VOLUME 43 OCTOBER 27, 1978 NUMBER 22 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

THE JOURNAL OF Organic Chemistry

Published by the
AMERICAN CHEMICAL SOCIETY

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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(22) 4259–4400 (1978)
ISSN 0022-3263

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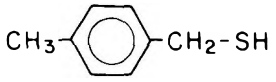

1374
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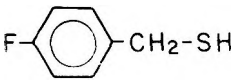

1011
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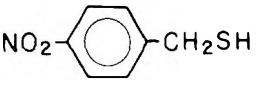
5g 34.85

2819
m-Fluorobenzyl mercaptan
5g 34.85

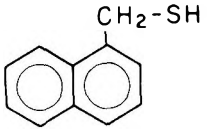
2914
p-Fluorobenzyl mercaptan
5g 22.50



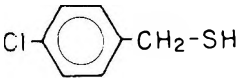
1377
o-Nitrobenzyl mercaptan (80%)
5g 15.95

1376
m-Nitrobenzyl mercaptan
10g 12.50

1378
p-Nitrobenzyl mercaptan
10g 12.50

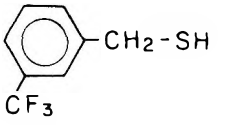


1369
1-Mercaptomethylnaphthalene
25g 18.00



1362
o-Chlorobenzyl mercaptan
25g 16.50

1363
p-Chlorobenzyl mercaptan
50g 13.25



1012
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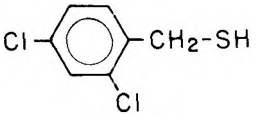
5g 21.25



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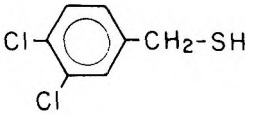
10g 12.25



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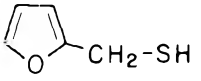
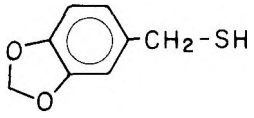
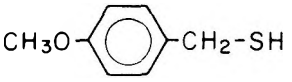
10g 13.75



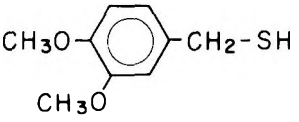
2442
Furfuryl mercaptan
25g 10.00 100g 31.25



1026
3,4-Methylenedioxybenzyl mercaptan
5g 18.50



1372
p-Methoxybenzyl mercaptan
25g 12.50



1019
3,4-Dimethoxybenzyl mercaptan
5g 18.50

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THE JOURNAL OF Organic Chemistry®

VOLUME 43, NUMBER 22

OCTOBER 27, 1978

Dynamic NMR Study of 3-Methylene-1-oxaspiro[4.5]decan-2-one and Single-Crystal X-ray Diffraction Analysis of *cis*-8-*tert*-Butyl-3-methylene-1-oxaspiro[4.5]decan-2-one

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Received May 16, 1978

A dynamic NMR study of 3-methylene-1-oxaspiro[4.5]decan-2-one, a dynamic molecular system, was made to determine the thermodynamic and kinetic properties of the ring reversal process. Low temperature measurements of the integrated areas under the signals corresponding to the individual conformers clearly showed a conformational preference for an axial C–O group rather than an axial methylene group. Measurements of the equilibrium constants at higher temperatures were made using the chemical-shift method. Extrapolation of the chemical-shift data to the lower temperatures yielded a value of $-\Delta G°_{177} = 0.058$ kcal/mol, in excellent agreement with the values obtained via integrated areas. Complete line-shape analysis permitted the determination of the absolute rate constant for the reversal process. An average value of ΔG^* was 10.9 kcal/mol as determined over a 30° temperature range. A temperature dependence study of the rate constant allowed calculation of values of $\Delta H^* = 9.60$ kcal/mol and $\Delta S^* = -5.9$ eu. A discussion of factors which may influence the thermodynamic and kinetic properties of the ring reversal is also given. In addition, a single-crystal analysis by X-ray diffraction of *cis*-8-*tert*-butyl-3-methylene-1-oxaspiro[4.5]decan-2-one was completed. The compound crystallized in a noncentrosymmetric space group $P2_12_12_1$ via apparent selective crystallization of one of the puckered forms, with unit cell dimensions of $a = 11.455$ (2), $b = 18.356$ (2), and $c = 6.100$ (1) Å. The structure was solved from 1551 diffractometer data. The final R factor is 0.038. The cyclohexyl ring is significantly flattened near the spiro ring.

The isolation of a wide variety of natural products containing an α-methylene-γ-butyrolactone ring which have displayed diverse biological activities[1a,b] has promoted the synthesis of compounds containing this function for use as possible antitumor agents.[2a,b,3] A series of spiro α-methylene-γ-butyrolactones were synthesized in this laboratory in conjunction with a search for such agents.[4] To the best of our knowledge, no study has appeared which has focused on both the thermodynamics and kinetic aspects of a dynamic α-methylene spiro lactone even though such a system has reported activity.[5a]

We have undertaken a dynamic NMR (DNMR) study of 3-methylene-1-oxaspiro[4.5]decan-2-one using three different techniques to obtain values for the various thermodynamic and kinetic parameters associated with the ring reversal process in this particular compound. These data are reported herein, along with a discussion of some of the effects which may influence the preferred conformation of this spiro lactone.

Results and Discussion

The synthesis of the spiro lactones is outlined in Scheme I.[4] In all cases, the Reformatsky reaction was employed under identical conditions for reaction with an appropriate cyclohexanone. Addition of each reaction mixture to H_2SO_4 at 0 °C yielded either an oil or a crystalline product, which was extracted with ether. However, careful recovery of the crude product, followed by purification either by distillation or recrystallization, gave, upon cooling, a crystalline material for each compound listed in Scheme I.[5a,b] All spectral and synthetic data are reported in Table I for the various compounds synthesized.

DNMR Data: Thermodynamic Evaluation of the Ring Reversal Process. Compounds **4a** and **5a** are interconvertable conformers (Scheme I). At temperatures below 198 K (−75 °C) the frequency of interconversion between these two isomers is sufficiently low that signals for each conformer are distinguishable in the low-temperature ^{1}H NMR spectra, i.e.,[6]

$$k_r \ll \pi|\nu_a - \nu_e|/\sqrt{2}$$

where k_r is the reaction rate constant, ν_a is the chemical shift of H(4) in **4a**, and ν_e is the chemical shift of H(4) in **5a**. Under these conditions, both conformers are easily detected, and the relative peak areas can be measured by integration. In this particular case, **4a** and **5a** give rise to two separate three-line spin patterns (X_2 of an AMX_2 pattern) between 177 and 185 K which are below the compound's coalescence temperature

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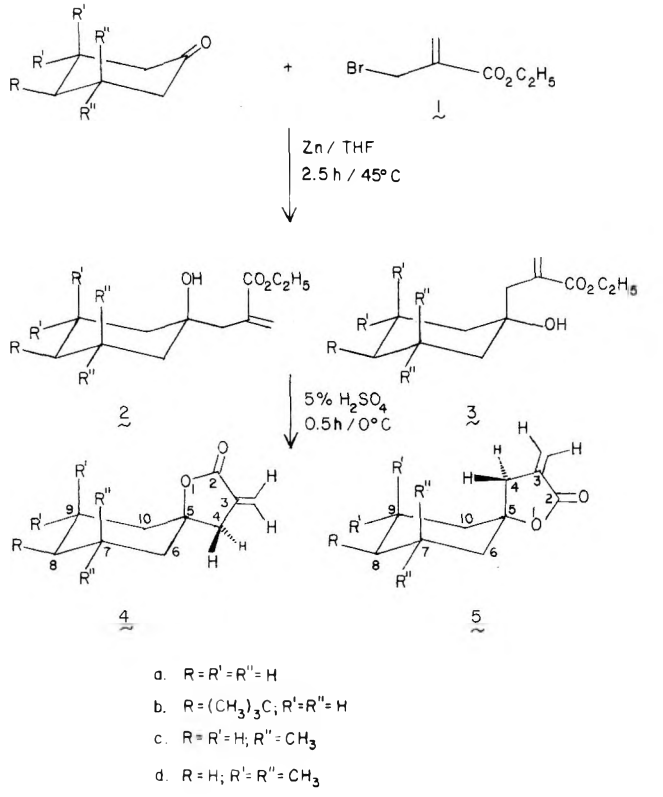
Table I. Spectral and Synthetic Data for Some Simple Spiro Lactones

compd	R	R′	R″	mp, °C	bp, °C	NMR[d]	IR, cm^{-1}
4a ⇌ 5a	H	H	H	26–27.5	76–77 (0.05 mm)	1.2–1.9 (m, 10 H), 2.78 (2 H),[a] 5.62 (1 H),[b] 6.05 (1 H)[b]	$\nu_{C=O}$ 1761 $\nu_{C=C}$ 1664 (film)
4b	*t*-Bu	H	H	84–85		0.88 (s, 9 H), 1.0–2.0 (m, 9 H), 2.74 (2 H),[a] 5.62 (1 H),[b] 6.05 (1 H)[b]	$\nu_{C=O}$ 1748 $\nu_{C=C}$ 1653 (KBr)
5b	*t*-Bu	H	H	83–84		0.89 (s, 9 H), 1.0–2.0 (m, 9 H), 2.85 (2 H),[a] 5.64 (1 H),[b] 6.05 (1 H)[b]	$\nu_{C=O}$ 1751 $\nu_{C=C}$ 1653 (KBr)
4c ⇌ 5c	H	CH_3	H	38.5–39.5	100–102 (0.25 mm)	0.94 (s, 3 H), 1.04 (s, 3 H), 1.1–1.95 (m, 8 H), 2.78 (2 H),[c] 5.62 (1 H),[b] 6.04 (1 H)[b]	$\nu_{C=O}$ 1757 $\nu_{C=C}$ 1664 (film)
4d ⇌ 5d	H	CH_3	CH_3	102–103		0.95 (s, 6 H), 1.18 (s, 6 H), 1.0–1.9 (m, 6 H), 2.77 (2 H),[a] 5.68 (1 H),[b] 6.08 (1 H)[b]	$\nu_{C=O}$ 1754 $\nu_{C=C}$ 1658 (KBr)

[a] Three-line pattern resulting from X_2 portion of AMX_2, where $J_{AX} \sim J_{MX}$. [b] A or M portion of AMX pattern where $J_{AM} < J_{AX} \sim J_{MX}$. [c] Four-line portion of an AMXY pattern. [d] Ppm from Me_4Si in acetone-d_6.

Scheme I



(T_c) of 209 K (−64 °C). The two concentrations used were 0.024 and 0.036 M solutions in acetone-d_6. A partial spectrum of a solution (0.036 M) of **4a ⇌ 5a** is shown in Figure 1. The equilibrium constant for the ring reversal can be determined from the relative areas and, using these values, calculation of $\Delta G°$ follows:

$$\Delta G° = -RT \ln ([\mathbf{5a}]/[\mathbf{4a}])$$

where [**4a**] and [**5a**] are the measured areas of the separate peaks corresponding to the individual conformers. Values for $\Delta G°$ at various temperatures for the two different concentrations are given in Table II. Qualitative values for $\Delta H°$ are also given. However, the very narrow temperature range accessible because of solubility limitations in the determination of K_{eq}, as well as the very small change in K_{eq} over this temperature range, does not permit extremely accurate $\Delta H°$ values to be obtained. The values of $\Delta H°$ at the different concentrations were calculated to permit relative comparisons between this method of evaluating $\Delta G°$ and the chemical shift method[7] also used in the study.

The values for $\Delta G°$ in Table II clearly show that the conformer corresponding to the upfield signal in the low-temperature NMR spectra of this equilibrating system is favored thermodynamically by a modest amount. Previous work reported in the literature[8] suggested that steric compression due to typical 1,3 interactions with protons on the cyclohexyl ring would cause proton signals for axially situated methylene groups to be shifted to lower field. Based on these observations, we initially concluded that structure **4a** represented the predominant conformer in our system. In order to establish

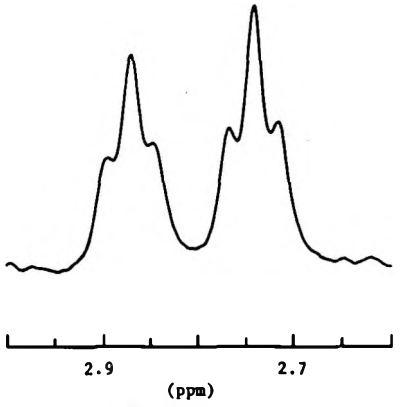
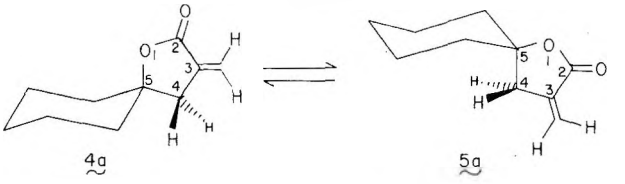


Figure 1. Spectrum of **4a ⇌ 5a**: 177 K; 0.036 M in acetone-d_6; sweep width = 40 Hz; offset = 260 Hz.

Table II. Calculation of Thermodynamic Parameters by Integrated Areas[a]



T, K	K_{eq} ([**5a**]/[**4a**])	$\Delta G°$, kcal/mol	$\Delta H°$, kcal/mol[b]
		0.036 M	
185	0.754 ± 0.009	+0.105 ± 0.005	−0.563 (r^2 = 0.99)
181	0.779 ± 0.023	+0.090 ± 0.011	
177	0.808 ± 0.006	+0.075 ± 0.003	
		0.024 M	
185	0.763 ± 0.005	+0.099 ± 0.002	−0.480 (r^2 = 0.94)
181	0.776 ± 0.020	+0.091 ± 0.009	
177	0.811 ± 0.019	+0.074 ± 0.008	

[a] Samples were prepared in acetone-d_6 with Me_4Si as an internal standard. [b] $\Delta H°$ calculated by least-squares fit of ln K_{eq} vs. $1/T$ using average values of K_{eq}.

