure of **7b** to methanol containing hydrochloric acid afforded only the 3-aza lactam enol ether **8** in 86% yield. Subsequent hydrolysis by hydrochloric acid in 2-propanol afforded 3-aza lactam **9** quantitatively, mp 211–214 °C (lit.[6] 213–215 °C).

These improved and simple procedures for the Beckmann rearrangement may afford a convenient method for the synthesis of salamander alkaloids,[3] especially cycloneosamandaridine.

Acknowledgment. This work was supported by the Ministry of Education of Japan (Grant-in-Aid 977389).

Supplementary Material Available: Experimental section describing rearrangement of **1a, 1c, 7a,** and **4b** (3 pages). Ordering information is given on any current masthead page.

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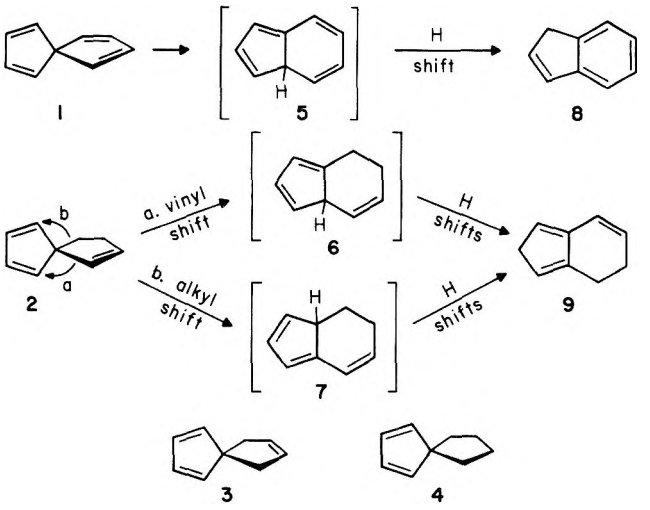
Rapid Vinyl Shifts in Spiro[4.4]polyenes: Verification of the Rate-Determining Step and the Identity of the Migrating Group.

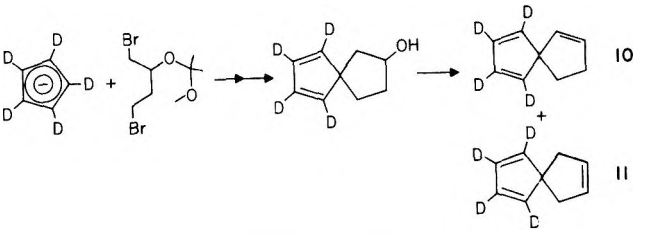
Summary: Pyrolysis studies of 1,2,3,4-tetradeuteriospiro[4.4]nona-1,3,6-triene (**10**) show that the 1,5-sigmatropic shift proceeds with negligible primary deuterium isotope effect, eliminating a rate-determining H shift in this multistep rearrangement. Pyrolysis of 1,2,3,4-tetramethylspiro[4.4]nona-1,3,6-triene leads to specific vinyl migration, thereby establishing preferential vinyl as opposed to alkyl migration. The structure of the pyrolysis product was determined by an X-ray diffraction structure determination on a crystalline adduct with dimethyl 3,6-dicarboxy-1,2,4,5-tetraazabenzene; the adduct is the result of an unprecedented reaction of the tetrazine.

Sir: Migratory aptitudes in 1,5-sigmatropic shifts are presently not well understood. Examples suggest that sp^2-hybridized carbon migrates at an especially high rate compared to similar saturated carbon substituents.[1-3] This is particularly dramatic in rearrangements of 1,1-disubstituted cyclopentadiene derivatives.[1,2] We were first attracted to the question after observing high rates of unimolecular rearrangement for spiro[4.4]nonatetraene (**1**) and spiro[4.4]nona-1,3,6-triene (**2**) compared to spiro[4.4]nona-1,3,7-triene (**3**) and spiro[4.4]nona-1,3-diene (**4**).[2] Using a picture in which the transition state for carbon shift in compounds **1–4** resembles a carbon unit migrating around a cyclopentadienyl radical, we[2] and others[1] have proposed that the rate enhancement ($\sim 10^4$ for **1**, 10^3 for **2**) is due to π^* (LUMO) of a migrating vinyl substituent interacting with the HOMO for the cyclopentadienyl unit.



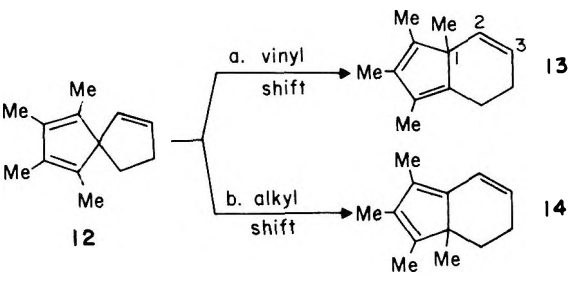
Experimental support of this mechanism has been lacking, however, due to the fact that the expected first products (**5**, **6**) from rearrangement of **1** and **2** have not been observed or trapped; presumably, they rearrange rapidly via 1,5-hydrogen shifts to the more stable (observed) isomers, **8** and **9**. This allows at least two alternate explanations for the high reactivity of **1** and **2**. First, it might be that the carbon shift (**1** → **5** and **2** → **6**) is fast and reversible and then the hydrogen shift is rate determining.[4] Second, it might be that the presence of a vinyl group facilitates the migration of the geminal substituent (vinyl for **1**, alkyl for **2**). With **2**, a vinyl shift would give **6** and a "vinyl-assisted" alkyl shift would give **7**; both products could reasonably produce the observed product, **9**, via hydrogen shifts. In the present work, we have focused on rearrangement of **2** and established that: (1) the hydrogen shift is *not* rate determining; and (2) the vinyl substituent *is* the migrating group.

Since deuterium isotope effects for 1,5-hydrogen shifts in substituted cyclopentadienes fall in the range k_H/k_D = 4.5–7.7,[5] a rate-determining hydrogen shift in the rearrangement of **2** would mean a substantially slower rate of rearrangement for the deuterium-labeled analogue **10**. Our synthesis[2] of **2** is not readily amenable to the preparation of **10**, so we developed a new approach via the reaction[7] of the cyclopentadienyl anion (perdeuterio[8]) with 1,4-dibromo-2-(1-methyl-1-methoxyethoxy)butane.[9] The initial adduct was converted (a. thionyl chloride; b. potassium *tert*-butoxide) to a mixture of 1,2,3,4-tetradeuteriospiro[4.4]nonatriene isomers **10** and **11** (92–93% deuterium incorporation by ^1H NMR analysis). The isomers were separated by GLC and



subjected to gas-phase pyrolysis, as described before.[2] The isomers **2** and **3** were pyrolyzed in a precisely parallel way. Comparing rearrangement of **2** and **10** at 95.7 °C showed k_H/k_D = 1.0 ± 0.1 (average of five runs). Comparing rearrangement of **3** and **11** at 158.2 °C showed k_H/k_D = 1.1 ± 0.2 (average of three runs). Therefore, the rate-determining step for rearrangement of **2** and **3** is not the hydrogen shift.

To support the idea that the vinyl group in **2** is migrating preferentially, we studied reactions of 1,2,3,4-tetramethylspiro[4.4]nona-1,3,6-triene (**12**). This analogue of **2**, prepared according to the method of Criegee,[10] can undergo either vinyl migration (to give **13**) or alkyl migration (to give **14**); isomerization via 1,5-hydrogen shift is not available, and the corresponding 1,5-methyl shift (in **13** or **14**) is expected to have a substantially higher activation barrier, perhaps 45 kcal/mol.[11]



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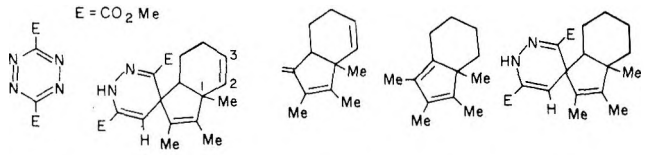
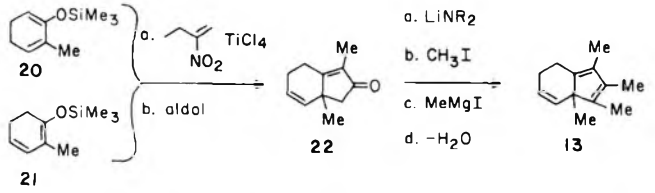
Preparative-scale flow pyrolysis[2] of **12** at 345 °C (0.04 Torr) led to partial conversion to a single product, X; more complex mixtures were obtained at higher temperatures. Product X was isolated by preparative GLC and found to show ^{1}H NMR, IR, and mass spectral data[12] consistent with either structure **13** or **14**. In order to define the structure of X, a crystalline adduct (mp 166–166.5 °C) was prepared by reaction (25 °C, 12 h, dichloromethane solution) with 3,6-dicarbomethoxytetrazine (**15**). Our expectation that the adduct arose via Diels–Alder reaction, with **15** as the diene component, followed by loss of dinitrogen[13] was supported by the elemental composition ($C_{19}H_{24}N_2O_4$), but was clearly inconsistent with the ^{1}H NMR spectrum of the adduct.[14] Therefore an X-ray diffraction study was undertaken.

Crystals formed in the triclinic space group $P\bar{1}$ with a = 8.085 (3), b = 10.326 (4), and c = 12.207 (5) Å, α = 109.83 (1), β = 88.53 (1), and δ = 109.70 (1)°, and one molecule of $C_{19}H_{24}O_4$ in the asymmetric unit. A total of 2379 unique intensity data ($2\theta \leq 114°$, Cu K_α radiation) were measured and 1530 (64%) were judged observed after correction for Lorentz, polarization, and background effects. Solution via a weighted, multiple solution sign determining procedure[15] and refinement[16] were uneventful. The final crystallographic residual is 0.095 for the observed reflections and metric details agree well with generally accepted values.[17] The structure of the adduct is **16**.



While **16** is formally the [4 + 2] adduct (loss of dinitrogen) of tetrazine **15** with the *exo*-methylene isomer (**17**), the actual mechanim of the formation of **16** is not clear. It is clear that the structural relationship between the isolated double bond (C_2–C_3) and the quaternary methyl group (at C_1) is the same in **13** and **16**. There remains the possibility, however, that the isolated double bond started out as in **14** and migrated to the observed position in **16** during reaction with the tetrazine. The fact that the saturated analogue[18] **18** reacts with tetrazine **15** in a precisely parallel way (to give **19**)[20] shows that the isolated double bond in **13** is not necessarily involved in this type of reaction.

Further evidence for the structure of X was provided by rational synthesis. Reaction of 2-methylcyclohex-2-en-1-one with chlorotrimethylsilane and triethylamine in dimethylformamide at reflux led to a mixture of sensitive products, tentatively characterized as enol ethers **20** and **21**. Reaction



of this mixture with 2-nitro-1-butene according to the method of Yoshikoshi,[19] followed by aldol condensation, led to a single distillable product (**22**) in low overall yield.[20] Methylation of the kinetic enolate anion of **22**, followed by addition of methylmagnesium bromide and spontaneous elimination of water, afforded a hydrocarbon identical[21] with the pyrolysis product (X = **13**).

We conclude that 1,5-vinyl shifts are favored over 1,5-alkyl migrations in the spirocycles, and that subsequent hydrogen shifts are not rate determining. It is now appropriate to focus on the central question: Why does the vinyl group migrate easily?[22]

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(11) For example a 6,6-dimethyl-1,3-cyclopentadiene undergoes methyl shift with E_a = 45 kcal/mol: J. W. De Haan and H. Klosterzeil, *Recl. Trav. Chim. Pays-Bas*, **87**, 298 (1968).

(12) ^{1}H NMR (90 MHz, CCl_4) δ 5.30–5.75 (m, 2 H), 2.00–2.80 (m, 4 H), 1.75 (s, 9 H), 0.95 (s, 3 H); IR 3010 (w), 2940 (m), 2900 (s), 2850 (m), 1630 (w); mass spectrum *m/e* 174.

(13) M. Avram, I. G. Dinulescu, E. Marcia, and C. D. Nenitzescu, *Chem. Ber.*, **95**, 2248 (1962); J. Sauer and G. Heinrichs, *Tetrahedron Lett.*, 4979 (1966).

(14) The product had mp 166–166.5 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.00 (s, 1 H), 5.50–5.70 (m, 3 H), 3.80 (s, 3 H), 3.75 (s, 3 H), 2.25–2.45 (m, 2 H), 1.80–2.10 (m, 3 H), 1.67 (s, 3 H), 1.57 (s, 3 H), 1.14 (s, 3 H); IR 3450 (m), 3000 (w), 2980 (w), 2950 (m), 2900 (w), 1720 (s); UV (EtOH); λ_{max} 270 (ϵ 8400), 357 nm (ϵ 2800); mass spectrum *m/e* 344.1753, calcd for $C_{19}H_{24}N_2O_4$, 344.1734.

(15) G. Germain, P. Main, and M. Woolfson, *Acta Crystallogr., Sect. B*, **24**, 274 (1970).

(16) The following library of crystallographic programs was used: W. R. Busing, K. O. Martin, and H. A. Levy, "ORFFE: A Fortran Crystallographic Function and Error Program", Report ORNL-TM-306, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1964. C. K. Johnson, "ORTEP: A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations", Report ORNL-TM-3794, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1965.

(17) Full experimental details can be found in ref 7.

(18) Compound **18** was prepared according to the general scheme shown for preparation of **13** (**20** + **21** → **22** → **13**) starting from 2-methyl-1-(trimethylsilyloxy)-1-cyclohexene; the general method and the specific first steps are reported.[19]

(19) M. Miyashita, T. Yanami, and A. Yoshikoshi, *J. Am. Chem. Soc.*, **98**, 4679 (1976).

(20) Compounds **13**, **16**, **18**, **19**, and **22** showed ^{1}H NMR, IR, UV, and mass spectral data consistent with the proposed structures. Crystalline derivatives were prepared which gave either satisfactory microanalyses or exact mass spectra.

(21) Compound **13** prepared from **22** showed ^{1}H NMR and IR spectral data and GLC retention time identical with parallel measurements for **13** obtained from pyrolysis, and reacted with **15** to give **16**.

(22) We are pleased to acknowledge support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

(23) Recipient of a Camille and Henry Dreyfus Teacher–Scholar Grant.

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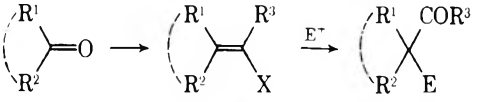
Homologation–Alkylation of Carbonyl Compounds via Regiospecifically Generated Metallo Enamines

Summary: A novel and efficient synthetic strategy for effecting the geminal substitution at a carbonyl center has been

developed which features a one-pot procedure for the regiospecific conversion of carbonyl compounds into the metallo enamines of the homologous aldehydes or ketones via intermediate 2-aza dienes; subsequent trapping of these metallo enamines with a variety of electrophiles occurred with a high degree of regioselectivity.

Sir: The nucleophilic properties of enamines,[1] enolates,[2] and metallo enamines[3,4] have long played a commanding role in processes involving the formation of new carbon–carbon bonds by alkylation, hydroxyalkylation, and acylation reactions. Since most of the procedures for the generation of these important synthetic intermediates commence with the corresponding aldehyde, ketone, or a suitable derivative thereof, the use of these nucleophiles in organic synthesis is restricted by the availability of the parent carbonyl compound. Unfortunately, the requisite carbonyl compounds are not always readily accessible, and therefore the development of an efficient procedure for the regioselective construction of enamines, enolates, or metallo enamines by the carbonyl olefination of less complex aldehydes or ketones, **1 → 2**, would constitute an important addition to the arsenal of synthetic reactions. If these carbonyl derivatives were subsequently treated in situ with assorted electrophiles, the α-substituted, homologous carbonyl compounds **3** would be produced. The combination



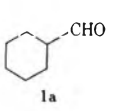
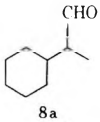
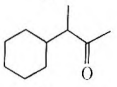
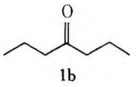
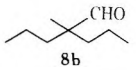
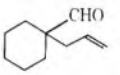
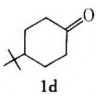
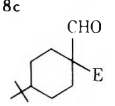
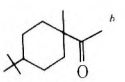
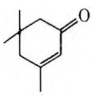
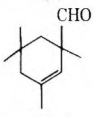
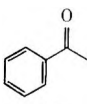
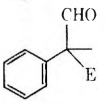
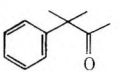
1 **2**, X = R^4_2N, O^-, R^4N^- **3**

of these two steps in tandem would result in a simple process for geminal substitution via a sequence that features the initial nucleophilic acylation[5] of a carbonyl compound, followed by the formation of an additional carbon–carbon or a carbon–heteroatom bond at the original electrophilic center.

In accordance with this general strategy, we have recently described an approach to geminal alkylation in which ketones were converted directly into the enamines of the homologous aldehydes, **1 → 2** (R^3 = H; X = R^4_2N).[6-8] The subsequent reaction of these enamines with a variety of electrophiles, including allyl bromide,[6] methyl vinyl ketone,[7] and 2,3-dibromopropene,[8] resulted in several effective procedures for the formation of quaternary carbon centers.[9] Enamines are, however, relatively weak nucleophiles which may also suffer irreversible N-alkylation, and thus there are some inherent limitations in the above methods which may attenuate their general application in organic synthesis. On the other hand, since metallo enamines exhibit a high reactivity toward electrophiles coupled with a low propensity to suffer proton transfer, they are frequently superior to both enamines and enolates for the introduction of new substituents α to a carbonyl group. In order to circumvent the limitations attendant to our previous procedures for the geminal alkylation of a carbonyl group involving enamines as the key intermediates,[6-8] we initiated a search for an efficient means of transforming aldehydes or ketones into metallo enamines by carbonyl homologation operations.[10] As a result of these investigations, we have discovered a facile, one-pot procedure for the homologation–alkylation of carbonyl compounds via metallo enamine intermediates, **1 → 2** (X = R^4N^-) **→ 3.**

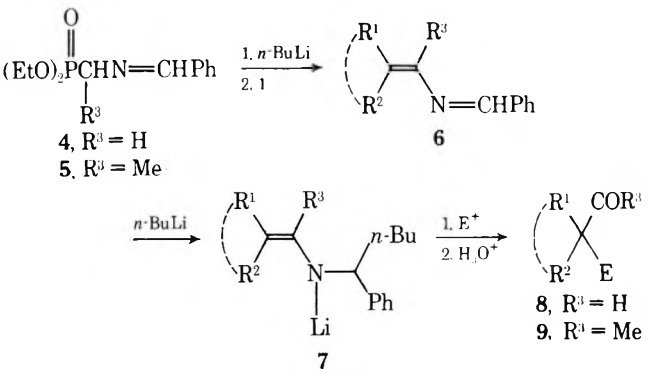
This new strategy for carbonyl homologation with α substitution (Scheme I) was based upon the prediction that the 2-aza dienes **6** would react smoothly with organometallic reagents such as *n*-butyllithium to give the metallo enamines **7.**[11] The synthesis of the requisite 2-aza dienes **6** (R^3 = H) was easily achieved by allowing diethyl lithio-*N*-benzylideneaminomethylphosphonate, prepared by metalation of **4**[12]

Table I. Homologation–Alkylation of Carbonyl Compounds 1

carbonyl compd	phosphonate	electrophile	product	overall yield, %[a]
 **1a**	**4**	MeI	 **8a**	43
1a	**5**	MeI	 **9a**	41
 **1b**	**4**	MeI	 **8b**	58
 **1c**	**4**	CH_2=C-HCH_2Br	 **8c**	51
 **1d**	**4**	MeI	 **8d**, E = Me[b]	63
		CH_2=C-HCH_2Br	**8e**, E = CH_2CH=CH_2[b]	51
		$(MeS)_2$	**8f**, E = SMe[b]	40
1d	**5**	MeI	 **9b**	60
 **1e**	**4**	MeI	 **8g**	80
 **1f**	**4**	MeI	 **8h**, E = Me	77
		CH_2=C-HCH_2Br	**8i**, E = CH_2CH=CH_2	81
1f	**5**	MeI	 **9c**	63

[a] Yields are of distilled product, but have not been optimized. [b] Obtained as a mixture of diastereomers.