Table III. Calculation of Thermodynamic Parameters by Chemical Shifts for 4a ⇌ 5a[a]

T, K	K_{eq}	$\Delta G°$, kcal/mol	$\Delta S°$, eu[b]	$\Delta H°$, kcal/mol[c]
286.5	0.681 ± 0.011	+0.218 ± 0.010		
274.3	0.684 ± 0.022	+0.208 ± 0.009	−1.5	−0.207
251.9	0.720 ± 0.012	+0.164 ± 0.009		(r^2 = 0.96)
232.6	0.736 ± 0.023	+0.142 ± 0.015		
185.0		+0.099 ± 0.002[d] (+0.070)[e]		
181.0		+0.091 ± 0.009[d] (+0.064)[e]		
177.0		+0.074 ± 0.008[d] (+0.058)[e]		

[a] Samples were prepared as 0.24 M solutions in acetone-d_6 with Me_4Si as an internal standard. [b] Calculated from $\Delta S° = (\Delta H° - \Delta G°)/T$. [c] $\Delta H°$ calculated by least-squares fit of ln K_{eq} vs. $1/T$ using average values of K_{eq}. [d] Values calculated from integrated areas (Table II). [e] Values extrapolated from chemical shift data.

unequivocally the conformer in predominance, compounds **4b** and **5b** were synthesized and isolated as shown in Scheme I. Separation of the two isomers was achieved by column chromatography over Florisil. The compound isolated in predominance was submitted for X-ray analysis and was determined to be **4b.** Independent NMR analysis of both isomers in solution showed distinctly that protons of the methylene group at C(4) in **4b** resonate at higher field (δ 2.74) than the analogous protons in **5b** (δ 2.85).

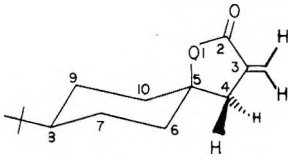
Although the low-temperature method of integrated areas is the most theoretically satisfying technique for determining the equilibrium constant and subsequent calculation of $\Delta G°$, it suffers from several limitations in this case. It was difficult to maintain constant probe temperatures below the coalescence temperature T_c for extended periods of time. The range of temperatures in which determinations could be made was governed by the coalescence process and by the freezing point of the solvent. No other solvents were found to be suitable due to the low solubility of the compound. While the values obtained for $\Delta G°$ for **4a** ⇌ **5a** are of good accuracy, one cannot assume that they represent the equilibrium at higher temperatures, especially in view of the rather high value estimated for $\Delta H°$.

The chemical shift method of determining the equilibrium constant[7] was used to obtain values for $\Delta G°$ at tempertures above T_c, for which $k_r \ll \pi|\nu_a - \nu_e|/\sqrt{2}$. Since a specific signal will result from a time averaging of the independent signals for the individual conformers, weighted by the mean lifetime of the mobile system in each conformational orientation,[9] the equilibrium constant can therefore be calculated by $K_{eq} = (\delta_e - \delta)/(\delta - \delta_a)$. The shifts for δ_a and δ_e were obtained from the spectra of the conformationally locked *tert*-butyl-substituted compounds **4b** and **5b.** The results of this method of determining K_{eq} as well as $\Delta G°$ (and $\Delta H°$) are shown in Table III. Again, the positive values of $\Delta G°$ indicate the conformational preference of **4a** over **5a.** The magnitudes of the values for $\Delta G°$ are greater for this method of calculation than those values obtained by the low-temperature area method by a factor of 3. However, values for $\Delta G°$ at the lower temperatures may be calculated from the higher temperature chemical shift data using $\Delta G° = \Delta H° - T\Delta S°$ and the values calculated for $\Delta H°$ and $\Delta S°$. Comparison of the extrapolated values with actual values calculated at low temperatures by the use of integrated areas (Table III) shows good agreement. A least-squares analysis of the combined chemical shift and integrated area data for the 0.024 M solutions permitted calculation of overall values for $\Delta H°$ and $\Delta S°$ of −0.133 kcal/mol (r^2 = 0.94) and −1.2 eu, respectively, over a temperature range of 109 K.

While this evidence supports the chemical shift method, a special note of caution must be added. Several studies in the past have cast doubt on the validity of this technique in the evaluation of an equilibrium constant.[10,11] It has been pointed out that there are possible effects which the *tert*-butyl group may have on the chemical shifts of protons *bonded directly to the six-membered ring.* It was later argued that the 4-*tert*-butyl group is the best choice for model compounds, and, in cases where the object protons are insulated from the six-membered ring, effects of the 4-*tert*-butyl group would probably be minimal.[12a,b] In our case, not only are the H(4) protons insulated from the ring by a carbon atom, but the X-ray analysis of **4b** shows distortion in the cyclohexyl system due to the spiro ring junction is greater than the distortions due to the *tert*-butyl group. This can best be seen by comparison of the torsion angles listed in Table IV. Angles C(9)–C(10)–C(5)–C(6) and C(10)–C(5)–C(6)–C(7) clearly show a deviation at the spiro end from the normal value of 57° for cyclohexane[13a,b] by 7.6 and 8.2°, respectively. Angles C(6)–C(7)–C(8)–C(9) and C(7)–C(8)–C(9)–C(10) show a deviation at the *tert*-butyl end of 2.4 and 3.4°, respectively. These values of course cannot be extrapolated directly to a solution of **4b.** However, studies of a few simple and substituted cyclohexanes as well as a variety of pentamethylene heterocycles in solution[13a] have shown agreement with X-ray data within ±2°. This suggests that structural changes for such systems upon dissolution are small. Hence, it would be expected that chemical shift differences between biased and unbiased systems in solution due to the *tert*-butyl group would be small relative to the effects at the spiro part of the molecule. The agreement of the extrapolated values in Table III with those values obtained by integrated areas clearly supports this contention.

As stated previously, the thermodynamic parameter $\Delta G°$ calculated displays a small but distinct conformational preference for the conformer **4a** (C–O bond axial). Values in the literature for similar spirodioxolane systems[14] have yielded comparable results for $\Delta G°$ at low temperatures. The $\Delta G°$

Table IV. Torsion Angles from X-ray Analysis of *cis*-8-*tert*-Butyl-3-methylene-1-oxaspiro[4.5]decan-2-one (4b)



five-membered ring		six-membered ring	
O(1)–C(2)–C(3)–C(4)	6.7°	C(5)–C(6)–C(7)–C(8)	−55.1°
C(2)–C(3)–C(4)–C(5)	−18.6°	C(6)–C(7)–C(8)–C(9)	59.4°
C(3)–C(4)–C(5)–O(1)	23.1°	C(7)–C(8)–C(9)–C(10)	−60.4°
C(4)–C(5)–O(1)–C(2)	−20.5°	C(8)–C(9)–C(10)–C(5)	56.5°
C(5)–O(1)–C(2)–C(3)	8.9°	C(9)–C(10)–C(5)–C(6)	−49.5°
		C(10)–C(5)–C(6)–C(7)	48.8°

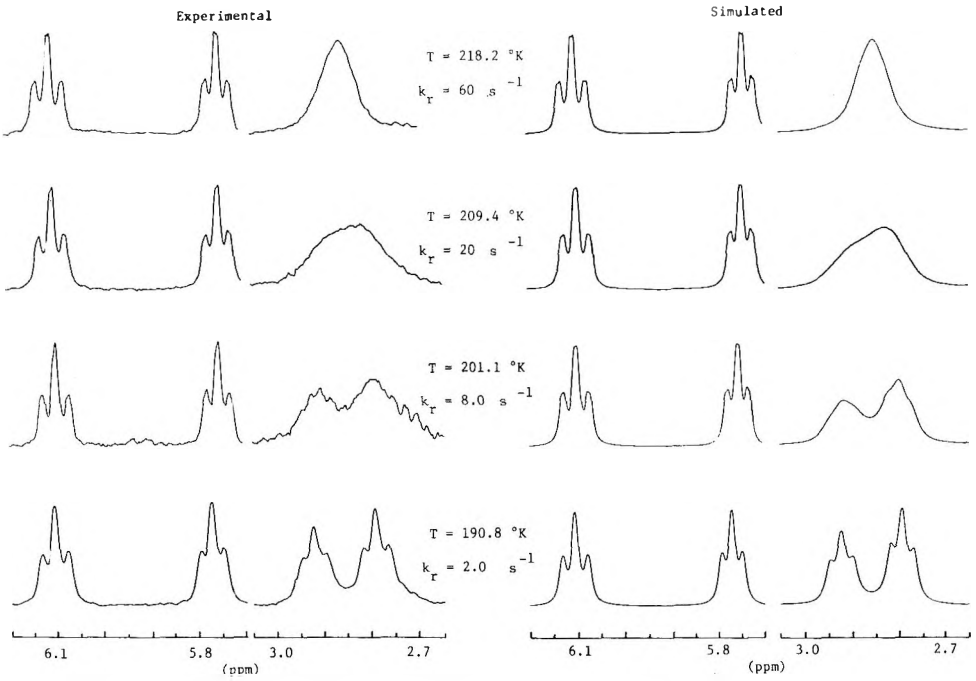


Figure 2. Experimental (left) and simulated (right) $AMX_2 \rightleftarrows AMX'_2$ DNMR spectra of **4a** ⇌ **5a**. Samples were prepared as 0.024 M solutions in acetone-d_6 with Me_4Si as an internal standard.

values obtained at higher temperatures are consistent with those obtained at low temperatures, if one assumes a value of −1.4 eu to be representative for $\Delta S°$. This value is not unreasonable when compared to published values obtained for the entropy change favoring, for example, the less associated OH group in the axial conformer of 3,3,5-trimethylcyclohexanol in strongly associating solvents.[12a] It has also been shown that aprotic, polar solvents can strongly influence the position of an equilibrium when there exists a possible preferential solvation effect for one of the isomers.[12b] Such a preference is likely here and may contribute to the observed thermodynamic values.

In this regard, it should be noted that the ^1H NMR spectrum of the 7,7-dimethyl analogue **4c** ⇌ **5c**, showed an unusual solvent dependence. Chemical shift difference between the spectrum in CCl_4 compared to that in acetone-d_6 for protons on the two C(7) methyl groups was −9 Hz (upfield relative to the shift in CCl_4) for protons on one methyl group and 0.0 Hz for the proton on the other methyl group. Also, H(4) protons appeared as a pseudo triplet in CCl_4, but in acetone-d_6 these signals were shifted +18 Hz *downfield* and were changed to the expected two doublets. It appeared that the more polar acetone solvated **4c** ⇌ **5c** with a preferred solvent orientation around the polar part of the lactone ring. Moreover, the solvation sphere must be of such nature to involve nonsymmetrical shielding of the methyl protons at C(7). In addition, the dissimilar solvent shifts of the H(7) methyl protons, coupled with the appearance of the two doublets for the H(4) protons, strongly suggested that the solvation was dissymmetric with respect to the planes of both the five-membered and the six-membered rings.

Kinetic Evaluation of the Ring Reversal Process. To investigate the kinetics of the ring reversal, a study of the NMR spectra of the mobile system **4a** ⇌ **5a** was undertaken using complete line-shape analysis (LSA).[9] The system was particularly suited to this type of evaluation because of the spiro ring junction which effectively isolates the five-membered ring of the lactone from the six-membered ring. This reduces the spectral pattern of the protons in the lactone ring to a first-order AMX_2 pattern which can be simulated by a DNMR3[15] program. Because of the extensive H–H coupling in the spectrum, as well as the need to evaluate the rate constant over a range of temperatures, the approximate equations[16] which were derived from line-shape theory were not deemed feasible.

Table V. Activation Parameters Calculated from Line Shape Analysis[a]

T, K	k_r (by LSA)	ΔG^*, kcal/mol
218.2	60 ± 5	10.9 ± 0.11
209.4	20 ± 2	10.9 ± 0.11
201.1	8 ± 1	10.9 ± 0.13
190.8	2 ± 0.2	10.7 ± 0.10
$\Delta H^* = +9.60 \pm 1.3$ kcal/mol[b]		
$\Delta S^* = -5.9 \pm 6.3$ eu[b]		

[a] Samples were prepared as 0.024 M solutions in acetone-d_6 with Me_4Si as an internal standard. [b] ΔH^* and ΔS^* were calculated from a least-squares fit of ln (k_r/T) vs. $1/T$, $r^2 = 0.998$.

The chemical shifts and coupling constants used in the analysis were determined at low temperatures by direct measurement and were extrapolated to higher temperatures assuming a linear relationship. Values for the transverse relaxation time (T_2) were estimated by measuring the width at half-height of the Me_4Si internal standard. Visual comparison of the simulated spectra with the experimental spectra was used to assess the closeness of the fit. Estimations of the deviations in the rate constant were also done in this fashion. The results of the simulations are shown in Figure 2, and the calculated activation parameters are tabulated in Table V.

Sidebands resulting from a large solvent peak (upfield) are noticeable in the experimental spectrum obtained at 201 K, as shown in Figure 2. Repeated attempts to remove this interference failed at this temperature. However, this problem was minor or did not exist at the other temperatures used in the investigation.

It is interesting that values from the literature[17a,b] for ΔG^* in simple and 1,1-disubstituted cyclohexyl systems are in close agreement with our values for the various temperatures investigated. A comparison of published ΔS^* and ΔH^* for the simple systems with those found for **4a** ⇌ **5a** is difficult, since there appear to be large discrepancies for the magnitudes of

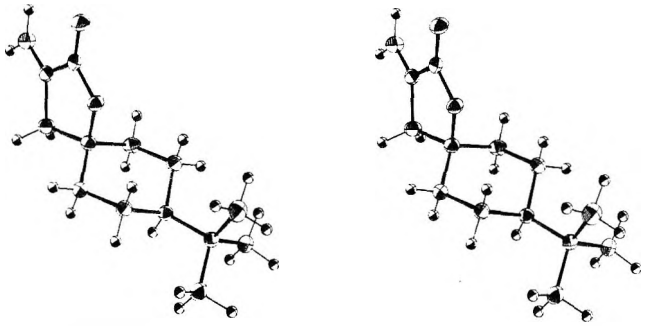


Figure 3. A stereoview of a single molecule of **4b**.[26]

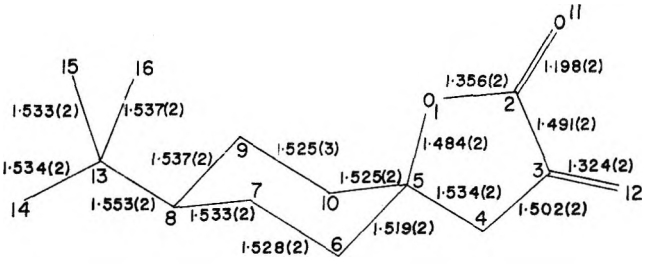


Figure 4. Bond distances and numbering scheme for **4b**. Estimated standard deviations are given in parentheses.