Scheme I



with *n*-butyllithium, to react with aldehydes or ketones **1.**[13] Although the 2-aza dienes **6** (R^3 = H) could be isolated, it was more convenient and efficient to treat them in situ with *n*-butyllithium at −78 °C, thereby generating the metallo enamines **7** (R^3 = H). Subsequent addition of various electrophiles such as methyl iodide, allyl bromide, or methyl disulfide

followed by aqueous acid completed the synthetic sequence, affording the aldehydes 8 (E = Me, CH_2=$CHCH_2$, and MeS, respectively) in generally good to very good overall yields (Table I).[14]

An important variant of the above method entails the use of homologous *N*-benzylideneaminoalkylphosphonates such as **5**.[15] For example, treatment of cyclohexanecarboxaldehyde (**1a**) with the anion obtained by metalation of **5**, followed by the sequential addition of *n*-butyllithium, methyl iodide, and then aqueous acid cleanly produced the methylated ketone **9a**. Since the methyl ketone **9a** appeared to be formed exclusively, the generation and trapping of the metallo enamines **7** (R^3 = Me) occurred with a high degree of regioselectivity. The attainment of a similar degree of regiocontrol in the production of metallo enamines such as **7** (R^3 = alkyl) by the simple deprotonation of the corresponding ketimines is not generally feasible. Thus, by appropriately varying the carbonyl precursor and the alkyl substituent on the phosphonates **4** (R^3 = alkyl), it should now be possible to effect the regioselective generation and trapping of *either* of the two possible metallo enamines of an unsymmetrical, acyclic ketone.

The efficiency and particular ease with which the entire reaction sequence may be executed in one pot is illustrated by the following general procedure. A solution of diethyl *N*-benzylideneaminomethylphosphonate (**4**)[12] (12.0 mmol) in anhydrous THF (5 mL) was added to a stirred solution of *n*-butyllithium (12.0 mmol, 3.3 N hexane) in anhydrous THF (50 mL) at −78 °C. After 1 h, a solution of the carbonyl compound **1** (10.0 mmol) in anhydrous THF (5 mL) was added, and the reaction mixture was allowed to warm to room temperature. After heating the reaction at reflux for 3 h, the solution of 2-aza diene was cooled to −78 °C, whereupon *n*-butyllithium (20.0 mmol, 3.3 N hexane) was added. The reaction mixture was stirred at −78 °C for 1 h, the resulting metallo enamine was treated with the appropriate electrophilic reagent (50.0 mmol), and the mixture was then allowed to warm to room temperature. Following the hydrolysis of the intermediate imine with 1 N hydrochloric acid (2 h at room temperature), extractive workup afforded the crude product **8** or **9**, which was purified by vacuum distillation.

As clearly evidenced by the entries in Table I, this new synthetic strategy for the efficient homologation–alkylation of the carbonyl function via metallo enamines, some of which were heretofore inaccessible, is applicable to a variety of carbonyl compounds and alkylating agents. Furthermore, these intermediate metallo enamines may also be sulfenylated to give β-oxo sulfides, which are known precursors of, inter alia, α,β-unsaturated carbonyl compounds[16] and 1,2-dicarbonyl compounds.[17] The applications of this procedure for geminal substitution to other synthetic transformations, including annelation operations and directed aldol processes, are under active investigation and will be reported independently. The feasibility of extending this methodology to the enantioselective construction of quaternary carbon centers is also being examined.

Acknowledgement. We wish to thank the Robert A. Welch Foundation, the Donors of the Petroleum Research Fund, administered by the American Chemical Society, and the University Research Institute of the University of Texas at Austin for their generous financial support.

Supplementary Material Available: Characterization of all new compounds together with representative experimental details (3 pages). Ordering information is given on any current masthead page.

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(6) S. F. Martin and R. Gompper, *J. Org. Chem.*, **39**, 2814 (1974).
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(10) For a review of homologations of carbonyl compounds, see S. F. Martin, *Synthesis*, in press.
(11) Subsequent to the completion of this work another application of this strategy to the synthesis and regioselective trapping of metallo enamines was reported.[4k]
(12) R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Lett.*, 4645 (1973).
(13) During the course of this investigation several other syntheses of 2-aza dienes appeared: (a) A. Dehnel, J. P. Finet, and G. Lavielle, *Synthesis*, 474 (1977); (b) T. Kauffmann, U. Koch, F. Steinseifer, and A. Vahrenhorst, *Tetrahedron Lett.*, 3341 (1977); (c) T. Kauffmann, H. Berg, E. Köppelmann, and D. Kuhlmann, *Chem. Ber.*, **110**, 2659 (1977).
(14) All compounds were adequately characterized by spectral methods (IR, NMR, MS) and all new compounds gave satisfactory high-resolution mass spectral and/or combustion analytical data.
(15) Prepared in 75% yield from **4** by the sequence of metalation–methylation.
(16) C.f., B. M. Trost, T. N. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.*, **98**, 4887 (1976).
(17) B. M. Trost and G. S. Massiot, *J. Am. Chem. Soc.*, **99**, 4405 (1977).

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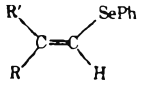
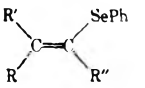
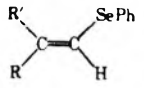
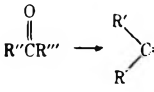
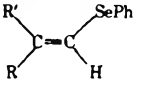
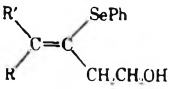
Deprotonations with Potassium Diisopropylamide–Lithium *tert*-Butoxide. Alkylation of 1-(Phenylseleno)alkenes and Bis(phenylseleno) Acetals[1]

Summary: A readily prepared, nonnucleophilic, strongly basic mixture of potassium diisopropylamide–lithium *tert*-butoxide (KDA) rapidly deprotonates both 1-(phenylseleno)alkenes (**1**) and bis(phenylseleno) acetals (**3**); in contrast, neither lithium diisopropylamide nor potassium bis(trimethylsilyl)-amide were able to deprotonate these compounds at a perceptible rate. The deprotonation–alkylation of both **1** and **3** is described.

Sir: Nonnucleophilic, strong bases such as lithium diisopropylamide (LDA) have been of invaluable utility in organic chemistry.[2] Although the *rate* of deprotonation of weakly acidic compounds may be changed by several orders of magnitude simply by altering the cation accompanying the amide

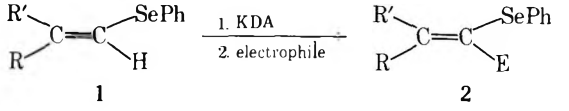
0022-3263/78/1943-3794$01.00/0

Table I. Products and Yields for the α-Deprotonation–Alkylation of 1-(Phenylseleno)alkenes

entry	R	R′	electrophile[a]	% yield 2[b]
			R″X →	
a	H	H	CH_3I	98
b	H	H	n-$C_{10}H_{21}Br$	94
c	n-C_4H_9[c]	H	CH_3I	85
d	H	n-C_4H_9	CH_3I	85
e	$(CH_3)_2CH$	H	CH_3I	80
f	$(CH_3)_2CH$	H	n-$C_{10}H_{21}Br$	88
				
g	H	H	$(CH_3)_2CHCHO$	92
h	H	H	2-cyclohexenone	80[d]
i	$(CH_3)_2CH$	H	$(CH_3)_2CHCHO$	95
			epoxide → 	
j	H	H	ethylene oxide	92

[a] 1.05–1.2 equiv of electrophile/equiv of 1. [b] Isolated yields, see ref 14. [c] Starting material contained <10% of (Z)-1-(phenylseleno)hexene. [d] 1,2 addition product.

Scheme I



1 2

base,[3] the majority of synthetic applications have involved lithium salts.[4]

We now wish to report that a readily prepared mixture of potassium diisopropylamide–lithium *tert*-butoxide (KDA) rapidly α-deprotonates[5] 1-(phenylseleno)alkenes (1);[6,7] in contrast, neither lithium diisopropylamide nor potassium bis(trimethylsilyl)amide were able to deprotonate 1 at a perceptible rate.[9]

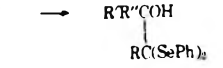
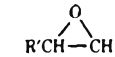
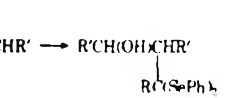
KDA may be prepared by the addition of diisopropylamine to a mixture of *n*-butylpotassium–lithium *tert*-butoxide[10] in hexane at 0 °C. Although it is possible to prepare *n*-butylpotassium free of lithium alkoxides,[11] their presence has no detrimental effect on the deprotonation of 1. Alternatively, KDA may be prepared with comparable results by the addition of *n*-butyllithium to a solution of potassium *tert*-butoxide and diisopropylamine in THF at −78 °C.[12]

The selenium-stabilized carbanions derived by KDA α deprotonation of 1-(phenylseleno)alkenes (1) react rapidly[13] with a variety of electrophiles including primary alkyl halides, epoxides, aldehydes, and ketones (Table I).[14] The deprotonation–alkylation occurs with retention of stereochemistry about the double bond (entries c–f, i). Carbonyl compounds which contain α hydrogens undergo nucleophilic addition rather than enolate formation (entries g–i); 2-cyclohexenone undergoes 1,2 addition (entry h).

The readily available 1-(phenylseleno)alkenes 1[6] may be utilized as acyl carbanion equivalents by conversion to 2 followed by hydrolysis[15] to the corresponding carbonyl compounds (Scheme I).

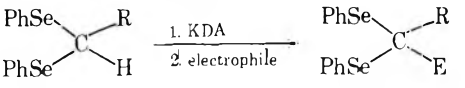
Although LDA is unable to deprotonate bis(phenylseleno) acetals 3 (R = alkyl) at a perceptible rate,[16,17] KDA rapidly deprotonates 3 at −78 °C. The resulting selenium-stabilized carbanions react smoothly with primary and secondary alkyl halides, aldehydes, ketones, enones, and epoxides to give 4 in high overall yield (Scheme II, Table II).[18] It is noteworthy that carbonyl compounds which contain α-hydrogens undergo

Table II. Products and Yields for Alkylations of $RCH(SePh)_2$

entry	R	electrophile[a]	% yield 4[b]
	$RCH(SePh)_2$	R′X →	$RR'C(SePh)_2$
a	CH_3	CH_3I	98
b	CH_3	n-C_4H_9I	95
c	CH_3	$(CH_3)_2CHI$	70[c]
d	CH_3	n-$C_{10}H_{21}Br$	95
e	CH_3	$PhCH_2Br$	88
f	$(CH_3)_2CH$	$PhCH_2Br$	71
g	n-$C_{10}H_{21}$	$PhCH_2Br$	98
	$RCH(SePh)_2$	R′CR″ → 	
h	CH_3	CH_3COCH_3	77
i	CH_3	2-cyclohexenone	76[d]
j	CH_3	$(CH_3)_2CHCHO$	90
k	$(CH_3)_2CH$	$(CH_3)_3CHCHO$	63
l	n-$C_{10}H_{21}$	$(CH_3)_2CHCHO$	84
	$RCH(SePh)_2$	 → 	
m	CH_3	ethylene oxide	82
n	n-$C_{10}H_{21}$	cyclohexene oxide	91

[a] 1.05–1.2 equiv of electrophile/equiv of bis(phenylseleno) acetal. [b] Isolated yields, see ref 18. [c] ~20% 1,1-bis(phenylseleno)-ethane recovered. [d] 1,2-Addition product.