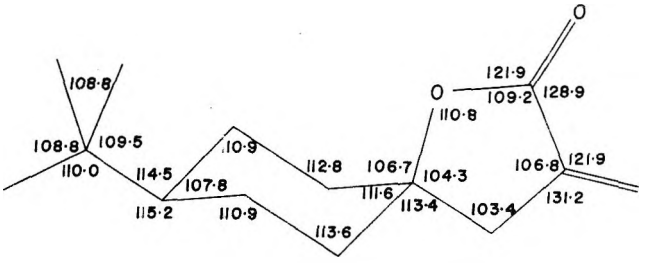


Figure 5. Bond angles for **4b**. The standard deviations are between 0.11 and 0.16°. Additional bond angles are O(1)–C(5)–C(6) = 107.2°, C(4)–C(5)–C(10) = 113.0°, C(8)–C(13)–C(15) = 112.0°, and C(14)–C(13)–C(16) = 107.6°.

these parameters even in simple systems. For example, values for ΔS^* ranging from +4.9 to −5.8 eu have been reported for cyclohexane itself.[17] In this regard, it is known that errors in ΔH^* and ΔS^* are coupled (due to the methods used to calculate them) so that high ΔH^* values correspond to low ΔS^* values and vice versa.[9] While it has been suggested that extension of the temperature range would reduce the error in ΔH^* and ΔS^*, the spectra must remain reasonably sensitive to changes in the rate constant at the extremes of this range.[9] We did not detect any significant change in the spectrum for our system above 235 K (−38 °C).

It will be discussed later that the five-membered lactone ring is puckered in the solid state. Indeed, even though the molecule **4b** does not possess an asymmetric carbon, it crystallizes in the noncentrosymmetric space group $P2_12_12_1$ due to selective crystallization of one of the puckered forms. Although the mirror image of this form would be expected to be of equal energy, the space requirements of a disordered lactone would be too great to allow both conformers of the puckered ring to exist together in a disordered crystal structure.

In solution, the barrier to interconversion of the five-membered ring between two conformers must be very small. One can see from the NMR data in Table I for the 7,7-dimethyl analogue **4c** ⇄ **5c** that this interconversion can be biased indirectly by destroying the symmetry of the system because of increased 1,3 interactions experienced by the five-membered ring, which results in nonequivalence of the H(4) protons. This symmetry of interaction is restored in the 7,7,9,9-tetramethyl-substituted analogue **4d** ⇄ **5d**, resulting in the familiar AMX_2 spin pattern for lactone ring protons. This interconversion (or "breathing motion") of the five-membered ring must occur in solution simultaneously with the six-membered reversal process. Although not strictly analogous, the barrier for interconversion of conformers in cyclopentanone has been determined to be between 2.1 and 3.7 kcal mol^{-1}.[18] This corresponds to a rate of reversal (assuming small ΔS^*) at 190 K of 2.2×10^8 to 1.5×10^{10} s^{-1}. Thus, it would seem to be much too rapid to be detectable via NMR methods. However, if the NMR spectrum is sensitive to changes induced by this process, the possibility of the breathing motion affecting the magnetic field around certain nuclei in the spectrum cannot be eliminated and may be a source of error, especially at the lower temperatures. However, this process would not be expected to interfere with evaluation of the thermodynamic parameters, assuming that this motion in the five-membered ring does not impart any dissymmetric operation preferentially on either of the six-membered conformers.

Single-Crystal Analysis of 4b. A stereoview of a single molecule of **4b** is shown in Figure 3, the numbering scheme and bond distances are shown in Figure 4, and bond angles are shown in Figure 5. The structure consists of a six-membered ring in the chair conformation, a spiro-fused α,β-unsaturated γ-lactone, and an anchoring *tert*-butyl group. The chair conformation of the six-membered ring is significantly flattened near the spiro carbon atom, as can be seen from the torsion angles reported in Table IV. This is most likely due to a 1,3,5 interaction involving the axial O atom attached to the spiro carbon atom, since all other axial positions are occupied by H atoms. The lactone ring is in a flattened twist (C_2) conformation as can be seen from the values of the internal torsion angles in Table IV. The approximate twofold axis passes through atom C(2) and bisects the C(4)–C(5) bond. The α,β-unsaturated γ-lactones in a group of natural products[19-24] show a wide range of conformations for the five-membered ring. Both the envelope (C_s) and twist (C_2) conformations are observed with varying degrees of flatness. The factors affecting the conformation in the present compound may include an attempt to minimize contacts with O(1) and the axial hydrogen atom or atoms C(7) and C(9) and at the same time minimize contacts between the hydrogen atoms on atom C(4) and the axial hydrogen atoms of atoms C(6) and C(10). In addition, crystal packing forces may also affect the conformation. It is interesting to point out that, since many compounds possessing an α,β-unsaturated γ-lactone show biological activity which is attributed to this functional group, a structure–activity relationship might exist which involves the conformation of the lactone ring. At this time, however, sufficient data is not available to test this hypothesis. The *tert*-butyl group which anchors the conformation by occupying the equatorial position on C(8) is staggered with respect to its attachment to the ring. The values of two representative torsion angles are C(7)–C(8)–C(13)–C(16) = 174.8° and C(9)–C(8)–C(13)–C(14) = 182.6°. One of the primary reasons for using X-ray diffraction to determine this structure was to ascertain whether the O atom or $>CH_2$ group occupies the axial position of the spiro C atom. All data including electron densities, bond lengths, least-squares refinement, and location of H atoms show conclusively that the O atom occupies the axial position with no evidence for a disordered structure.

The bond lengths in the lactone compare well with the values reported for several natural products.[19-24] The weighted averages compiled from the literature are O(1)–C(2) = 1.356, C(2)–C(3) = 1.486, C(3)–C(4) = 1.506, C(4)–C(5) = 1.542, C(5)–O(1) = 1.461, C(2)–O(11) = 1.205, and C(3)–C(12)

= 1.324 Å. The largest difference (0.023 Å) is for the C(5)–O(1) distance; all other differences are <0.01 Å. The C(8)–C(13) bond length is slightly lengthened, which is not unexpected for a bond to a bulky substituent. Inspection of bond angles indicates that the surroundings of atoms C(2) and C(3) are planar having the sum of bond angles equal to 360.0 and 359.9°, respectively. The bond angles in the lactone ring show the same trends as those observed for the natural products.

The molecule could contain a mirror plane passing through atoms C(5), C(8), C(13) and the midpoints between C(7)–C(9) and C(6)–C(10). However, if one calculates a least-squares plane through these points one finds that the entire lactone group is significantly out of the plane. The distances from this plane are as follows: O(1), 0.019; C(2), 0.477; C(3), 0.601; C(4), 0.010; C(5), 0.003; O(11), 0.711; and C(12), 1.146 Å. One could also construct a stereoisomer of the molecule in the present structure by taking the mirror image through the least-squares plane, thus flipping the lactone group to the opposite side. This molecule would have exactly the same energy and most likely occurs in both solution and the solid state. Although one enantiomer is selectively crystallized in the present structure, no attempt was made to determine which conformer, although the question could be resolved using the anomalous scattering of the oxygen atoms.[25] It is not possible for both conformers to exist in a disordered crystal structure because the space requirements of a disordered lactone would be too great. Experimentally no evidence for disorder was found, as the refinement of thermal parameters for all C, O, and H atoms of the lactone group was normal and no residual electron density was found in this area of the final difference Fourier map. A calculation of intermolecular distances revealed an unusually short contact between O(11) and H(12A) of 2.41 Å [H(12)] transformed by $(x,y,z-1)$, which is about 0.2 Å shorter than the sum of the van der Waal radii.

Conclusions

The thermodynamic parameters found in this study show a slight predominance of conformer **4a** (C–O bond axial), which suggests that the steric requirements for the methylene group are greater than those for the endocyclic axial C–O bond in 3-methylene-1-oxaspiro[4.5]decan-2-one. It should be noted that, while it is these groups which directly occupy the axial–equatorial positions on the six-membered ring, the substituents on the adjacent carbons may also play an important role in directing the equilibrium, especially in regard to their ability to interact with the solvent. A study involving determination of $\Delta G°$ at one temperature for a series of substituted spirodioxolanes[14] has indicated that these types of interactions can markedly influence the equilibrium process so that predictions of values for the thermodynamic parameters, based on analogous systems in which substituents in the five-membered ring are different, must be done with care.

Interestingly, the ΔG^* values (10.9 kcal/mol) determined for **4a** ⇌ **5a** are similar to those reported for several 1,1-disubstituted cyclohexanes (e.g., 1,1-dimethoxycyclohexane, $\Delta G^* = 10.8$ kcal/mol).[17] Comparison with the values of ΔG^* determined for cyclohexane (10.5 kcal/mol)[17b] suggests that the spiro substitution actually stabilizes the ground-state conformers relative to the transition state by a modest amount. Additional substitution on the six-membered ring, which might increase the energy of the two conformers relative to the transition state via steric 1,3-interactions, might be expected to lower the ring reversal energy barrier. Studies of 1,1,3,3-tetra- and 1,1,3,3,5,5-hexasubstituted cyclohexanes support this conclusion.[17a] Hence it is not surprising that the coalescence phenomenon is not observed for either **4c** ⇌ **5c** or **4d** ⇌ **5d** for temperatures as low as 177 K (−96 °C).

The X-ray analysis conclusively identified *cis*-8-*tert*-butyl-3-methylene-1-oxaspiro[4.5]decan-2-one as structure **4b**. Several novel features of this molecule were notable. The significant flattening of the six-membered ring of the spiro end implied that a distinct interaction exists between the axial oxygen and the axial H atoms on carbons 7 and 9. It was also evident from the X-ray analysis that two forms of the twisted lactone ring could exist, and that these forms probably would rapidly interconvert in solution.

Experimental Section

General. Cyclohexanone and 4-*tert*-butylcyclohexanone were obtained commercially and purified by vacuum distillation. The solvent tetrahydrofuran was dried over NaH and then distilled from $LiAlH_4$. The IR spectra were recorded on a Beckman IR-5A spectrometer. Melting and boiling points were not corrected.

Preparation of Ethyl α-Bromomethylacrylate (1). Ester 1 was synthesized by the procedure of Ferris:[27] bp 56 °C (2.0 mm); reported bp 44–45 °C (1.7 mm).

General Procedure for Synthesis of the α-Methylene Spiro Lactones from the Ketones. A solution of 5.3 g (0.0275 mol) of ester 1 in 15 mL of dry THF was added slowly with stirring to a suspension of 1.7 g (0.027 g-atom) of Zn (20 mesh) in 0.025 mol of the appropriate ketone in 8 mL of dry THF (under N_2). The temperature was allowed to rise during the addition to 45 °C and was maintained at 50 °C for an additional 2 h. After cooling to room temperature, the reaction mixture was poured directly into 200 mL of ice-cold 5% H_2SO_4 with stirring. Stirring was continued for 0.5 h, the product separating either as an oil or as a crystalline solid. This product was taken up with ether and dried ($MgSO_4$). Data for the lactones are in Table I.

Purification of 3-Methylene-1-oxaspiro[4.5]decan-2-one (4a ⇌ 5a).[5a,b] The product resulting from the above reaction using cyclohexanone as the general ketone was isolated from the ether solution as an oil. The oil was dissolved in 50 mL of commercial hexanes (bp 67–71 °C) and filtered. The resulting solution was chilled slowly to −78 °C. A crystalline product formed and was filtered at −78 °C using a jacketed funnel. Vacuum drying of the crystals at room temperature (20 °C) gave 5.2 g of **4a** ⇌ **5a** (86%): mp 26–27.5 °C; bp 76–77 °C (0.05 mm).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.05; H, 8.29.

Isolation and Purification of *cis*- and *trans*-8-*tert*-Butyl-3-methylene-1-oxaspiro[4.5]decan-2-one (4b, 5b). The product of the reaction as described above using 4-*tert*-butylcyclohexanone was isolated as a crystalline mixture of cis and trans isomers from the ether solution. NMR analysis (in CCl_4) of the product (mp 63–71 °C) revealed a ratio of 4:1 for **4b/5b**. Careful fractional crystallization (CH_3OH) initially afforded colorless crystals, mp 83–84 °C, in which the trans isomer **5b** was no longer detectable via NMR analysis. Subsequent fractions showed evidence of both isomers. These latter fractions of isomers were chromatographed on a column of Florisil (Research Specialties Co.) in a ratio of 30:1 adsorbant/substrate, using 150 mL of hexane, followed by 100 mL of 50:50 benzene/hexane and then 100 mL of benzene. Those fractions containing the trans isomer **5b** identified via NMR analysis were combined and rechromatographed as described above. The trans isomer **5b** (50 mg) was isolated from the benzene fractions, mp 84–85 °C. The total yield was 3.6 g (65%), composed of 2.65 g (48%) of cis isomer **4b** and 50 mg (1.0%) of *trans*-**5b** along with 0.91 g (16.4%) of a mixture of the two. Analysis of the two separate isomers gave the following results.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.73; H, 10.00 (cis); C, 75.48; H, 9.88 (trans).

Synthesis of 7,7-Dimethyl-3-methylene-1-oxaspiro[4.5]-decan-2-one (4c ⇌ 5c). 5,5-Dimethyl-2-cyclohexenone was prepared by the method of Frank and Hall.[28] This ketone (31.7 g) was reduced over a 12-h period by the addition of H_2 (1 atm) using Pd–C (10%) with $CH_3CO_2C_2H_5$ as the solvent. Distillation afforded 18.9 g (60%) of 3,3-dimethylcyclohexanone: bp 181 °C (762 mm); reported bp 174–175 °C (757 mm).[29]

This saturated ketone was allowed to react with 1 in the general procedure described previously. The product was isolated as an oil from the ether extract and crystallized upon standing under refrigeration. Recrystallization from commercial hexanes (bp 67–71 °C) afforded 3.64 g of **4c** (or **5c**) (75%): mp 38.5–39.5 °C; bp 100–102 °C (0.25 mm).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.51; H, 9.28.

Purification of 7,7,9,9-Tetramethyl-3-methylene-1-oxaspiro[4.5]decan-2-one (4d ⇌ 5d). The product of 3,3,5,5-tetramethylcyclohexanone participating in a reaction as described above was isolated as a crystalline material from the ether extract. Recrys-

tallization of the solid (hexanes) afforded 4.06 g of **4d** (or **5d**) (73%): mp 101.5–103 °C.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.86; H, 9.98.

DNMR Spectroscopic Studies. The NMR spectra were recorded on a Varian XL-100 (15) NMR spectrometer equipped with a TT-100 PFT accessory, operating at 100.1 MHz with $(CH_3)_4Si$ as an internal reference. All controlled temperature spectra were recorded in acetone-d_6 in the FT mode, with the solvent providing the necessary deuterium lock. A pulse width of 5.7 s was used with a 6-s delay between pulses. Temperature control was provided by a Varian temperature controller. A capillary of CH_3OH with a trace of HCl present was placed in a 5-mm NMR tube containing 0.5 mL of acetone-d_6 and was used to calibrate the temperature according to the method of Van Geet.[30] Calibrations were done before and after each spectrum, and those spectra whose temperature calibrations differed by more than 1 °C were discarded and the shifts were reexamined at that temperature. Integrations were done electronically on the TT-100 computer and cross-checked using hand planimetry on the plotted spectra.

X-ray Analysis and Structure Refinement. Crystals suitable for X-ray intensity measurement were obtained by cooling a solution prepared by dissolving a small amount of **4b** in hot methanol. Initial diffraction experiments showed the crystals to be orthorhombic. The crystal data are: $C_{14}H_{22}O_2$; M_r = 222.32; space group $P2_12_12_1$; a = 11.455 (2), b = 18.356 (2), c = 6.100 (1) Å; V = 1282.6 Å^3 (at −135 °C); Z = 4; $F(000)$ = 488; Ni filtered Cu Kα radiation, λ (Cu Kα_1) = 1.54051 Å for determination of cell constants and λ(Cu K$\overline{\alpha}$) = 1.54178 Å for intensity data. The unit cell parameters were determined by least-squares fit to the $+2\theta$ and -2θ values of 44 reflections distributed throughout all regions of reciprocal space.

A total of 1551 intensities representing all unique reflections with $2\theta \leq 150$ were measured using a Nonius CAD-4 automatic diffractometer and θ–2θ scan techniques. The intensities were corrected for Lorentz and polarization effects and structure factor magnitudes derived. In the data analysis, an experimental weight, based on counting statistics, was assigned to each structure factor.[31] The structure was solved using direct methods and the computer program MULTAN.[32] All structure refinement was performed using the block-diagonal least-square program of Ahmed[33] and all Fourier maps were calculated using Ahmed's Fourier transform program.[34] The refinement of the model using anisotropic thermal parameters for C and O atoms and isotropic thermal parameters for H atoms was terminated when all shifts were small fractions of the corresponding estimated standard deviation. The R value based on the final parameter was 3.8%. While the standard error in the observation of unit weight was 1.18 e, a final difference Fourier map contained no peaks >0.16 e Å^{-3}. Scattering factors for C and O atoms were taken from the "International Tables for X-ray Crystallography"[35] and those for H atoms were from Stewart, Davidson, and Simpson.[36] The final structure factor analysis showed that $\Sigma w \Delta F^2$ did not vary with either $\sin^2\theta$ or $|F_o|$, thus validating the weighting scheme used.[37]

Acknowledgments. We (K.D.B.) gratefully acknowledge partial support of this work by the U.S. PHS, National Cancer Institute, Grant CA 14343. Partial support by the Presidential Challenge Grant from OSU in the form of salary (K.D.B.) is also greatly acknowledged. Acknowledgment is given for the generous support of the National Science Foundation for Department grants to purchase the XL-100(15) NMR spectrometer (Grant GP 17641) and TT-100 accessory (Grant HE76-05571). The X-ray analysis (D.v.d.H.) was supported by Grant CA 17562, awarded by the National Cancer Institute. We are also very grateful for the advice of Professor. L. M. Raff on various aspects of this work. One of us (D.J.O.) greatfully acknowledges summer support in the form of a fellowship from Phillips Petroleum Company for the summers of 1976 and 1977.

Registry No.—**1**, 17435-72-2; **4a**, 52978-85-5; **4b**, 67464-47-5; **4c**, 67464-48-6; **4d**, 67464-49-7; **5b**, 67464-50-0; cyclohexanone, 108-94-1; 4-*tert*-butylcyclohexanone, 98-53-3; 3,3-dimethylcyclohexanone, 2979-19-3; 3,3,5,5-tetramethylcyclohexanone, 14376-79-5.

Supplementary Material Available: Listing of positional and anisotropic thermal parameters for C and O atoms (Table VI) and H atoms (Table VII) of **4b** (2 pages). Ordering information can be found on any current masthead page.

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Effects of Axial *tert*-Butyl Substituents on Conformations and Geometries of Saturated Six-Membered Rings. Crystal and Molecular Structures of *trans*-2-Methoxy-2-oxo-5-*tert*-butyl- and *cis*-2,5-Di-*tert*-butyl-2-thio-1,3,2-dioxaphosphorinane

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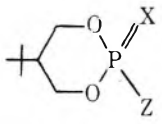
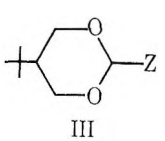
Received October 28, 1977

The title compounds crystallize in the orthorhombic system, the 2-methoxy compound (I) in the space group *Pnma*, and the 2-*tert*-butyl material (II) in space group *Pmcn*. Lattice parameters are: (I) a = 6.123 (4), b = 10.02 (1), c = 17.65 (1) Å, z = 4; (II) a = 10.077 (3), b = 10.662 (3), c = 12.703 (3) Å, z = 4. Compounds I and II both have chair-form ring conformations with the 5-*tert*-butyl group axial in both. For I the methoxy on phosphorus is axial and the phosphoryl oxygen is equatorial. The 2-*tert*-butyl is equatorial in II with the thiophosphoryl sulfur axial. In comparison to the structures of a large number of other phosphoranes, these rings systems, especially II, appear to be somewhat flattened about the C(5) end of the molecule. This apparently results from steric interactions involving the axial *tert*-butyl groups and the ring atoms C(4), C(6), O(1), and O(3) and hydrogens bonded thereto. Bond angle deformations within the 5-*tert*-butyl and at its point of attachment to the ring also attest to this fact. The phosphorus end of the ring associated with II is highly puckered. This property is shown to be a general one for 1,3,2-dioxaphosphorinanes with double-bonded O, S, or Se axial. For II the ring pucker is unusually large. Explanations based on nonbonded interactions of the 2-*tert*-butyl with ring oxygens O(1) and O(3) or across the ring with the axial 5-*tert*-butyl group are suggested.

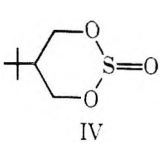
The 2-oxo- and 2-thio-1,3,2-dioxaphosphorinanes are readily substituted in a variety of ways both at phosphorus and on the ring carbons. As they are generally crystalline materials, they provide attractive systems for the determination of structural information on six-membered rings by X-ray crystallographic techniques. The present study presents unambiguous knowledge of the conformations of two such compounds, *trans*-2-methoxy-2-oxo-5-*tert*-butyl-1,3,2-dioxaphosphorinane (I) and *cis*-2,5-di-*tert*-butyl-2-thio-1,3,2-dioxaphosphorinane (II). A special structural feature of these compounds is the axial orientation of the 5-*tert*-butyl in both I and II in the solid phase, which provides an unusual opportunity to examine the effects on ring geometry of strain effects associated with so sterically bulky an axial substituent. Findings in the rings I and II are of wider interest as well, in relation to conformations of the corresponding 1,3-dioxanes (III)[1] and trimethylene sulfites (IV).[2]



I, X = O; Z = MeO
II, X = S; Z = *t*-Bu



III



IV

Experimental Section

The preparation of the phosphate I was reported earlier,[3] mp (*n*-hexane) 90–91 °C. Compound II was prepared from 2-*tert*-butyl-1,3-butanediol and *t*-BuP(S)Cl_2 in ether solution at 0–5 °C. The isomeric forms were separated by column chromatography on Florisil. Elution solvent was initially 3% ether in ligroin (60–90 °C). The fraction ether was gradually increased during chromatography. Compound II was crystallized from ligroin (60–90 °C), mp 96–97 °C (uncorrected).

Both substances crystallize in an orthorhombic space group with extinctions consistent with either $Pn2_1a$ or *Pnma*. The centric space group has been shown to be correct. (I is in space group *Pnma* while II is in *Pmcn*; these are identical space groups with different axial orientations consistent with the conventions for reporting orthorhombic lattice dimensions.) Extinctions and crystal data are provided in Table I for each of the crystals.

Data were collected on a General Electric XRD-5 diffractometer equipped with a scintillation counter, pulse-height discriminator, and GE single-crystal orientor, using θ–2θ scan technique. Details of the experimental procedures for each crystal are given in Table II. Three standard reflections were monitored to check crystal deterioration. No deterioration was observed in either case. Both crystals were enclosed in Lindeman glass capillaries to prevent loss by sublimation.

Solution of the structures was accomplished by Patterson methods, by locating the phosphorus atoms and subsequently calculating phases from the phosphorus atom positions. All remaining nonhydrogen atomic positions were seen on these Fourier maps. Refinement was carried out by full-matrix least-squares procedures,[4] weighting according to counting statistics. Atomic scattering factors for the nonhydrogen atoms were taken from the International Tables for X-ray Crystallography; both real and imaginary terms were applied to phosphorus. Hydrogen scattering factors were those of Stewart, Davidson and Simpson.[5] Final R factors are reported in Table II. For crystal I a difference synthesis allowed location of some of the hydrogen atoms. The remaining hydrogen atom positions were calculated and included in the final structure factor calculation. All hydrogen atom positions were located from the difference maps for compound II and these were included in the refinement with fixed temperature factors.

Results

Bond distances and angles are given in Figures 1, 2, 3, and 4, and the conformations are shown in the ORTEP drawings of Figures 5 and 6. No intermolecular distances short enough to affect geometry were encountered.

Both molecules I and II lie on a crystallographic mirror plane. For compound I, atoms P(2), O(13), C(5), C(7), and C(10) are on the mirror plane in special positions y = ¼ and ¾. The methoxy carbon C(11) of I is disordered, being found on either side of the mirror plane with an occupation factor of 0.5. The ring is a distorted chair with the *tert*-butyl and methoxy groups trans to each other in axial positions.

For compound II, atoms P(2), S(15), C(5), C(7), C(10), C(11), and C(14) lie on the mirror plane in special positions x = ¼ and ¾. The ring is a distorted chair with the *tert*-butyl groups cis to each other. The *tert*-butyl group on the C(5) position is axial while that on the P(2) position is equatorial. In both I and II the *tert*-butyl groups are perfectly staggered

0022-3263/78/1943-4266$01.00/0

Table I

5-*tert*-Butyl-2-methoxy-2-oxo-1,3,2-dioxaphosphorinane (registry no. 26344-06-9)

$C_8PO_4H_{17}$
fw 208.19
orthorhombic: space group *Pnma*
a = 6.123 (4) Å
b = 10.02 (1) Å
c = 17.65 (1) Å
vol of unit cell 1083 Å^3
molecules/unit cell = 4
D_{exp} = 1.25 g/cm^3
D_{calcd} = 1.277 g/cm^3
$F(000)$ = 448
systematic absences: hkl, no conditions; $hk0$, $h \neq 2n$; $0kl$, $k + l \neq 2n$; $h0l$, no conditions; $h00$, $h \neq 2n$; $0k0$, $k \neq 2n$; $00l$, $l \neq 2n$

2,5-Di-*tert*-butyl-2-thio-1,3,2-dioxaphosphorinane (registry no. 67271-57-2)

$C_{11}PSO_2H_{23}$
fw 250.32
orthorhombic: space group *Pmcn*
a = 10.077 (3) Å
b = 10.662 (3) Å
c = 12.703 (3) Å
vol of unit cell 1364.8 Å^3
molecules/unit cell = 4
D_{exp} = 1.210 g/cm^3
D_{calcd} = 1.218 g/cm^3
$F(000)$ = 544
systematic absences: hkl, no conditions; $h0l$, $l \neq 2n$; $hk0$, $h + k \neq 2n$; $0kl$, no conditions; $h00$, $h \neq 2n$; $0k0$, $k \neq 2n$; $00l$, $l \neq 2n$

Table II. Experimental Details

	I	II
crystal size	0.3 × 0.5 × 1.0 mm^3	0.16 × 0.26 × 0.58 mm^3
crystal mounted on	*a*	*a*
scan time	100 s	60 s
background count time	50 s/side	10 s/side
scan rate	2°/min	2°/min
takeoff angle	4°	4°
no. of reflections scanned	1008	818
obsd reflections ($I_{obsd} > 2\sigma(I)$)	585	763
μ (linear absorption coeff.)	2.41 cm^{-1}	3.33 cm^{-1}
final R factors: R	0.059	0.048
R_w	0.060	0.038

Radiation used in each case was Mo K(α) λ = 0.710 698 Å)
Functions minimized in least-squares refinement was $\sum w(|F_o| - 1/k|F_c|)^2$

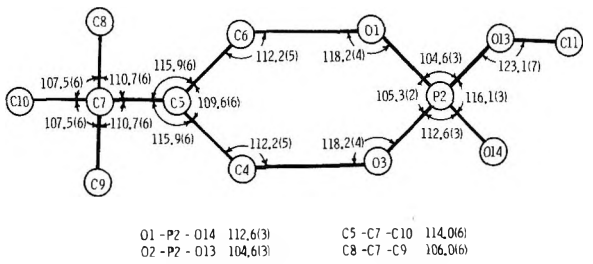


Figure 1. Bond angles for I.