Scheme II



3 4

nucleophilic addition rather than enolate formation (entries h–l). Not surprisingly, 2-cyclohexenone undergoes 1,2 addition (entry i).

Bis(phenylseleno) ketals (4) may be utilized in a number of valuable synthetic transformations.[19] In addition, hydrolysis of 4 to the corresponding carbonyl compounds occurs readily under extremely mild conditions (2 equiv of $CuCl_2$, 4 equiv of CuO, 99% acetone, 0 °C, 30 min).[20] For example, **4e** gave phenylacetone (86%), **4g** gave 1-phenyl-2-dodecanone (90%), and the benzoate ester of **4m** gave 4-benzoyloxy-2-butanone (85%).

We believe that KDA will prove to be extremely useful as a nonnucleophilic, strong base for the rapid deprotonation of weakly acidic compounds,[9] and we are currently investigating the use of KDA for the formation of other selenium-stabilized carbanions.[21]

Acknowledgment. We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Supplementary Material Available: Full NMR data for compounds 2 and 4 (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) Organoselenium Chemistry. 4. For previous paper in this ser es, see: S. Raucher, *Tetrahedron Lett.*, 2261 (1978).
(2) For leading references concerning the use of lithium diisopropylamide, lithium isopropylcyclohexylamide, lithium dicyclohexylamide, lithium 2,2,6,6-tetramethylpiperidide, and lithium bis(trimethylsilyl)amide, see the appropriate entries in: L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1–6, Wiley-Interscience, New York, N.Y., (1967–1977).
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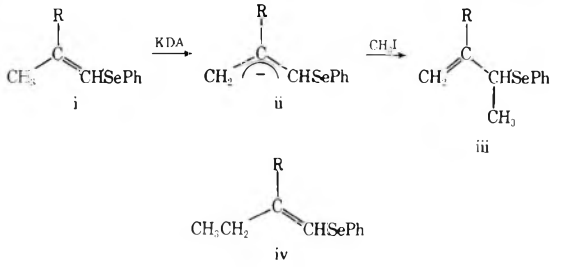
(4) We have found no examples for the preparation of *hindered* potassium *dialkyl*amides; preparation of the less basic potassium bis(trimethylsilyl)-amide and potassium *N*-isopropylanilide has been reported: (a) U. Wannagat

and H. Niederprum, *Chem. Ber.*, **94,** 1540 (1961); (b) G. Stork, J. O. Gardner, R. K. Boeckman, Jr., and K. A. Parker, *J. Am. Chem. Soc.*, **95,** 2014 (1973); (c) C. A. Brown, *J. Org. Chem.*, **39,** 3913 (1974); (d) C. A. Brown, *Synthesis*, 427 (1974).

(5) (a) Reaction of 2-methyl-1-(phenylseleno)alkenes (i, R = H or CH_3) with KDA leads to allylic deprotonation rather than α-deprotonation; the resulting selenium-stabilized allyl carbanions (ii) react with methyl iodide to give mixtures (4:1) of α and γ alkylation products, iii and iv, respectively.



(b) For the formation and alkylation of selenium-stabilized allyl carbanions from the corresponding allyl phenylselenides, see: H. J. Reich, *J. Org. Chem.*, **40,** 2570 (1975).

(6) 1-(Phenylseleno)alkenes are easily prepared from the corresponding alkenes: S. Raucher, *J. Org. Chem.*, **42,** 2950 (1977).

(7) Attempts to deprotonate **1** with alkyllithiums led to other reactions,[8] including carbon–selenium bond cleavage: H. Gilman and F. J. Webb, *J. Am. Chem. Soc.*, **71,** 4062 (1949).

(8) S. Raucher and G. A. Koolpe, submitted for publication.

(9) The ability of KDA to deprotonate weakly acidic compounds that are uneffected by LDA is undoubtedly a *kinetic* rather than a *thermodynamic* effect; thus, quantitative deprotonation of compounds which are intrinsically less acidic than diisopropylamine under equilibrium conditions should not be expected. Attempts to deprotonate 1-butyl phenyl selenide with KDA (THF, −78 °C, 30 min; or hexane, 0 °C, 4 h) were unsuccessful.

(10) (a) L. Lochmann, J. Pospisil, and D. Lim, *Tetrahedron Lett.*, 257 (1966); (b) M. Schlosser and J. Hartmann, *Angew. Chem., Int. Ed. Engl.*, **12,** 508 (1973); (c) M. Schlosser, *J. Organomet. Chem.*, **8,** 9 (1967). See also: (d) E. Weiss and G. Sauerman, *Chem. Ber.*, **103,** 265 (1970); (e) G. Thirase and E. Weiss, *J. Organomet. Chem.*, **81,** C1 (1974).

(11) L. Lochmann and D. Lim, *J. Organomet. Chem.*, **28,** 153 (1971).

(12) (a) Potassium diisopropylamide–lithium *tert*-butoxide is stable in hexane at 0 °C for at least 1 h; KDA decomposes rapidly at 0 °C in THF. (b) After the initial portion of this research was completed, Professor D. Seebach informed us that he has utilized potassium diisopropylamide–lithium *tert*-butoxide, prepared in a similar manner, for the deprotonation of nitrosamines.

(13) Formation of $PhSe^-$, presumably by α-elimination, occurs to some extent at −78 °C if the carbanions are not utilized immediately.

(14) (a) A typical experimental procedure for the synthesis of **2a** follows. To a solution of potassium *tert*-butoxide (168 mg, 1.50 mmol) and diisopropylamine (152 mg, 1.50 mmol) in THF (4 mL) cooled to −78 °C under an atmosphere of argon was added *n*-butyllithium in hexane (2.4 M, 0.50 mL, 1.2 mmol) over 30 s. The mixture was stirred for 10 min at −78 °C, and a solution of (phenylseleno)ethene (183 mg, 1.00 mmol) in THF (1.5 mL) was added over 1 min. The reaction mixture was stirred at −78 °C for 1 min,[13] a solution of methyl iodide (213 mg, 1.50 mmol) in THF (0.5 mL) was added over 5 s, and stirring at −78 °C was continued for 10 min. The reaction was quenched with methanol (0.5 mL) and poured into saturated aqueous NH_4Cl (4 mL). the THF was removed in vacuo, and the residue was extracted with hexane. Evaporation of the hexane, and purification by evaporative distillation (85 °C, 0.5 mm) gave 2-(phenylseleno)propene (194 mg, 98%): ^1H NMR (CCl_4) δ 2.07 (d, J = 1 Hz, 3 H), 5.08 (s, 1 H), 5.43 (q, J = 1 Hz, 1 H), 7.2–7.7 (m, 5 H). (b) All new compounds were fully characterized by spectroscopic methods. Yields are given for isolated, purified compounds. (c) Additional data: Anal. $C_9H_{10}Se$ (**2a**) *m/e* calcd 197.9948, found 197.9940; $C_{15}H_{22}OSe$ (**2l**) *m/e* calcd 298.0836, found 298.0824; $C_{10}H_{12}OSe$ (**2j**) *m/e* calcd 228.0053, found 228.0066.

(15) (a) Hydrolyzed with $HgCl_2$ in CH_3CN/H_2O: E. J. Corey and J. I. Shulman, *J. Org. Chem.*, **35,** 777 (1970); (b) N. Petragnani, R. Rodrigues, and J. V. Comasseto, *J. Organomet. Chem.*, **114,** 281 (1976).

(16) (a) It is possible to deprotonate the more acidic $(PhSe)_2CH_2$ with LDA in THF at −30 °C. We have successfully alkylated the resulting carbanion with methyl iodide (98% yield), *n*-decyl bromide (95% yield), and benzyl bromide (92%) yield). It is noteworthy that $(PhSe)_2CH_2$ undergoes no detectable dialkylation even in the presence of excess LDA and alkylating agent. (b) Deprotonation of $(PhSe)_2CH_2$ with lithium diisobutylamide in THF at −78 °C, and subsequent reaction with benzophenone, methyl iodide, and D_2O has been reported: D. Seebach and N. Peleties, *Angew. Chem., Int. Ed. Engl.*, **8,** 450 (1969); D. Seebach and N. Peleties, *Chem. Ber.*, **105,** 511 (1972).

(17) Bis(phenylseleno) acetals are available either from the corresponding aldehydes and selenophenol–zinc chloride, or by the alkylation of bis(phenylseleno)methane: (a) W. Dumont and A. Krief, *Angew. Chem., Int. Ed. Engl.*, **16,** 540 (1977), and references cited therein; (b) ref 16.

(18) (a) A typical experimental procedure for the synthesis of **4e** follows. To a suspension of KDA prepared as above[14a] was added a solution of 1,1-bis(phenylseleno)ethane (340 mg, 1.00 mmol) in THF (1.5 mL) over 2 min. After 10 min at −78 °C, a solution of benzyl bromide (180 mg, 1.05 mmol) in THF (1.5 mL) was added over 15 s, and stirring at −78 °C was continued for 15 min. The reaction was quenched with methanol (0.5 mL) and poured into saturated aqueous NH_4Cl (4 mL), the THF was removed in vacuo, and the residue was extracted with hexane. Evaporation of the hexane gave a white solid which was crystallized from methanol to yield 1-phenyl-2,2-bis(phenylseleno)propane (**4e**): 380 mg (88%); mp 109–110 °C; ^1H NMR ($CDCl_3$) δ 1.48 (s, 3 H), 3.27 (s, 2 H), 7.0–7.8 (m, 15 H). (b) All new compounds were fully characterized by spectroscopic methods. Yields are given for chromatographically pure, isolated products. (c) Additional data: Anal. $C_{21}H_{20}Se_2$ (**4e**) *m/e* calcd 429.9903, found 429.9896; $C_{17}H_{20}OSe_2$ (**4h**) *m/e* calcd 397.9852, found 397.9902.

(19) For example, see: (a) ref 16; (b) D. Seebach and A. K. Beck, *Angew. Chem., Int. Ed. Engl.*, **13,** 806 (1974); (c) W. Dumont, P. Bayet, and A. Krief, *ibid.*, **13,** 804 (1974); (d) W. Dumont and A. Krief, *ibid.*, **14,** 350 (1975); (e) W. Dumont and A. Krief, *ibid.*, **15,** 161 (1976); (f) A. Anciaux, A. Eman, W. Dumont, D. Van Ende, and A. Krief, *Tetrahedron Lett.*, 1613 (1975); (g) A. Anciaux, A. Eman, W. Dumont, and A. Krief, *ibid.*, 1617 (1975); (h) J. N. Denis, W. Dumont, and A. Krief, *ibid.*, 453 (1976); (i) J. Remion, W. Dumont, and A. Krief, *ibid.*, 1385 (1976); (j) M. Sevrin, D. Van Ende, and A. Krief, *ibid.*, 2643 (1976).