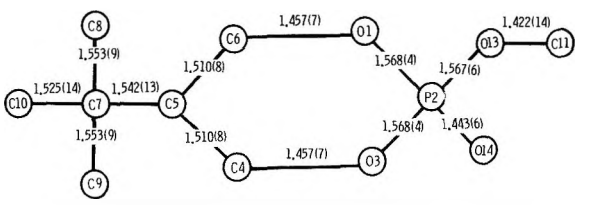


Figure 2. Bond distances for I (2-methoxy-2-oxo-5-*tert*-butyl-1,3,2-dioxaphosphorinane).

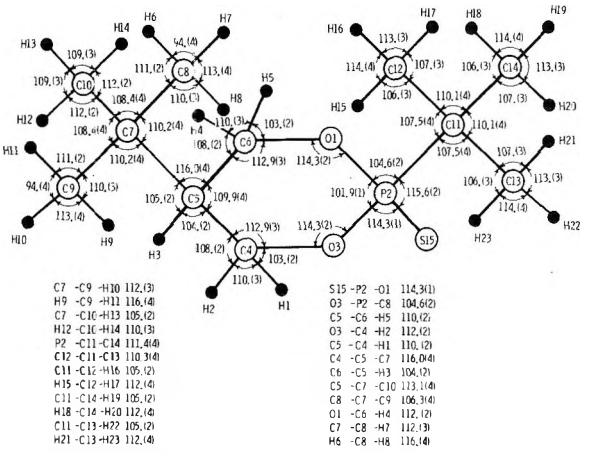


Figure 3. Bond angles for II.

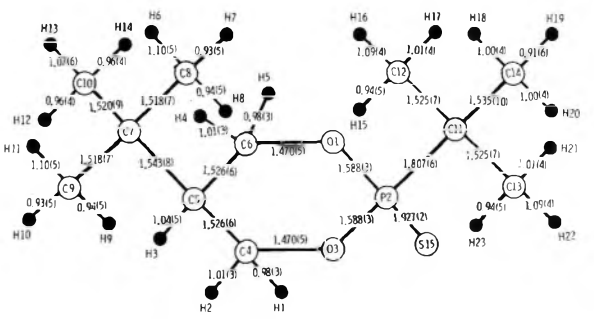


Figure 4. Bond distances for II (2,5-di-*tert*-butyl-2-thio-1,3,2-dioxaphosphorinane).

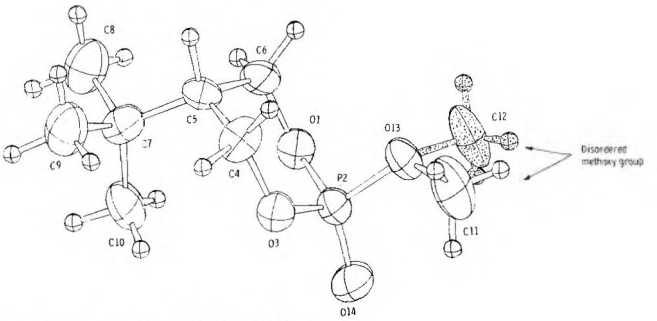


Figure 5. ORTEP drawing for I.

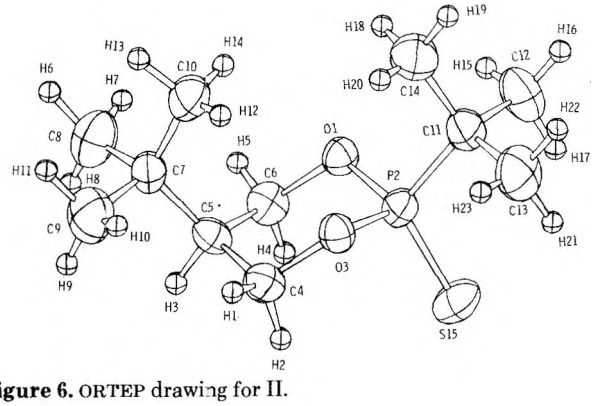
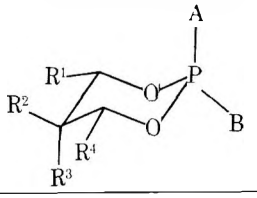
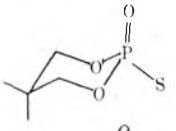
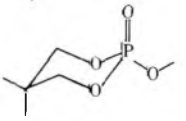


Figure 6. ORTEP drawing for II.

with respect to rotation about the C(5)–C(7) and P(2)–C(11) bonds. This symmetry also extends to the C–C bonds within the *tert*-butyl groups themselves such that, e.g., H(12) and H(14) in II are equivalent as are H(18) and H(20) and so forth. Bonding distances in I and II are not significantly different from those found for other 1,3,2 dioxaphosphorinanes.

Table III. X-ray Crystallographic Data for Various Substituted 1,3,2-Dioxaphosphorinanes



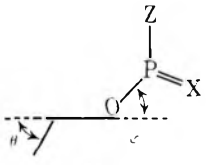
compd	R_1	R_2	R_3	R_4	A	B	∠P-O-C	∠φ	∠θ	ref
1	H	H	H	H	HO	=O	120, 121	40	54	*a*
2	H	H	H	H	PhO	=O	118, 118	37	53	*b*
3	H	CH_3	CH_3	H	Cl	=O	119, 123	35	52	*c*
4	H	CH_3	CH_3	H	Ph	=O	119, 120	33	51	*d*
5	H	CH_3	CH_3	H	PhNH	=O	118, 121	34	56	*e*
6	H	CH_3	CH_3	H		=O	120,121	31	55	*f*
7	H	CH_3	CH_3	H		=O		36		*g*
8	H	CH_3	CH_3	H	OCN	=O		34		*h*
9	H	CH_3	CH_3	H	PhO	=S	119, 119	37	54	*i*
10	H	CH_3	CH_3	H	CH_3O	=Se	116, 118	39	52	*j*
11	H	CH_3	CH_2Br	H	Br	=O	120, 121	37	53	*k*
12	CH_3	H	H	H	*t*-BuNH	=Se	118, 119	37	53	*l*
13	CH_3	H	H	CH_3	CH_3O	BH_3	119, 120	38	54	*m*
14	CH_3	H	H	CH_3	Ph_3C	=O	127, 128	3.7	53	*n*
15	H	*t*-Bu	H	H	CH_3	=O	120, 120	34	55	*o*
16	H	*t*-Bu	H	H	Ph	=S	117, 120	36	56	*p*
17	H	H	*t*-Bu	H	CH_3O	=O	118, 118	38	50	*q*
18	H	CH_3	CH_2Cl	H	=O		116, 116			*r*
19	H	CH_3	CH_3	H	=S	CH_3	116, 116	46	52	*s*
20	CH_3	H	H	H	=Se	*t*-BuNH	115, 118	44	56	*t*
21	H	H	*t*-Bu	H	=S	*t*-Bu	114, 114	50	46	*q*

[a] Reference 7. [b] Reference 6. [c] Reference 8. [d] Reference 9. [e] Reference 10. [f] Reference 11. [g] Reference 12. [h] Reference 13. [i] Reference 14. [k] Reference 15. [l] Reference 16. [m] Reference 17. [n] Reference 18. [o] Reference 19. [p] Reference 20. [q] This work. [r] Reference 21. [s] Reference 22. [t] Reference 23.

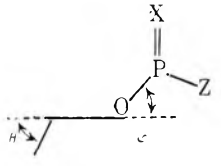
Discussion

That the 2-*tert*-butyl group of II has sufficient steric bulk to force the 5-*tert*-butyl group into the axial position is not surprising. This simply means that the repulsive interactions between the 2-*tert*-butyl methyls and the C(4), C(6) carbons and hydrogens are greater than the interactions between the C(5)-*tert*-butyl methyls and the O(1), O(3) oxygens. What would not have been predicted necessarily is the axial position for the 5-*tert*-butyl of I. Clearly the preferences of the MeO(axial) and P=O(equatorial) are so great as to determine which chair form is energetically favored. Although such preferences for RO and P=O have been noted before in crystals of 2-phenoxy-2-oxo-1,3,2-dioxaphosphorinane[6] (compound 2 of Table III) and in liquid phase ^1H NMR work with 2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane,[24] these systems were not energetically biased against such a conformation by substituents on ring carbons. In 1,3-dioxanes[1a,c] (III) and the trimethylene sulfite (IV),[2b,d] $\Delta G°_{25}$ for the process of 5-*t*-Bu(equatorial) → 5-*t*-Bu(axial) is unfavorable by 1.4 to 1.8 kcal/mol. The close similarity of the O(1)–C(6)–C(5)–C(4)–O(3) geometries in 1,3-dioxanes[25] and 1,3,2-dioxaphosphorinanes[26] indicates that the steric interactions for an axial 5-*tert*-butyl should be about the same in the two systems. Thus, neglecting effects of crystal packing forces, the sum of the energetic preferences of the MeO(axial) and phosphoryl oxygen(equatorial) is of the order 1.5 to 2.0 kcal/mol or greater.

The dihedral angle φ (see structures V and VI) between the planes O(1)–O(3)–C(4)–C(6) and O(1)–P(2)–O(3) in I is 37.9° and in II is 50.3°. Thus I, with P=O equatorial (V), is considerably more flattened about phosphorus than is II with P=S axial (VI). The greater pucker in the ring of II also shows itself in the angles C(4)–O(3)–P(2) and C(6)–O(1)–P(2) which are decreased to 114.3° from the value of 118.2° in I.



V



VI

The effect on angle φ of inverting configuration about phosphorus seems to be very general and not merely a consequence of the presence of the 2-*tert*-butyl in II. Table III gives the dihedral angle φ and/or the ring angles C(4)–O(3)–P(2) and C(6)–O(1)–P(2) as determined by X-ray crystallography for a large variety of 1,3,2-dioxaphosphorinanes. For those of structure V, compounds 1–17 (excluding 14), φ ranges 31–40°. As we first pointed out[19] and as has been reemphasized recently[11] with the larger series of compounds now available, this variation primarily reflects changes in the steric size of Z. As Z becomes larger, the ring flattens to reduce the

Table IV. Selected Short Nonbonded Intramolecular Distances (Å) in I and II

compound I			
C-C (3.5)[a]	C-O (3.3)	O-O (3.0)	P-C (3.6)
C(7)-C(6) 2.6	C(7)-O(3) 3.2	O(13)-O(1) 2.5	P(2)-C(11) 2.6
C(7)-C(4) 2.6	C(7)-O(1) 3.2	O(13)-O(3) 2.5	
C(9)-C(4) 3.1	C(10)-O(3) 3.1	O(13)-O(14) 2.6	
C(8)-C(6) 3.1	C(10)-O(1) 3.1	O(14)-O(3) 2.5	
C(10)-C(4) 3.2	C(4)-O(13) 3.1	O(14)-O(2) 2.5	
C(10)-C(6) 3.2	C(6)-O(13) 3.1		
compound II			
C-C (3.5)	C-O (3.3)	H-O (2.7)	H-H (2.4)
C(7)-C(4) 2.6	C(10)-O(3) 3.2	H(12)-O(3) 2.7	H(1)-H(10) 2.2
C(7)-C(6) 2.6	C(10)-O(1) 3.2	H(14)-O(1) 2.7	H(5)-H(7) 2.2
C(9)-C(4) 3.0	C(7)-O(1) 3.3	H(20)-O(3) 2.7	H(1)-H(12) 2.8
C(10)-C(6) 3.0	C(7)-O(3) 3.3	H(18)-O(1) 2.7	H(5)-H(14) 2.8
C(10)-C(4) 3.0	C(11)-O(3) 2.7	H(23)-O(3) 2.7	H(12)-H(20) 2.7
C(10)-C(6) 3.0	C(11)-O(1) 2.7	H(15)-O(1) 2.7	H(14)-H(18) 2.7
C(10)-C(14) 3.7	C(14)-O(3) 3.1		H(3)-H(9) 2.4
	C(14)-O(1) 3.1		H(3)-H(8) 2.4
CH (3.0)		misc.	
C(4)-H(10) 2.9	C(10)-H(1) 3.2	S(15)-H(2) 3.1 (3.0)[a]	S(15)-C(4) 3.5 (3.5)
C(4)-H(7) 2.9	C(10)-H(5) 3.2	S(15)-H(4) 3.1 (3.0)	S(15)-C(12) 3.5 (3.5)
C(4)-H(12) 2.9	C(7)-H(3) 2.1	S(15)-H(16) 2.9 (3.0)	S(15)-C(13) 3.5 (3.5)
C(5)-H(14) 2.9	C(10)-H(20) 3.3	S(15)-H(22) 2.9 (3.0)	S(15)-C(11) 3.2 (3.5)
C(7)-H(1) 2.7	C(10)-H(18) 3.3	S(15)-C(6) 3.5 (3.5)	
C(7)-H(5) 2.7	C(14)-H(12) 3.3		
C(9)-H(1) 2.6	C(14)-H(14) 3.3		
C(8)-H(5) 2.6			

[a] Number in parentheses is van der Waals sum. van der Waal radii used are: C, 1.75; O, 1.5; P, 1.85; H, 1.2A. These agree with those given by Bondi.[29]

syn axial repulsions between Z and the C(4), C(6) axial hydrogens.

The highly distorted compound **14** particularly shows the effect of size of Z (−3.7°). By contrast compounds **19–21**, which have structure VI, exhibit values between 44 and 50°. Compound **18**, for which ϕ was not reported, has the ring angle reduced to 116° as expected for increased puckering about phosphorus. Particularly convincing are comparisons of compounds with identical or closely similar substituents on phosphorus, as for example **12** vs. **20** and **19** vs. **4**, **15**, and **16**.