(20) (a) T. Mukaiyama, K. Narasaka, and M. Furusato, *J. Am. Chem. Soc.*, **94,** 8641 (1972); (b) T. Mukaiyama, K. Narasaka, K. Maekawa, and M. Furusato, *Bull. Chem. Soc. Jpn.*, **44,** 2285 (1971).

(21) **Note Added in Proof:** Professor Seebach's research involving KDA has now been published: B. Renger, H. Hugel, W. Wykypiel, and D. Seebach, *Chem. Ber.*, **111,** 2630 (1978).

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Received April 27, 1978

Allylation of Quinones with Allyltin Reagents. New Synthesis of Coenzyme Q_1 and Plastquinone-1[1]

Summary: Lewis-acid catalyzed allylation of *p*-benzoquinone with allyltributyltins is examined; coenzyme Q_1 and plastquinone-1 are prepared in good yields.

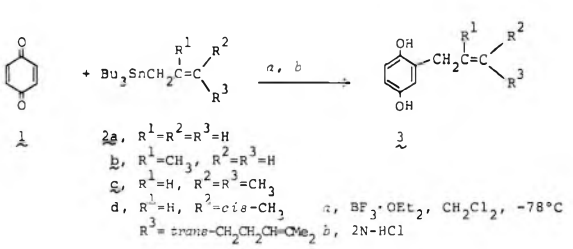
Sir: Prenylated quinones, which are widely distributed in nature, play an important role in the life of living things, e.g., in electron transport, oxidative phosphorylation, and blood clotting.[2] Regiospecific and direct introduction of the prenyl group into a quinone ring has been a challenging subject for organic chemists. So far, the direct introduction of an allyl or prenyl group into the quinone ring has met limited success,[4] though the successful allylation of protected quinones has been attained.[3]

In this communication, we wish to report on the successful direct introduction of the prenyl group into the quinone ring using allyltributyltin reagent. With our procedure regiospecific synthesis of coenzyme Q_1 (**4**) and plastquinone-1 (**5**) was

4 5

successfully accomplished. Typically the reaction was carried out by dropwise addition of an allyltributyltin (**2**) (2 mmol) to a dichloromethane solution (10 mL) of quinone (**1**) (1 mmol) and BF_3·OEt_2 (1 mmol) under N_2 at −78 °C. After addition was completed, the temperature of the reaction mixture was

Scheme I



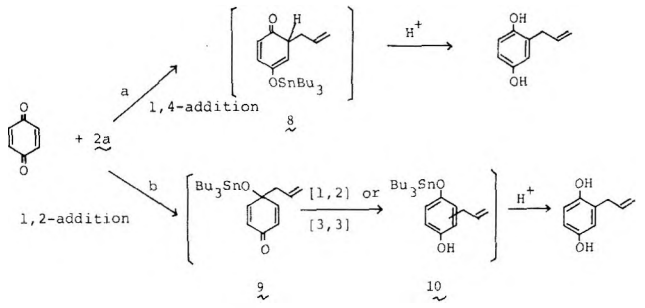
0022-3263/78/1943-3796$01.00/0

Table I. Allylation of Quinones with Allyltributyltin

quinone	allyltin	product[a]	% yield[b]
p-benzoquinone	**2a**	allylbenzoquinone[c]	66 (85)
p-benzoquinone	**2b**	(2-methyl-2-propenyl)benzoquinone[c]	45
p-benzoquinone	**2c**	(3-methyl-2-butenyl)benzoquinone[c]	55
p-benzoquinone	**2d**	geranylbenzoquinone[c,d]	58
2,3-dimethylbenzoquinone	**2a**	5-allyl-2,3-dimethylhydroquinone	72
2,3-dimethylbenzoquinone	**2c**	2,3-dimethyl-5-(3-methyl-2-butenyl)hydroquinone	61
2,5-dimethylbenzoquinone	**2a**	3-allyl-2,5-dimethylhydroquinone	90
2,5-dimethylbenzoquinone	**2c**	2,5-dimethyl-3-(3-methyl-2-butenyl)hydroquinone	69
2,6-dimethylbenzoquinone	**2a**	3-allyl-2,6-dimethylhydroquinone	82
2,6-dimethylbenzoquinone	**2c**	2,6-dimethyl-3-(3-methyl-2-butenyl)hydroquinone	70
trimethylbenzoquinone	**2a**	allyltrimethylhydroquinone	37
trimethylbenzoquinone	**2c**	trimethyl(3-methyl-2-butenyl)hydroquinone	35
2,5-di-*tert*-butylbenzoquinone	**2a**	2-allyl-6-*tert*-butylhydroquinone	36
2,3-dimethoxy-5-methylbenzoquinone	**2a**	2-allyl-5,6-dimethoxy-2-methylbenzoquinone[c]	61
2,3-dimethoxy-5-methylbenzoquinone	**2c**	coenzyme Q_1 (**4**)[c]	75
1,4-naphthoquinone	**2a**	2-allyl-1,4-naphthoquinone[c]	42
2-methoxy-1,4-naphthoquinone	**2a**	1-allyl-1-hydroxy-5-methoxy-4-naphthalenone (**6**)	90
2,6-dimethoxybenzoquinone	**2a**	4-allyl-4-hydroxy-3,5-dimethoxycyclohexan-2,5-dien-1-one (**7**)	52

[a] Characterized by infrared, NMR, and mass spectra, and elemental analysis. [b] Yield in parentheses determined by GLC; all others are of purified products after isolation based on quinone. [c] Products after oxidation with silver oxide or ferric chloride. [d] Stereochemistry at Δ^2, cis/trans 7:93.

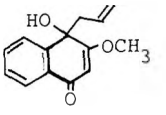
Scheme II



gradually elevated to room temperature within 1 h. The reaction was quenched by the addition of 2 N hydrochloric acid and crude products were extracted with ether. The ethereal extract was usually worked up and precipitated allylhydroquinone was purified by recrystallization from ether–hexane. In the cases of air-sensitive allylhydroquinones, the ethereal extract was immediately treated with an amount of ferric chloride solution to give allylated quinones, which were purified by preparative thin-layer chromatography on silica gel (developing solvent: 4:1 hexane–ether mixture). The products and their yields are summarized in the Table I.

The yield of the present allylations is high and the generality is obvious. The characteristics of our reaction are: (i) allylation occurs at the nonsubstituted site of the quinone ring with the exception of 2,5-di-*tert*-butylbenzoquinone; (ii) the prenyl group is introduced into the quinone ring without allylic isomerization; and (iii) the fair yields (61–90%) are not affected by the presence of two methyl groups on the quinone ring, but the allylations of trimethylbenzoquinone using **2a** and **2c** give rather unsatisfactory yields (35–37%). When our procedure was applied to the synthesis of coenzyme Q_1 and plastquinone-1, the attained yields reached to 75 and 61%,[6] respectively. Hitherto coenzyme Q_1 was prepared from 2,3-dimethoxy-5-methylbenzoquinone with the use of π-allylnickel complex, but in an unsatisfactory yield (26%) with lack of regioselectivity.[4c,7] Coupling reactions between the π-allylnickel complex and the protected quinone have also been reported to yield coenzyme Q_1 in an overall yield of ~20% via eight steps.[3b] In contrast, our procedure gives a single product in a fairly high yield accompanied by no regioisomers, and excludes several disadvantages observed in other allylations of quinones.[8]

Though the mechanism of the present allylation remains to be clarified, the present results are reasonably explained by either of two possible routes (paths a and b, see Scheme II). However, path a seems to be less probable, for in the allylation of 1,3-diphenyl-2-propen-1-one 3-methyl-2-butenyltributyltin (**2c**) adds to it to give 4,4-dimethyl-1,4-diphenyl-5-hexen-1-one.[9] In addition, the allylation of 2-methoxynaphthoquinone and 2,6-dimethoxybenzoquinone gives stable quinols, **6** and **7**, which also supports the path a.



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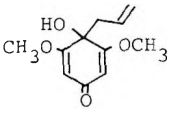

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Together with its easy accessibility,[5] allyltin reagents are a promising allylating reagent of the quinone ring.[10,11] The scope and the detailed mechanism of the reaction are under investigation.

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(5) Allyltributyltin (**2a**) and 2-methyl-2-propenyltributyltin (**2b**) were prepared according to the literature (ref 10d). 3-Methyl-2-butenyltributyltin (**2c**) and geranyltributyltin (**2d**) were prepared by the coupling of tributyltinlithium in THF with prenyl chloride and geranyl chloride, respectively, at −50 °C to room temperature: cf. E. Matarasso-Tchiroukhine and P. Cadiot, *J. Organomet. Chem.*, **121**, 155 (1976).

(6) Using the general oxidant, Ag_2O or $FeCl_3$, plasthydroquinone-1 was quantitatively converted to plastquinone-1.

(7) In their first communication. Hegedus et al. reported the 30% yield of

coenzyme Q_1 without comments on the formation of regioisomers, using 4 equiv of π-allylnickel complex to 1 equiv of the quinone (see ref 4b).

(8) In other allylations of quinones polyalkylation, chromanol formation, side-chain cyclization, and other numerous difficulties concerned with product isolations are often observed: D. E. Wolf, C. H. Hoffman, N. R. Trenner, B. H. Arison, C. H. Shunk, B. O. Lin, J. F. McPherson, and K. Folkers, *J. Am. Chem. Soc.*, **80**, 4752 (1958); U. Gloor, O. Isler, R. A. Morton, R. Rüegg, and O. Wiss, *Helv. Chim. Acta*, **41**, 2357 (1958).

(9) Under the similar conditions to that of quinones, the α,β-unsaturated ketone gave the usual 1,4-conjugate addition product with allyltin.

(10) In addition, using BF_3-OEt_2 as activator of carbonyl, our reaction proceeds under mild conditions in contrast to the usual insertion reaction of the carbonyl group (ketone or aldehyde) into the allyltin Sn–C bond. Without BF_3-OEt_2 the usual reaction is limited to polarized carbonyls attached to electron-withdrawing groups or needed higher reaction temperature: (a) K. König and W. P. Neumann, *Tetrahedron Lett.*, 495 (1967); (b) C. Servans and M. Pereyre, *J. Organomet. Chem.*, **26**, C4 (1971); (c) *ibid.*, **35**, C20 (1972); (d) E. A. Abel and R. J. Rowley, *ibid.*, **84**, 199 (1975).