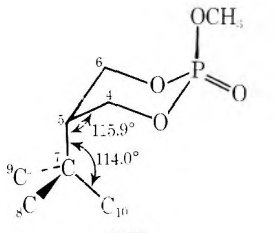
The simplest explanation of this effect seems to be based on the fact that regardless of the configuration at phosphorus, the bond angles about the P=X side of the phosphorus tetrahedron are increased well beyond 109°.[6-23] When Z is axial, this then has the effect of forcing the group Z close to the axial hydrogens at C(4) and C(6). To reduce the accompanying strain, the ring becomes flattened at phosphorus, increasing the Z···H(5), H(6) distances. Such flattening is not required with P=X axial. Inspection of intramolecular distances in Table IV shows that in compound II the S(15)-C(4), -C(6) distances are just at or slightly longer than van der Waal radii sums, while O(13)-C(4), -C(6) of I in which the ring has presumably been flattened to reduce that distance to 3.1 Å are slightly shorter (0.2 Å) than van der Waals sums.

Inspection of Table III shows that if one excludes the compounds I and II of this study (**17** and **21** in Table III), the angle θ covers a range of just 5°, 51–56°. Thus θ is remarkably independent of changes in φ at the other end of the molecule (φ = 3.7 to 46°). Especially compare **13** with **14** and **4**, **5**, **10**, **11** with **19**.

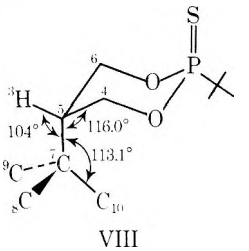
The axial 5-*tert*-butyl compounds of the present study, I and II (**17** and **21** of Table III), have low values of θ, 49.9° and 46.0°. This is evident when compared to the average θ for the other compounds of Table III, 54°, and especially to compounds **15** (θ = 55°) and **16** (θ = 56°) with 5-*tert*-butyl equatorial. The flattening which occurs at the C(5) end of rings I and II appears to come from repulsive steric interactions involving the axial *tert*-butyl group and the C(4), C(6), and associated hydrogen atoms as well as O(1) and O(3). In Table IV one finds that a number of the corresponding intramolecular distances are very near to or less than the sum of the van der Waals radii. Note, e.g., the C(8), C(9), and C(10) interactions with C(4) and/or C(6) and C(10) with O(1), O(3) in both I and II. Also note in II, H(10)-H(1), H(7)-H(5), H(1)-C(7), H(1)-C(9), H(5)-C(8), H(12)-O(3) and H(14)-O(1).

Since the locations of the hydrogens are less well defined than those of the carbons and oxygens, one may also evaluate the C···O and C···C intramolecular distances with the usually assumed radius of the methyl group (2.0 Å[27]). Again contacts well under van der Waals sums (3.5 Å for CH_3 plus oxygen) are encountered for C(10)-C(1), O(3) interactions, and C(10)-C(4), -C(6).

The strain in I and II engendered by the axial 5-*tert*-butyl is also relieved by an increase in the angles C(4)-C(5)-C(7) and C(6)-C(5)-C(7) to 115.9° in I and 116.0° in II (see structures VII and VIII). The H(3)-C(5)-C(7) angle is then reduced to 105° in II. No such deformations are seen in **19** of Table III. In addition, the angle C(5)-C(7)-C(10) is increased to 114.0° in I and to 113.1° in II.



VII



VIII

Another significant structural effect in these compounds is the 4° increase in angle φ of II compared to compound **19** of Table III for which the equatorial substituent on phosphorus (CH_3) is much smaller. Some evidence that ring pucker at phosphorus in II occurs in relief of steric interaction between the ring oxygens and C(14) comes from the bond angle P(2)–C(11)–C(14) of 111.4°. At the same time the angles P(2)–C(11)–C(12) and P(2)–C(11)–C(13) are 107.5°, as though the whole *tert*-butyl group had tipped at the C(11) slightly toward S(15). The angle O(1)– or O(3)–P(2)–C(11), 104.6°, is only slightly and hardly significantly increased over that of the methyl compound **19** of Table III (103.2°). Angle S(15)–P(2)–C(11) is decreased 1°. The C(11)–O(1), –O(3) interatomic distances are 3.1 or 0.2 Å below van der Waals sums. Furthermore, H(18)–O(1), H(18)–O(3), H(20)–O(1), and H(20)–O(3) distances are right at van der Waals sums. Use of the methyl radius estimate of 2.0 Å rather than the imprecisely determined hydrogen–oxygen distance puts H(18)–O(1) and H(20)–O(3) well under van der Waals distances. Slight ring puckering effects have been noted in certain cyclohexanes at the point of equatorial *tert*-butyl substitution.[28]

An alternative source of ring pucker at phosphorus in II could be the axial 5-*tert*-butyl if the two *tert*-butyl groups interact sterically in intermolecular fashion. The 4° decrease in θ in II compared with that for I makes this an attractive idea, especially since ring pucker at phosphorus has no demonstrable effect on θ (vida supra, Table III). In this view both ends of the molecule are repelled away from each other. From Table IV the *tert*-butyl–*tert*-butyl distances are C(10)–C(14) at 3.70 Å (van der Waals sum, 3.54 Å). Use of the 2.0 Å methyl radius concept,[27] however, puts the corresponding H–H contacts well under van der Waals sums (0.3 Å). Measured C···H and H···H distances are just above van der Waals sums, e.g., H(12)–H(20) and H(14)–H(18), 2.65 Å; C(10)–H(18) and C(10)–H(20), 3.30 Å. It should also be remembered that C–C rotations will bring the H···H contacts in solution closer than those in the crystal. If one considers also the measurement errors especially in H positions, it seems quite possible that the *tert*-butyl groups do repell each other. A final resolution of the question of the origin of the apparent concerted distortions of both ends of the ring of II awaits a crystallographic study of 2-*tert*-butyl-2-thio-1,3,2-dioxaphosphorinane itself.

Acknowledgment. This research was supported by a grant from the National Science Foundation (GP-33538) to C.N.C. and a grant from the National Cancer Institute of the Public Health Service (CA 11045) to W.G.B. The writeup of this work was accomplished while W.G.B. was a Fellow of the Alexander von Humboldt Foundation in the Technical University, Braunschweig, W. Germany. We also wish to thank Montana State University for a grant for computer funds.

Registry No.—2-*tert*-Butyl-1,3-butanediol, 67271-58-3; *t*-BuP(S)Cl_2, 21187-18-8.

Supplementary Material Available: Listing of structure factor amplitudes and positional and thermal parameters for compounds I and II (6 pages). Ordering information is given on any current masthead page.

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A New Aziridine Synthesis from 2-Azido Alcohols and Tertiary Phosphines. Preparation of Phenanthrene 9,10-Imine

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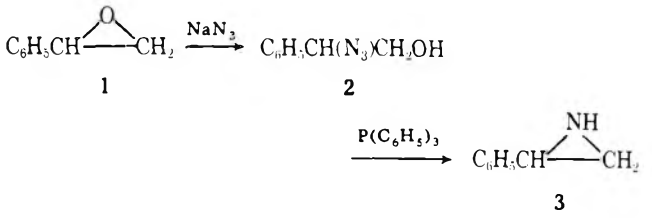
Received May 15, 1978

A new stereospecific synthesis of aziridines is described. It consists of the reaction of sodium azide with an oxirane, followed by treatment of the 2-azido alcohol formed with a tertiary phosphine. The method has been applied for the preparation of the first unsubstituted phenanthrene imine. The synthesis of 1a,9b-dihydrophenanthr[9,10-*b*]azirine proved to proceed via a phosphonium hydroxide intermediate which could be isolated under mild conditions. The unsubstituted arene imine proved to be thermally stable (up to 190 °C), but rearranges to 9-aminophenanthrene in the presence of hydrochloric acid.

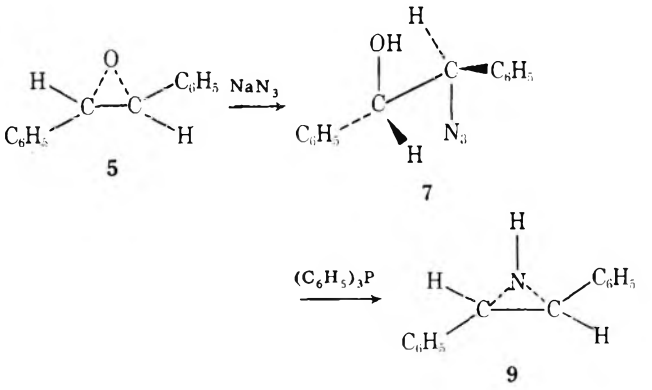
In a recent paper,[3] we discussed a hypothesis concerning the intermediary of arene imines in chemical carcinogenesis and described the syntheses of several *N*-acetyl- and *N*-alkylphenanthrene imines. However, unsubstituted arene imines that are isoelectronic with the well-documented arene oxides[4] could not be obtained by the available methods.

We now wish to report a new transformation of oxiranes to aziridines by which the first unsubstituted polycyclic arene imine has been synthesized. The process includes the reaction of epoxide with sodium azide followed by treatment of the 2-azido alcohol with a tertiary phosphine. 2-Phenylaziridine (**3**), e.g., was obtained in 72% yield simply by the addition of an ether solution of triphenylphosphine to 2-azido-2-phenylethanol (**2**).[5]



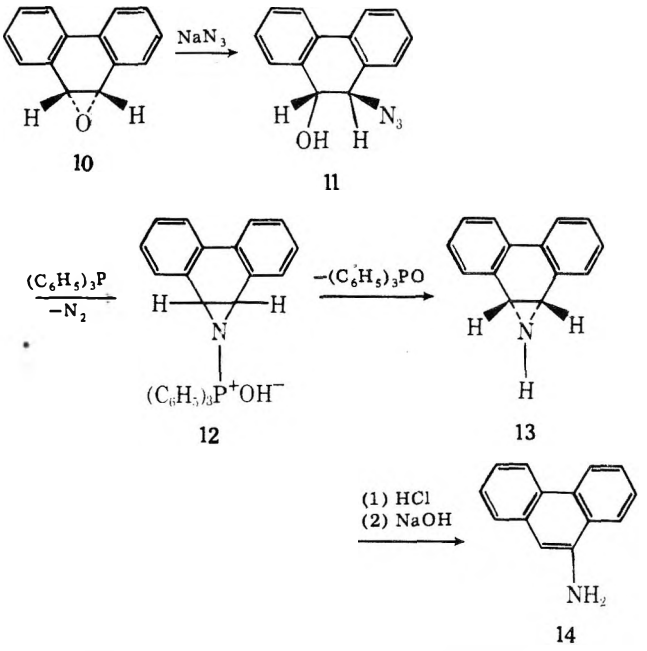
1 2 3

When *cis*- and *trans*-stilbene oxide (**4** and **5**) were converted into the corresponding *threo*- and *erythro*-2-azido-1,2-diphenylethanol (**6** and **7**)[6] followed by treatment with $(C_6H_5)_3P$, *cis*- and *trans*-2,3-diphenylaziridine (**8** and **9**) resulted in a highly selective fashion.



5 7 9

This process is thus particularly useful for epoxide to aziridine transformation in which an overall retention of configuration is required. Its greatest advantage is, however, its utility for the synthesis of unsubstituted arene imines. 1a,9b-Dihydrophenanthr[9,10-*b*]azirine (**13**) could be prepared by the reaction of triphenylphosphine with *trans*-10-azido-9,10-dihydrophenanthr-9-ol (**11**) [from phenanthrene 9,10-oxide (**10**) and NaN_3[7]]. When the phosphine was added to **11** below 20 °C, a labile phosphorus-containing compound,



10 11 12 13 14

$C_{32}H_{26}NOP$ (**12**), could be isolated. The ^1H NMR spectrum taken in $CDCl_3$ below 25 °C shows typical aziridine signals at δ 3.53 and 3.59[8] that suggest an aziridinylphosphonium structure **12** for this intermediate. At 30 °C the two peaks collapse into a sharp singlet at δ 3.56 that is characteristic for the phosphourus-free imine **13**.

The structure of **13** was established mainly on basis of elementary analysis and spectral data. An N–H absorption at 3180 cm^{-1} is observed in the IR spectrum. The ^1H NMR ($CDCl_3$) spectrum shows two equivalent aziridine protons that resonate at δ 3.56 and indicates that **13** does not exist to any detectable extent as an azepine derivative.[9] The principal fragment ions in the mass spectrum (see Experimental Section) are the molecular ion and the characteristic fragments of the 9,10-dihydrophenanthrene skeleton.[10]

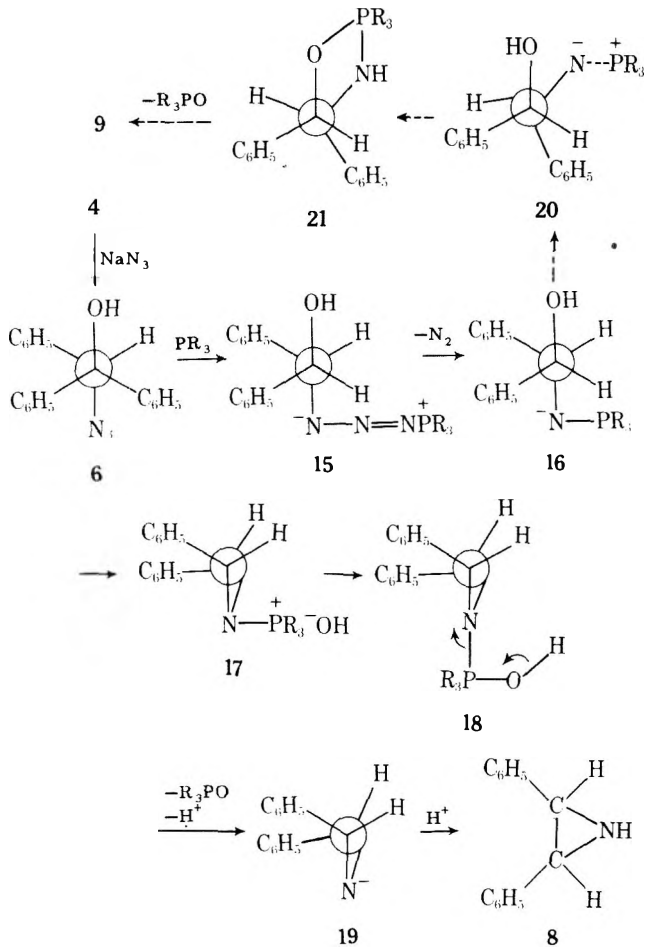
The unsubstituted phenanthrene 9,10-imine proved to be thermally more stable than the reported *N*-acetyl,[11] *N*-tosyl,[6] and *N*-alkyl derivatives[3] and more than the analogous phenanthrene 9,10-oxide.[12] It can be heated up to 190 °C (above the melting point) without any significant change. Only above 210 °C does rapid ring opening take place, and a mixture of compounds that contains ca. 30% of 9-aminophenanthrene (**14**) is formed. Smooth transformation of **13** to **14** can, however, be accomplished upon brief reflux in aqueous hydrochloric acid followed by neutralization with base. Triphenylphosphine oxide also promotes the conversion of **13** into the aromatic amine above 80 °C, albeit not in quantitative yield. Under nitrosating conditions (isoamyl nitrite and triethylamine), **13**, like aliphatic aziridines,[13] is deaminated to

0022-3263/78/1943-4271$01.00/0

give phenanthrene. This latter experiment thus provides the linking step for a reaction cycle in which phenanthrene 9,10-oxide and phenanthrene imine can be interconverted.