(11) Allylations using other allylating reagents such as allylsilane[4d] and π-allylnickel complex[4b,c] have been reported [see also Hegedus et al., *J. Am. Chem. Soc.*, **100**, 3461 (1978)]. However, coenzyme Q_1 was first prepared in a satisfactory yield by our procedure.

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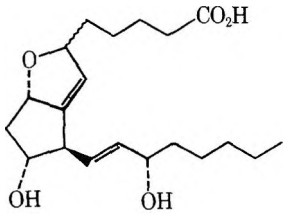
Received June 12, 1978

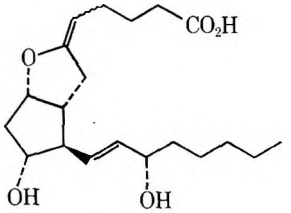
Synthesis of (6*R*)- and (6*S*)-6(9)-Oxy-11,15-dihydroxyprosta-7,13-dienoic Acids [(6*R*)- and (6*S*)-Δ^7-PGI_1]: Nonidentity with the Proposed Arachidonic Acid Metabolite

Summary: This report describes the chemical synthesis of (6*R*)- and (6S)-Δ^7-PGI_1; the spectral properties of the synthetic material were entirely different from those reported by Pace-Asciak and Wolfe for their proposed biosynthetic arachidonic acid metabolite.

Sir: In 1971, Pace-Asciak and Wolfe[1] reported the formation of two novel prostanoic acid derivatives during the incubation of arachidonic acid with rat stomach homogenates. The structure of the major component was assigned as 6(9)-oxy-11,15-dihydroxyprosta-7,13-dienoic acid (**1**) and the minor component as 6(9)-oxy-11,15-dihydroxyprosta-5,13-dienoic acid (**2**). The structural assignments of **1** and **2**[2] were based



1

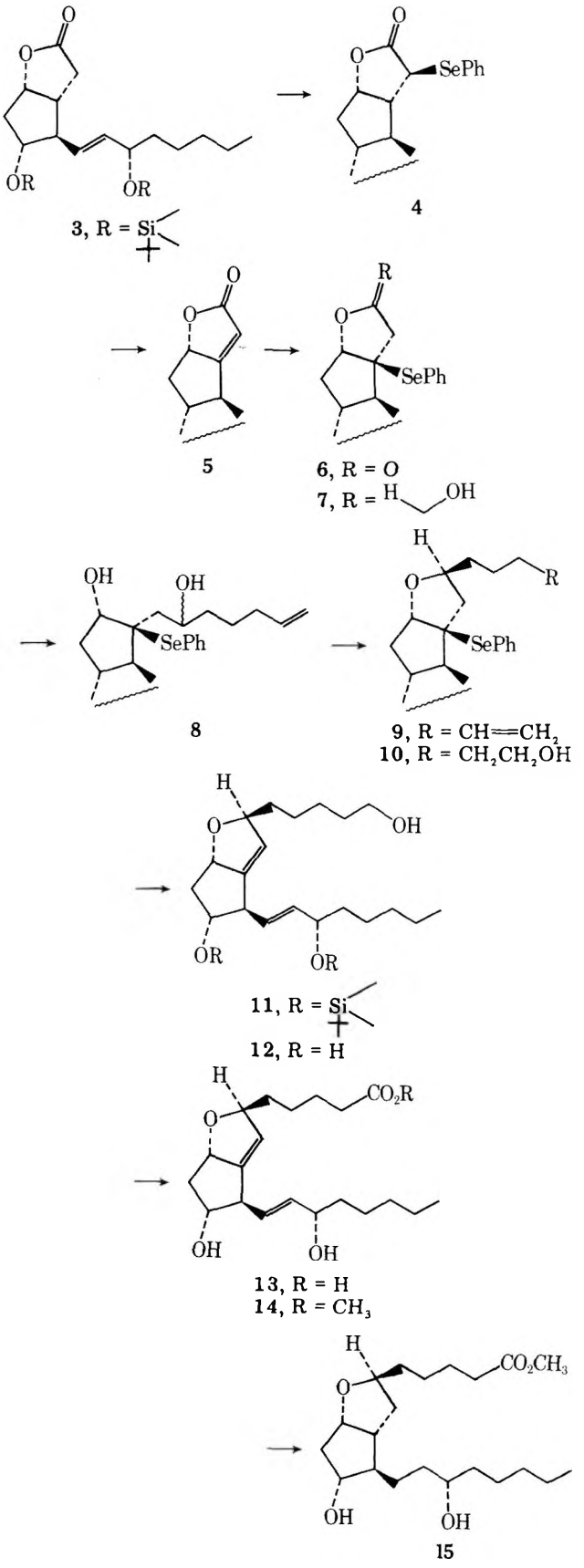


2

on mass spectrometric evidence and products derived from oxidative ozonolysis. The recent discovery[3] of prostacyclin (PGI_2), the 5*Z* isomer of **2**,[4-6] has revived interest in this area of prostaglandin research.[7-9] In view of the finding that PGI_2 is rapidly hydrolyzed to 6-oxoprostaglandin $F_1\alpha$ at pH's as high as 7.6,[4] the isolation of **2** under the acidic conditions employed[1] must be regarded as unlikely. However, the existence of a structurally related 6(9)-oxy-11,15-dihydroxyprosta-7,13-dienoic acid (**1**, Δ^7-PGI_1) cannot be excluded on this basis. In this communication we describe a chemical synthesis of (6*R*)- and (6*S*)-Δ^7-PGI_1 and compare the nuclear magnetic resonance and mass spectrometric properties of our synthetic material to those reported by Pace-Asciak and Wolfe for their alleged biosynthetic metabolite.

Reaction of the 11,15-bis(dimethyl-*tert*-butylsilyl) lactone

Scheme I



3, R = Si

4

5

6, R = O
7, R = H, OH

8

9, R = CH=CH$_2$
10, R = CH$_2$CH$_2$OH

11, R = Si

12, R = H

13, R = H
14, R = CH$_3$

15

3 in tetrahydrofuran (THF) with 1.1 equiv of lithium diisopropylamide (−78 °C, 15 min) and treatment of the resulting enolate with 1.3 equiv of PhSeCl for 20 min at −78 °C afforded the 7-phenylselenenyl lactone **4** in 90% yield (Scheme I).[10] Exposure of lactone **4** in CH_2Cl_2 to 10% aqueous H_2O_2 (10 equiv, room temperature for 1 h) gave via phenyl selenoxide elimination the α,β-unsaturated lactone **5** [mp 36.5–38 °C; UV

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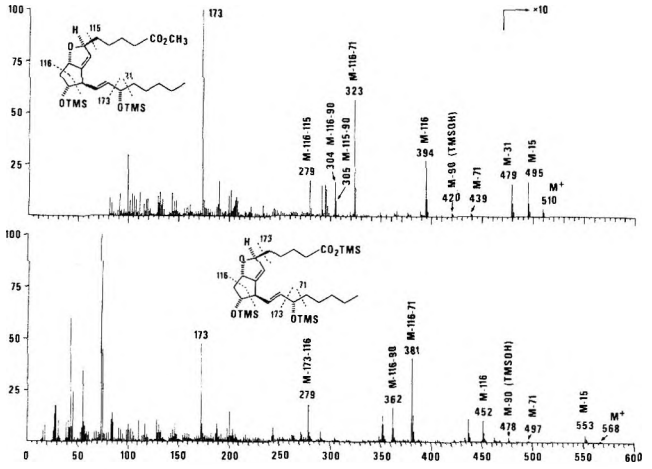
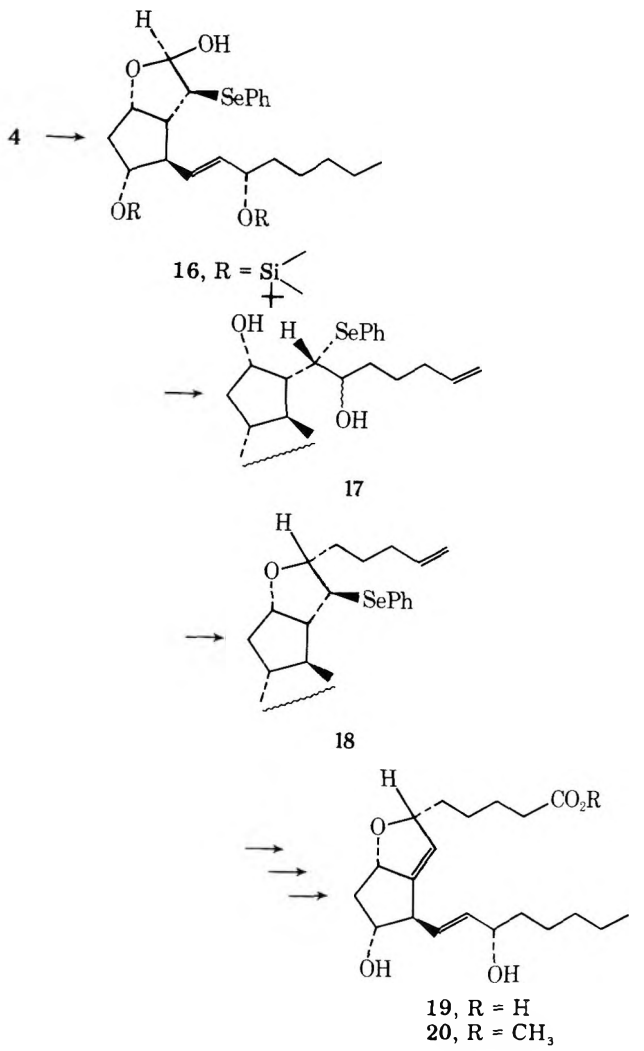


Figure 1. Mass spectra of synthetic **14** (trimethylsilyl ether methyl ester derivative) and **13** (trimethylsilyl ether trimethylsilyl ester derivative).