Since the separation of **13** from the accompanying triphenylphosphine oxide proved tedious and led to heavy losses of the desired product, we found it useful to employ tri-*n*-butylphosphine instead of triphenylphosphine for the transformation of **11** to **13**. The tri-*n*-butylphosphine oxide and the other impurities could be easily removed by washing with dry ether, leaving 72% of analytically pure imine.

The resemblance of the stereochemical course of the Staudinger reaction[14] of 2-iodoalkyl azides with tertiary phosphines[8] to that observed in our aziridine synthesis suggests similar features in the mechanisms of both processes. Thus, e.g., in the transformation of *cis*-stilbene oxide (**4**) to *cis*-2,3-diphenylaziridine (**8**), (±)-*threo*-azido alcohol **6** is assumed to add R_3P at the terminal nitrogen atom.[15] Loss of N_2 from **15** and intramolecular nucleophilic substitution in ylide **16** would then lead to the azyridinylphosphonium hydroxide **17**.



Elimination of triphenylphosphine oxide from **18** affords then *cis*-2,3-diphenylaziridine (**8**). Rotation of the C_1–C_2 bond of **16** to give conformer **20** followed by S_Ni ring closure would generate the precursor of *trans*-2,3-diphenylaziridine (**9**). Since no **9** is formed from **4**, the pathway leading to **21** must be ruled out.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are not corrected. Infrared and ultraviolet spectra were recorded on a Perkin-Elmer Model 157 and a Unicam SP-800 spectrophotometer, respectively. Proton magnetic resonance spectra were run using HA-100D and CFT-20 spectrometers. The latter instrument, equipped with a Fourier transformer, was also used for the recording of ^{13}C magnetic resonance spectra. Mass spectra were obtained with the aid of a Varian MAT-311 instrument at 70 eV.

2-Phenylaziridine (3). A solution of 8.15 g (50 mmol) of 2-azido-2-phenylethanol (**2**) [prepared in 85% yield from styrene oxide (**1**)[5]] and 13.10 g (50 mmol) of triphenylphosphine in 250 mL of dry ether was stirred at room temperature. Evolution of N_2 and precipitation of triphenylphosphine oxide started after 10 min. When gas evolution had ceased, the oxide was filtered off and the ether removed in vacuo. The residue was distilled at 75 °C (15 mm) to give 4.30 g (72%) of **3** that was identical with an authentic sample.[16]

(±)-*threo*-2-Azido-1,2-diphenylethanol (6). A mixture of 3.92 g (20 mmol) of *cis*-stilbene oxide (**4**) and 4.48 g (70 mmol) of NaN_3 in 60 mL of 50% aqueous acetone was refluxed for 3 h. The solvent was evaporated in vacuo and the residue extracted with $CHCl_3$. The organic solution was washed with water, dried ($MgSO_4$), and concentrated. Distillation of the residue afforded 3.70 g (77%) of **6** as a pale yellow oil: bp 122 °C (0.15 mm); IR 2118 (N_3), 3434 (OH) cm^{-1}; UV λ_{max} (log ϵ) (EtOH) 226 (3.21), 247 (2.87), 252 (2.89), 258 (2.88), 264 nm (2.76); ^1H NMR ($CDCl_3$) δ 3.10 (brd s, 1), 4.45 and 4.69 (AB pattern, 2, J_{AB} = 7.5 Hz), 7.20 (m, 10); MS *m/e* (relative intensity) 211 ($M^+ - N_2$, 0.4), 197 (1.1), 196 (1.1), 195 (1.1), 180 (1.1), 179 (1.4), 178 (1.7), 167 (2.9), 165 (2.3), 152 (1.4), 135 (4.6), 107 (100), 105 (31.4), 104 (25.7), 79 (78.6), 77 (68.6), 51 (27.7). Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.3; H, 5.4. Found: C, 70.2; H, 5.7.

***cis*-2,3-Diphenylaziridine (8).** A solution of 0.84 g (3.5 mmol) of **6** and 0.92 g (3.5 mmol) of triphenylphosphine in 25 mL of dry ether was refluxed for 1 h. Ether (50 mL) was added, and the mixture was allowed to stand overnight at 5 °C to allow complete precipitation of the triphenylphosphine oxide. Column chromatography on silica gel yielded 0.53 g (77%) of **8** that was identical with an authentic sample obtained by the method of Hassner et al.[17]

(±)-*erythro*-2-Azido-1,2-diphenylethanol (7). As for **6**, 3.92 g of **5** was reacted with 4.48 g of sodium azide. However, prolonged reflux was necessary as the last traces of *trans*-stilbene oxide (TLC test) disappeared only after 48 h. The azido alcohol was obtained in 88% yield (2.12 g), bp 158 °C (0.8 mm). On standing, **7** solidified to give colorless crystals of mp 60–61 °C: IR (Nujol) 2108 (N_3), 3430 (OH) cm^{-1}; UV λ_{max} (log ϵ) (EtOH) 226 (3.20), 252 (2.79), 258 (2.82), 264 (2.73), 268 nm (2.60); ^1H NMR ($CDCl_3$) δ 2.11 (brd s, 1), 4.63 and 4.76 (AB pattern, 2, J_{AB} = 8 Hz), 7.15 (m, 10); MS *m/e* (relative intensity) 211 ($M^+ - N_2$, 0.4), 197 (3.6), 196 (2.6), 195 (2.8), 165 (4.8), 152 (2.5), 107 (100), 106 (26.7), 105 (51.0). 104 (37.9), 79 (49.5), 77 (63.1), 51 (24.3). Anal. Calcd for $C_{14}H_{13}N_3O$: C, 70.3; H, 5.4. Found: C, 70.3; H, 5.7.

***trans*-2,3-Diphenylaziridine (9)** was obtained in 68% yield by the manner described for **3**. (Slight heating was required.) The colorless product of mp 45–46 °C proved to be identical with a sample prepared according to Heine et al.[18]

***trans*-10-Azido-9,10-dihydrophenanthr-9-ol (11)** was obtained in quantitative yield when the method of Shudo and Okamoto[6] was modified as follows. A solution of 20 g (0.31 mol) of sodium azide in 500 mL of acetone, 250 mL of water, and 0.5 mL of concentrated sulfuric acid was stirred at room temperature for 10 min. Phenanthrene oxide (**10**) (0.97 g, 5 mmol) was added, and stirring was continued for 48 h. The acetone was removed in vacuo and the organic residue taken in CH_2Cl_2. Evaporation of the solvent afforded 1.18 g of **11** with the same melting point and IR spectrum as reported[6]: ^1H NMR ($CDCl_3$) δ 1.26 (s, 1), 4.68 and 4.77 (AB pattern, 2, J_{AB} = 8 Hz), 7.2–8.4 (m, 8); ^{13}C NMR (Me_2SO-d_6) δ 135.98, 133.16, 132.55, 131.47, 128.03, 127.81 (12 C, aromatic), 74.96 (1 C, CHOH), 68.73 (1 C, CHN_3); MS *m/e* (relative intensity) 237 (M^+, 9.2), 209 (7.5), 208 (10), 180 (100), 165 (12.1), 152 (20.4).

(1a,9b-Dihydrophenanthr[9,10-*b*]azirin-1-yl)triphenylphosphonium Hydroxide (12). To a stirred solution of 2.62 g (10 mmol) of triphenylphosphine in 50 mL dry ether was added 2.37 g (10 mmol) of **11**. After 10 min at 18 °C, evolution of nitrogen started. Stirring was continued for 20 min further. The solution was concentrated in vacuo (below 15 °C) to a volume of 10 mL. The colorless phosphonium hydroxide (3.95 g, 84%) was filtered off and washed with 20 mL of *cold* ether: ^1H NMR ($CDCl_3$, 20 °C) δ 3.52 (brd s, 1), 3.58 (brd s, 1), 7.10–8.07 (m, 23). At 31 °C, the spectrum was identical with that of equimolar amounts of **13** and triphenylphospine oxide. MS *m/e* (relative intensity) 454 ($C_{32}H_{25}NP^+$·, 3.2), 278 [$(C_6H_5)_3PO^+$·, 31], 262 [$(C_6H_5)_3P^+$·, 7.7), 198 (7.1), 196 (9.0), 193 (13^+·, 100), 182 (11.6), 177 (13.5), 165 (60.6), 152 (11.0), 50 (42.6). At 25 eV, M^+· of the phosphorane of *m/e* 471 (0.7) was observed. Anal. Calcd for $C_{32}H_{26}NOP$: C, 81.5; H, 5.5; N, 3.0; P, 6.6. Found: C, 81.5; H, 5.7; N, 3.3; P, 6.2.

1a,9b-Dihydrophenanthr[9,10-*b*]azirine (13). A. Under an N_2 atmosphere and external cooling (ice water), there was added with vigorous stirring 3.1 g (15.3 mmol) of tri-*n*-butylphosphine to 3.40 g (14.3 mmol) of **11**. After the exothermic reaction had ceased, the

mixture was cooled to 0 °C and washed four times with 15 mL of dry ether to yield 2.0 g (72%) of colorless crystals: mp 163–164 °C (from benzene–cyclohexane); IR (Nujol) 3180 cm^{-1} (N-H); UV λ_{max} (log ϵ) ($CHCl_3$) 273 (4.12), 277 (4.15), 281 (4.17), 288 (4.02), 294 (3.90), 305 nm (3.59); ^1H NMR ($CDCl_3$) δ 3.56 (s, 2), 7.2–8.3 (m, 8); ^{13}C NMR ($CDCl_3$) δ 136.22, 134.53, 133.68, 132.54, 130.98, 127.76 (12 C, aromatic) 41.88 (2 C, CHNH); MS (relative intensity) *m/e* 193 ($M^{+\cdot}$, 100), 192 (11.6), 178 (34.0), 176 (9.6), 165 (74.0), 152 (6.4), 151 (3.6), 150 (3.2), 139 (6.4), 127 (5.2), 89 (5.2), 76 (6.0). Anal. Calcd for $C_{14}H_{11}N$: C, 87.0; H, 5.7; N, 7.3. Found: C, 87.3; H, 5.9; N, 7.0.

B. A solution of 0.942 g (2 mmol) of **12** in 100 mL of CH_2Cl_2 was refluxed for 15 min. The solvent was distilled, and most of the triphenylphosphine oxide was removed by extraction with ether (3 × 25 mL). The residue was dissolved in 2 mL of CH_2Cl_2 and purified by two dimensional PLC on alumina (5:1 hexane–ether eluent). In the best run we obtained 0.234 g of **13** (85% purity). Further purification by PLC and by recrystallization was associated with significant losses.

Conversion of 13 into 9-Aminophenanthrene (14). A mixture of 50 mg of the previous imine and 2 mL of 15% aqueous HCl was refluxed for 10 min. After cooling, 5 mL of benzene was added and the acid was neutralized with NaOH. The organic layer was dried and concentrated. The residue proved to be pure **14**, which was identical with an authentic sample prepared according to Schmidt and Heinle.[19]

Deamination of 13. A mixture of 0.97 g (5 mmol) of **13**, 6.4 g (50 mmol) of isoamyl nitrite, and 1.5 mL of triethylamine was stirred for 45 min at room temperature. Extraction with benzene and column chromatography on alumina afforded 0.63 g (71%) of phenanthrene.

Acknowledgment. We are grateful to the Israel Commission for Basic Research, The Israel Academy of Sciences and Humanities, for financial support of this study.

Registry No.—**2**, 67364-41-9; **3**, 1499-00-9; **4**, 1689-71-0; **5**, 1439-07-2; **6**, 67464-42-0; **7**, 67464-43-1; **8**, 1605-06-7; **9**, 25125-72-8; **10**, 585-08-0; **11**, 53581-32-1; **12** (uncharged), 67464-44-2; **12** (charged), 67464-45-3; **13**, 67464-46-4; **14**, 947-73-9.

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2-Chloroacrylonitrile as a Cyclodipolarophile in 1,3-Cycloadditions. 3-Cyanopyrroles

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Received December 19, 1977

The reaction of 2-chloroacrylonitrile with *N*-acyl-α-amino acids in acetic anhydride gave 3-cyanopyrroles, through an oxazolium 5-oxide (**2**) intermediate, with an overall yield of about 70%. Representative 3-cyanopyrroles, 7-cyano-2,3-dihydro-1*H*-pyrrolizines, and 1-cyano-5,6,7,8-tetrahydroindolizines were synthesized. Regiospecificity was achieved in some cases.

The 1,3-cycloaddition of oxazolium 5-oxides (**2**) with dipolarophiles has recently been utilized in the synthesis of a variety of heterocyclic systems,[1-3] the reaction pathway involving a cycloaddition to an azomethine ylide to give a N-bridged intermediate that loses carbon dioxide and forms a heterocycle.[4] This note describes the reaction between oxazolium 5-oxides and 2-chloroacrylonitrile to give 3-cyanopyrrole derivatives in a single pot operation starting from α-amino acids or their *N*-acyl derivatives.