(EtOH) 217 nm (ϵ 13 950)]. Addition of lactone **5** in EtOH to a solution of phenylselenenyl anion (generated in situ from 1.2 equiv of PhSeSePh and $NaBH_4$ in EtOH) yielded the 8-phenylselenenyl lactone **6** (R_f values observed on silica gel TLC plates with ethyl acetate–benzene, 50:1, as solvent: 0.49 for **4** and 0.42 for **6**). The lactol **7** was obtained by reduction of lactone **6** in toluene with diisobutylaluminum hydride (1.2 equiv, −78 °C for 20 min). Alkylation of lactol **7** in ether with 4-pentenylmagnesium bromide (3–4 equiv, 0–5 °C for 1.5 h) afforded the 6,9-dihydroxy olefin **8** (63% yield overall from **4**). The formation of the 6,9-epoxy linkage from diol **8** was achieved either with 5 equiv of *p*-toluenesulfonyl chloride in pyridine at 40 °C for 48 h, or with 2 equiv of methanesulfonyl chloride and 5 equiv of Et_3N in CH_2Cl_2 at −78 °C for 5 min. In each instance, the (6*S*)-6,9-epoxy isomer **9** was obtained as the exclusive 6,9-cyclized product.[11] The stereochemical assignment of **9** was made from the experiments later discussed. Conversion of **9** to (6*S*)-Δ^7-PGI_1 (**13**) was accomplished (50% overall yield) by the sequence: (a) hydroboration of **9** with 9-borobicyclo[3.1.1]nonane[12] followed by careful oxidative workup furnished the C-1 primary alcohol **10**; (b) oxidative treatment of **10** with 10% aqueous H_2O_2 yielded the unsaturated bis(silyl) ether **11**; (c) mild acid hydrolysis of **11** gave the 11,15-dihydroxy C-1 alcohol **12**; and (d) selective oxidation of **12** with Pt and O_2[13] afforded (6*S*)-Δ^7-prosta-7,13-dienoic acid **13** (R_f value 0.28, 2% acetic acid in ethyl acetate as solvent). Catalytic hydrogenation (5% Pd–C) of (6*S*)-Δ^7-PGI_1 methyl ester **14** (R_f value, 30% acetone in methylene chloride as solvent, 0.28 for **14**; R_f 0.33 for PGI_2 methyl ester) gave a single product. This material was identical by TLC, ^1H NMR, and MS with an authentic sample of (6*S*)-13,14-dihydro-PGI_1 methyl ester[14] (**15**), but different from (6*R*)-13,14-dihydro-PGI_1 methyl ester.[14]

The spectral data for **13** and **14** are consistent with their assigned structures. However, the ^1H NMR and MS spectral properties of synthetic **13** and **14** are clearly not in agreement with those published by Pace-Asciak and Wolfe for the biosynthetic metabolite **1**. High or low resolution mass spectra of **13** and **14** gave the correct molecular ion (Figure 1).[15] A characteristic pattern of mass fragmentation of **13** and **14** shows the preferential elimination of $CH_2{=}CHOSiMe_3$ ($M^+ - 116$), while in the spectra of the biosynthetic derivatives it is distinctly absent. Conversely, the base peak (*m/e* 225) present in Pace-Asciak and Wolfe's spectra is totally absent in **13** and **14**. The ^1H NMR ($CDCl_3$) spectrum of methyl ester **14** shows a three-hydrogen multiplet in the olefinic region (δ 5.60), a signal at δ 3.00 (C-12 hydrogen) characteristic for all

Scheme II



the Δ^7-intermediates prepared in this study, and a multiplet centered at δ 5.00 (C-6 and C-9 hydrogens). The latter absorption is unmistakably absent in the biosynthetic sample. The ^{13}C NMR of **14** reveals four unsaturated carbons. As expected, the chemical shifts (Me_4Si reference) of carbons C_{13} (130.0 ppm) and C_{14} (133.8 ppm) corresponded to those of the C_{13} and C_{14} carbons of (6*S*)-PGI_1 methyl ester. An off-resonance decoupling study allowed positive assignment of the chemical shifts at 146.8 and 122.7 ppm to the C_8 quaternary carbon and C_7 tertiary carbon, respectively.

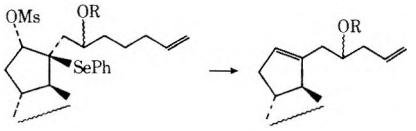
To unequivocally rule out the possibility that a difference in stereochemistry at C-6 was responsible for the variation in spectral properties, we sought a synthesis of (6*R*)-Δ^7-PGI_1. Following the reaction conditions previously described, reduction of lactone **4** gave lactol **16** (90%), which after Grignard alkylation, furnished the 7-phenylselenenyl diol **17** in 45% yield[16] (Scheme II).[10] Treatment of the diol **17** in CH_2Cl_2 with *N,N*-diethyl-*N*-methylmethanesulfonylammonium fluorosulfonate[17] (1.5 equiv, 0–5 °C) in a catalytic amount of pyridine yielded only the (6*R*)-epoxy isomer **18**.[18] Having achieved the synthesis of **18**, the remaining steps leading to (6*R*)-Δ^7-PGI_1 (**19**) were accomplished in the same manner[19] as discussed for the synthesis of (6*S*)-Δ^7-PGI_1 (**13**) from **9**. The (6*R*)-Δ^7-PGI_1 isomer (**19**) and its methyl ester derivative **20**, as well as the (6*R*)-Δ^7 intermediates, all appeared slightly less polar on TLC than the corresponding (6*S*)-Δ^7 compounds (R_f values, 2% acetic acid in ethyl acetate, 0.33 for **19**; 30% acetone in methylene chloride, 0.33 for **20**). With the exception of minor differences in ion intensities, the mass spectra of **19** and **20** are identical with those of the (6*S*)-Δ^7 isomers **13** and **14**.

The ^1H NMR spectra of **19** and **20** were very similar but not identical with those of **13** and **14**. As expected, the most noticeable differences appeared in the olefin absorption region.

From the data described above we must conclude that the structure proposed by Pace-Asciak and Wolfe for their biosynthetic metabolite is incorrect. Further aspects of this research regarding the origin of this unknown arachidonic acid metabolite are under investigation in our laboratory.

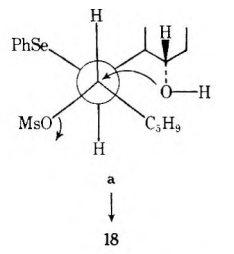
References and Notes

(1) C. Pace-Asciak and L. S. Wolfe, *Biochemistry*, **10**, 3657 (1971).
(2) These investigators[1] isolated **1** and **2** as an unseparable mixture termed fraction A; the mass spectral data were obtained with fraction A.
(3) S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, *Nature (London)*, **263**, 663 (1976); S. Moncada, E. A. Higgs, and J. R. Vane, *Lancet*, **1**, 18 (1977); G. J. Dusting, S. Moncada, and J. R. Vane, *Prostaglandins*, **13**, 3 (1977), and references contained therein.
(4) R. A. Johnson, D. R. Morton, J. H. Kinner, R. A. Gorman, J. C. McGuire, F. Sun, N. Whittaker, S. Bunting, J. Salmon, S. Moncada, and J. R. Vane, *Prostaglandins*, **12**, 915 (1976).
(5) E. J. Corey, G. E. Keck, and I. Szekely, *J. Am. Chem. Soc.*, **99**, 2006 (1977).
(6) R. A. Johnson, F. H. Lincoln, J. L. Thompson, E. G. Nidy, S. A. Mizsak, and U. Axen, *J. Am. Chem. Soc.*, **99**, 4182 (1977).
(7) J. Fried and J. Barton, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 2199 (1977).
(8) K. C. Nicolaou, W. E. Barnette, G. P. Gasic, and R. L. Magolda, *J. Am. Chem. Soc.*, **99**, 7736 (1977).
(9) C. J. Sih and Fu-Chih Huang, *J. Am. Chem. Soc.*, **100**, 643 (1978).
(10) All new compounds gave spectral data consistent with the assigned structures as well as satisfactory analytical figures via combustion analysis or high-resolution spectrometry. Complete spectral data are available upon request.
(11) With either reagent we obtained a 45–50% isolation yield of **9**. The remaining material (30–35%) consisted of Δ^8-olefins resulting from mesylation at C-9 followed by elimination. The rationale for the stereoselective outcome of this cyclization is under investigation.
(12) R. Liotta and H. C. Brown, *J. Org. Chem.*, **42**, 2836 (1977).
(13) J. Fried and J. C. Sih, *Tetrahedron Lett.*, 3899 (1973).
(14) The authors thank Dr. N. A. Nelson and Dr. R. A. Johnson for supplying authentic samples of (6*R*)- and (6*S*)-13,14-dihydro-PGI_1 methyl esters. For assignment of stereoconfiguration of 5,6-dihydroprostacyclins (PGI_1's) see N. A. Nelson, *J. Am. Chem. Soc.*, **99**, 7362 (1977).
(15) The low resolution spectra of **13** and **14** were recorded on the same derivatives and under the identical conditions as reported by Pace-Asciak and Wolfe in ref 1.
(16) Grignard addition to lactol **16**, in contrast to lactol **7**, was seriously hampered by reductive cleavage of the 7-phenylselenenyl group which gave after isolation the unsubstituted lactol in equal amount.



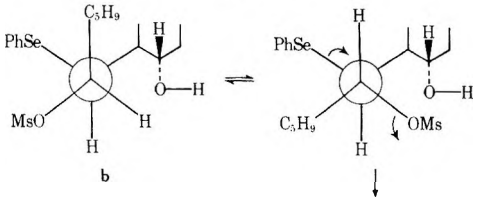
R = H, OSO_2CH_3

(17) J. F. King and J. R. duManoir, *J. Am. Chem. Soc.*, **97**, 2566 (1975).
(18) Use of mesyl chloride–Et_3N produced **18** in poorer yield (27%) and increased amounts of Δ^6-olefin derived products. The formation of a single (6*R*)-6,9-cyclized isomer (**18**) can be rationalized if one considers the preferred conformers available for an internal S_N2 displacement of the (6*R*)- and (6*S*)-mesylate isomers. The preferred conformer a leading to the formation of **18** would place the phenylselenenyl and pentenyl groups in a favored, sterically less crowded anti relationship. In contrast the required (6*R*)-mesylate conformer b forces the pentenyl group into a less favored gauche relationship with the phenylselenenyl group. In this instance 6,9-ether formation is diverted and elimination to olefin is the major pathway. However, as in the case of **8** one cannot exclude the possibility that Grignard addition to lactols **7** and **16** proceeded in a stereoselective manner to generate a single C-6 isomer.



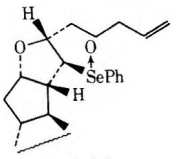
a

18



Δ^6-olefin derivatives

(19) Under the same conditions which affected selenoxide elimination from **4** and **10**, one is able to isolate selenoxide a. The desired Δ^7-olefin was obtained in 30% yield after warming a in CH_2Cl_2 at 45 °C. The low yield



→ 6-oxo derivatives

a

can be attributed in part to the nonselective elimination of selenoxide a. After aqueous workup and chromatography, we inevitably always isolated some 6-oxo derived products.

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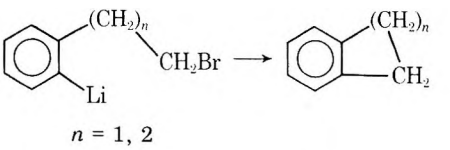
Received July 5, 1978

A New Anionic Cyclization of the Parham Type. Selective Ring Opening of Epoxides

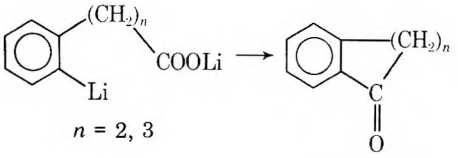
Summary: Epoxides derived from o-bromophenyl allyl ethers undergo bromine–lithium exchange with butyllithium at −100 °C. The resulting lithium reagents undergo cyclization by exo attack on the epoxide linkage as predicted by the Baldwin rules.

Sir: Of the synthetic possibilities opened up by Parham's development of functionalized aryllithium reagents,[1] the most important involve novel cyclization reactions which can be effected when the functional group is ortho to the lithium atom. While the majority of these ring closures involved the addition of an external electrophile, examples were provided of two novel reactions in which the electrophile is in the side chain, but remains passive until the halogen–metal exchange on the aryl nucleus is complete. These two reactions, the Parham cyclialkylation[2] (eq 1) and cycliacylation[3,4] (eq 2), have both found immediate application to important synthetic problems.[5–7]



(1)

n = 1, 2



(2)

n = 2, 3

It seemed likely that there should be other electrophilic groups which at −100 °C would remain passive long enough to permit halogen–metal exchange to occur. Of these the epoxide linkage appeared particularly interesting, for in theory rings of two different sizes might be produced. Reaction of monosubstituted epoxides with Grignard[8] and organolithium[9] reagents has been demonstrated to take place with anionic attack preferentially at the unsubstituted end. On the other

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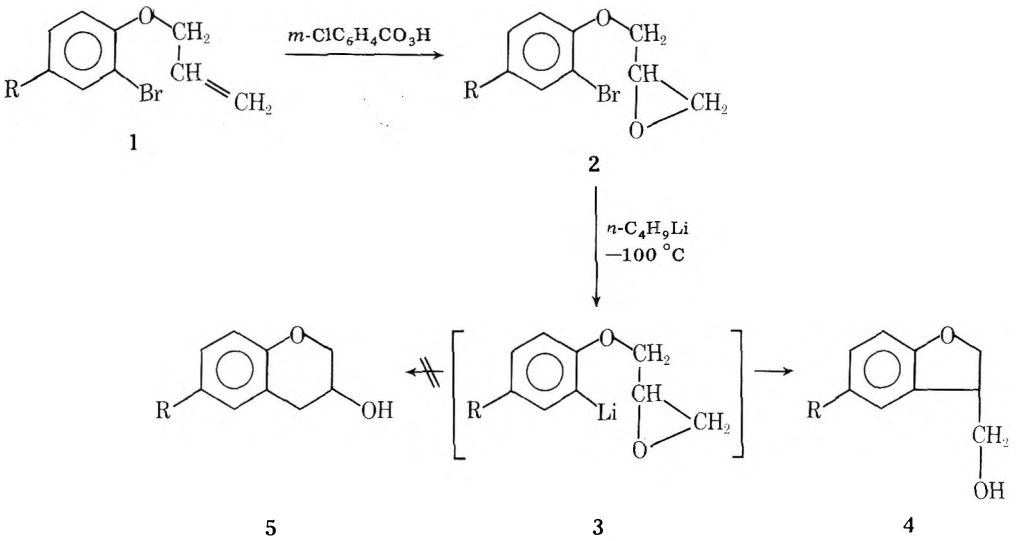

1 2 5 3 4

R = H, Me, Ph, Cl, OCH_3

hand, Stork et al.,[10] in a further study of their closely related epoxynitrile cyclization,[11] concluded that "the epoxynitrile cyclization always yields the smaller ring, when both ends of the epoxide are equally substituted."[12] Baldwin, in his "rules for ring closure",[13] did not consider the effect of substitution, but stated simply that "the rules for opening three-membered rings to form cyclic structures seem to lie between those for tetrahedral and trigonal systems, generally preferring exo modes."

It seemed desirable to test the new cyclization with an epoxide having no substituents on the more remote carbon atom, hence more likely to contravene the Baldwin rules. For convenience in the preparation of the requisite o-bromo compounds this preliminary study was carried out using epoxides (**2**) derived from *o*-bromophenyl allyl ethers (**1**). If a 2.5 M solution of *n*-butyllithium was added to the epoxides (**2**), approximately 0.12 M, in a 80:20 (v/v) mixture of tetrahydrofuran and hexane at such a rate that the temperature did not exceed −95 °C, complete halogen–metal exchange occurred in 15 min as evidenced by ^{1}H NMR of samples withdrawn from the reaction mixture and quenched in 5% sodium bicarbonate solution. After 2 h at −100 °C the anion (**3**) was still unchanged, but if the temperature was raised to −78 °C, ^{1}H NMR indicated that cyclization occurred to the extent of 40–65% after 2 h. In preparative experiments the mixture was stirred for 30 min at −100 °C, allowed to warm to room temperature (~2 h), and then allowed to remain at room temperature for an additional 3 h before workup. The results are summarized in Table I. Although the yields of cyclized product ranged from 90 to 53%, in no case was more than one cyclization product detectable by gas chromatography. The (2,3-dihydro-3-benzofuran)methanol (**4a**) expected from exo cyclization of **3a** was unknown, but what would be the product of endo cyclization, 3-chromanol (**5a**, mp 79 °C), obtained by reduction of 3-chromanone is reported[14] to show a three-proton multiplet in the δ 2.71 region of the ^{1}H NMR. This resonance was absent from the spectrum of each of our cyclization products. Interpretation of the 100-MHz ^{1}H NMR for **4a** [($CDCl_3$, Me_4Si internal standard) δ 1.90 (bs, 1, OH), 3.7 (m, 3, CH_2O, $CHCH_2O$), 4.6 (m, 2, $ArOCH_2$), 6.80–7.35 (m, 4, ArH)] was assisted by addition of 2.61 mol % of Eu(fod)$_3$-d_{27} [tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-d_6-octanedione-d_3)europium(III)]. The shifted spectrum showed: δ 3.82 (m, 1, $CHCH_2O$), 4.24 (d, 2, J = 6 Hz, CH_2OH), 4.66 (d, 2, J = 7 Hz, $ArOCH_2$), 5.46 (bs, 1, OH), 6.68–7.32 (m, 4, ArH). In decoupling experiments using the solution of **4a** containing shift reagent, irradiation of the resonance at δ 5.46 resulted in sharpening the doublet at δ 4.24. A similar result was observed when D_2O was added. Irradiation of the δ 3.82 multiplet gave a broad singlet at δ 4.24 (sharpened by addition of D_2O) and a singlet at δ 4.66.

Table I

R	% yield,[a] 4	bp, °C (mm)
a H	64 (90)	69–72 (0.05)
b CH_3	59 (84)	89–91 (0.08)
c C_6H_5	53	95.5–97.5[b]
d OCH_3	53	110–112 (0.10)
e Cl	63	99–102 (0.10)

[a] Yields in parentheses are by use of gas chromatography 10% SE-30 on 50/60 Chromosorb W, AW, DMCS, 6 ft × 1/4 in. stainless steel column at 130 °C. [b] Mp of sample recrystallized from chloroform–hexane.

Further evidence for the assigned structure of **4a** was afforded by the mass spectrum: *m/e* (rel intensity) 150 (39), 132 (47), 131 (68), 119 (100), 94 (26), 91 (79). The peak of *m/e* 119 corresponds to the loss of CH_2OH from the molecular ion (*m/e* 150). The ^{1}H NMR spectrum of each of the substituted epoxides (**4b–e**) showed the expected similarity to that of **4a**, evidence that each had been formed by exo cyclization. Endo cyclization has been achieved in the Stork epoxynitrile cyclization when the oxirane ring has fewer substituents at the more remote than at the near carbon.[11] That our system gives only exo products is probably due to the decreased flexibility resulting from incorporation of an aromatic ring into the chain. This stiffness evidently inhibits the achievement of the collinearity of the anion[10] with that C–O bond of the oxirane which must be broken if a six-membered ring is to be formed.

The new cyclization not only offers a convenient route to (2,3-dihydro-3-benzofuran)methanols (**4**), but also promises to provide homocyclic as well as heterocyclic analogues having rings of various size. Further work in this direction is in progress. All new allyl ethers, epoxides, and cyclization products gave satisfactory elemental analyses (C, H ± 0.36%).

Acknowledgment. This research was supported in part by Army Research Office Grant No. 15063-C.

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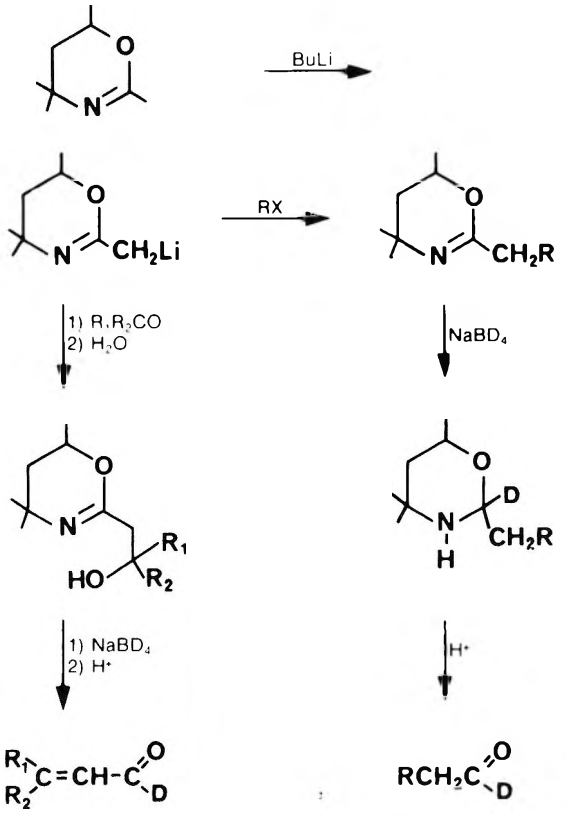
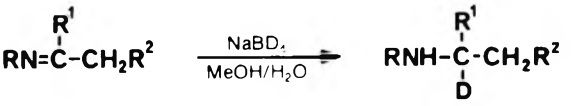


Deuteroaromatics[3]

α-*d*-Alkylamines[4]



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