The overall reaction is represented by the following sequence: N-acylation of the amino acid (**1**), oxazolium 5-oxide (**2**) formation, 1,3-cycloaddition to give a N-bridged intermediate (**3**), carbon dioxide elimination to give an unstable chlorocyanopyrroline (**4**), and elimination of hydrochloric acid[5] to give a 3-cyanopyrrole (**5**). When a cyclic α-amino acid (proline or pipecolic acid) was used, the corresponding 7-cyano-2,3-dihydro-1*H*-pyrrolizines (**14** and **15**) or 1-cyano-5,6,7,8-tetrahydroindolizines (**16** and **18**) were obtained.

This reaction can be carried out using aromatic, halogenated, or aprotic solvents or an excess of acetic anhydride at temperatures ranging between 20 and 100 °C. It represents a useful synthetic route to 3-cyanopyrroles with the same substituents in positions 2 and 5 (**6** and **12**) or when the reaction is regiospecific, giving only one isomer, as in the cycloaddition to the azomethine ylide system derived from *N*-formyl-*C*-phenylglycine, *N*-acylproline, or *N*-acylpipecolic acid (compounds **9** and **14–21**). As expected, a mixture of pyrroles is obtained when the reaction is not regiospecific, as with L-leucine, which gives compounds **7** and **8**. The same mixture of pyrroles **10** and **11** is obtained starting from either DL-α-phenylglycine or *N*-benzoylalanine. From this mixture, compound **11** was isolated. Both mixtures were hydrolyzed to the corresponding mixture of acids, which were decarboxylated to a single pyrrole **13**.

The presence of a substituent in position 4 in the oxazolium 5-oxide intermediate **2** seems to be necessary since no reaction was obtained with *N*-formylglycine, *N*-acetylglycine, or hippuric acid under experimental conditions described for the preparation of **9**. The oxazolone derived from hippuric acid (**2**; R = C_6H_5, R_1 = H) was isolated and does not react with 2-chloroacrylonitrile in the conditions described in this note. Anyhow, the desired compound **9** could be obtained using

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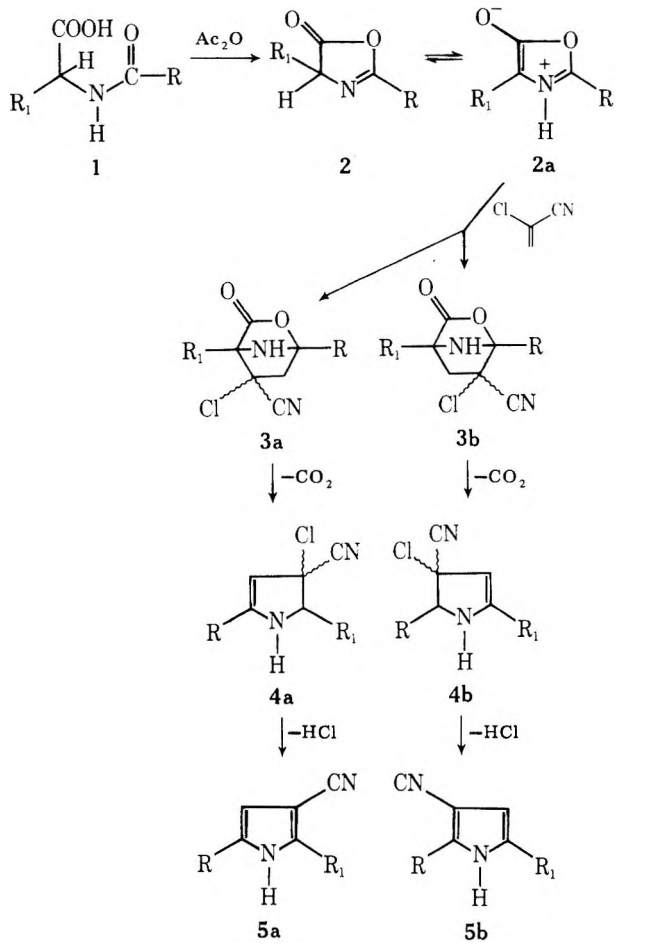
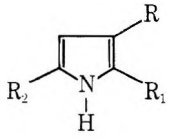


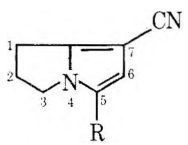
N-formyl-*C*-phenylglycine as starting material.

In spite of the interest in the pyrrole nucleus, only a few simple 3-cyanopyrroles have been previously prepared, usually by the use of ring synthesis, due to the difficulties associated with the selective substitution in the 3 position.[6]

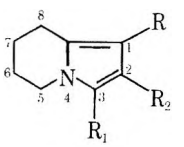
The regiospecificity found in some of these reactions was also found using ethyl propiolate[2,3] as a cyclodipolarophile and is caused by asymmetry of the dipole frontier orbitals produced by the substituents as calculated by Houk et al.[7] The NMR spectra of compounds **14, 16,** and **17** showed the presence of an AB quartet with $\Delta\nu$ values of 10, 7, and 10 Hz, respectively. Compound **16** was hydrolyzed to **17** and compared with an authentic sample.[8]



6, R = CN; R_1 = CH_3; R_2 = CH_3
7, R = CN; R_1 = CH_3; R_2 = $CH_2CH(CH_3)_2$
8, R = CN; R_1 = $CH_2CH(CH_3)_2$; R_2 = CH_3
9, R = CN; R_1 = C_6H_5; R_2 = H
10, R = CN; R_1 = CH_3; R_2 = C_6H_5
11, R = CN; R_1 = C_6H_5; R_2 = CH_3
12, R = CN; R_1 = C_6H_5; R_2 = C_6H_5
13, R = H; R_1 = C_6H_5; R_2 = CH_3



14, R = H
15, R = CH_3



16, R = CN; R_1 = H; R_2 = H
17, R = COOH; R_1 = H; R_2 = H
18, R = CN; R_1 = CH_3; R_2 = H
19, R = CN; R_1 = H; R_2 = Ac
20, R = CN; R_1 = CH_3; R_2 = Ac
21, R = CN; R_1 = CH_3; R_2 = COOH

During the preparation of compounds **16** and **18**, a small amount of 1-cyano-2-acetyl-5,6,7,8-tetrahydroindolizine (**19**) and 1-cyano-2-acetyl-3-methyl-5,6,7,8-tetrahydroindolizine (**20**), respectively, was isolated. Characterization of both **19** and **20** as 2-acetyl derivatives was made by their spectral data. The deshielding of the proton on C_3 in **19** and of the protons of the methyl on C_3 in **20** is due to the anisotropy of the carbonyl group. Furthermore, reaction of **20** with sodium hypoiodite gave iodoform and 1-cyano-2-carboxy-3-methyl-5,6,7,8-tetrahydroindolizine (**21**). Decarboxylation of 21 gave **18** in high yield.

The yield of 1-cyano-2-acetyl-5,6,7,8-tetrahydroindolizines (**19** and **20**) obtained is related to the concentration of acetic acid in the reaction media. When formation of the oxazolium 5-oxide is the only source of acetic acid, the concentration is low and the 2-acetyl derivatives are isolated in small yields, but if acetic acid is added to the media (see Experimental Section) compounds **19** and **20** become the major products of the reaction, emphasizing the importance of the purity of the acetic anhydride. Formation of **19** and **20** could not be detected after heating **16** or **18** with acetic anhydride pure or in mixtures with acetic acid;[9] therefore, the 2-acetyl derivatives must be produced during the reaction and not subsequently.

Experimental Section

Caution: *Hydrogen cyanide is evolved in small quantities during this reaction; it should be carried out with proper precautions.* Melting points were measured on a Kofler micro hot stage apparatus. Infrared spectra were recorded using a Perkin-Elmer 735 B spectrometer. NMR spectra were recorded on a Perkin-Elmer R 12 spectrometer. Microanalyses were performed by Mrs. Martha I. C. de Cassanello of this university. TLC and preparative thick-layer chromatography were performed on silica gel GF-254. Acetic anhydride was distilled before use. Mass spectra were obtained with an Atlas CH-7 spectrometer operating at an ionization potential of 70 eV.

2,5-Dimethyl-3-cyanopyrrole (6). A mixture of DL-alanine (178 mg, 2 mmol), 4 mL of acetic anhydride, and 1.8 mL (1.74 g, 20 mmol) of 2-chloroacrylonitrile was heated on a steam bath for 3 h. The excess reagents were evaporated in vacuo, and the residue was chromatographed through a silica gel column. The fraction eluted with methylene chloride gave 168 mg (70%) of **6**: mp 69–72 °C; IR ($CHCl_3$) 3400, 3250, 2900, 2200 cm^{-1}; NMR ($CDCl_3$) δ 5.98 (broad s, 1, proton on C_4, 2.32 and 2.18 (2s, 6, CH_3).

Anal. Calcd for $C_7H_8N_2$: C, 69.97; H, 6.71; N, 23.32. Found: C, 69.83; H, 6.61; N, 23.25.

2-Phenyl-3-cyanopyrrole (9). To a suspension of *N*-formyl-*C*-phenylglycine (358 mg, 2 mmol), prepared by us according to Shapiro and Newton,[10] in 4 mL of acetic anhydride was added 1.8 mL (1.74 g, 20 mmol) of 2-chloroacrylonitrile. The stirred suspension was heated at 90 °C (bath temperature) for 1.5 h. Solvent and excess dipolarophile were removed in vacuo, and the residue was chromatographed on 15 g of silica gel. The fraction eluted with chloroform gave 213 mg (64%) of **9**: mp 152–154 °C subl; IR (KBr) 3250, 2230, 1500, 1460, 760, 700 cm^{-1}; NMR ($CDCl_3$) δ 9.40–8.80 (s, 1, NH), 7.80–7.30 (m, 5, aromatic protons), 6.80 (m, 1, proton on C_5), 6.50 (m, 1, proton on C_4); NMR after D_2O exchange, 24 h) δ 7.80–7.30 (m, 5, aromatic protons), 6.80 (d, 1, J = 3 Hz, proton on C_5), 6.50 (d, 1, J = 3 Hz, proton on C_4).

Anal. Calcd for $C_{11}H_8N_2$: C, 78.57; H, 4.76; N, 16.67. Found: C, 78.50; H, 4.63; N, 16.65.

2-Methyl-5-phenyl-3-cyanopyrrole (10) and 2-Phenyl-5-methyl-3-cyanopyrrole (11). A solution of DL-α-phenylglycine (302 mg, 2 mmol), 2-chloroacrylonitrile (1.8 mL, 1.74 g, 20 mmol), and 4 mL of acetic anhydride was stirred and heated (80 °C) for 1 h. The solution was evaporated in vacuo, and the residue was purifed by a silica gel column. The fraction eluted with dichloromethane yielded 286 mg (80%) of a mixture of **10** and **11**: NMR ($CDCl_3$) δ 9.60–9.10 (s, 1, NH), 7.90–7.20 (m, aromatic protons). **10:** NMR 6.55 (d, 1, proton on C_4), 2.45 (s, 3, $-CCH_3$). **11:** NMR δ 6.20 (m, 1, proton on C_4), 2.30 (s, 3, $-CCH_3$). The isomer ratio of **10** to **11** was 1:2. From this mixture compound **11** was isolated: mp 149–150 °C; IR (KBr) 3400–2800 (broad), 2225, 1400 (strong) cm^{-1}.

Anal. Calcd for $C_{12}H_{10}N_2$: C, 79.12; H, 5.50; N, 15.38. Found: C, 78.95; H, 5.55; N, 15.30.

2-Methyl-5-phenyl-3-cyanopyrrole (10) and 2-Phenyl-5-methyl-3-cyanopyrrole (11) from *N*-Benzoylalanine. A mixture of **10** and **11** was obtained from *N*-benzoylalanine[11] under the same conditions described above for its preparation from DL-α-phenyl glycine (yield 70%).

2,5-Diphenyl-3-cyanopyrrole (12). Procedure A. A solution of α-benzamidophenylacetic acid[4] (225 mg, 1 mmol) in 0.16 mL of acetic anhydride, 2 mL of benzene, and 0.18 mL (174 mg, 2 mmol) of 2-chloroacrylonitrile was refluxed for 1.5 h. The solution was evaporated to dryness and the residue crystallized from benzene to give 190 mg (78%) of **12**: mp 228–230 °C (at 190 °C there is a change in the crystalline form) (lit.[12] mp 218.5–219.6 °C); IR (KBr) 3225, 3027, 2220, 1610, 1585, 1500, 800, 760, 680 cm^{-1}; NMR [$(CD_3)_2CO$] δ 8.60–8.25 (s, 1, NH), 7.90–7.20 (m, 10, aromatic protons), 6.90 (d, 1, proton on C_4).

Anal. Calcd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.50. Found: C, 83.20; H, 5.24; N, 11.35.

2,5-Diphenyl-3-cyanopyrrole (12). Procedure B. A solution of 2,4-diphenyl-Δ^2-oxazolin-5-one (237 mg, 1 mmol), prepared as described in the literature,[4] in 0.6 mL of xylene and 0.9 mL (880 mg, 10 mmol) of 2-chloroacrylonitrile was stirred for 45 min at a bath temperature at 100 °C. After cooling, 170 mg (70%) of **12** separated, mp 228–230 °C. The same reaction was carried out replacing xylene by 2 mL of benzene (80 °C, 1.5 h; 55% yield) or by 1.2 mL of DMF (45 °C, 1.5 h; 35% yield).

2-Phenyl-5-methylpyrrole (13). The crude mixture of **10** and **11** (150 mg) was saponified in 8 mL of boiling 40% NaOH solution in ethanol–water (1:1) for 24 h. The solution was diluted with water (10 mL), acidified with tartaric acid, and extracted with ether (3 × 10 mL). The ethereal extract was concentrated in vacuo and the residue sublimated at 60 °C (bath temperature), 0.08 torr, to give **13** in low yield. The melting point and mixture melting point with an authentic sample were 102–103 °C subl (lit.[13] 101 °C); IR (KBr) 3150, 3030, 1400 cm^{-1}.

7-Cyano-2,3-dihydro-1*H*-pyrrolizine (14). To a well-stirred solution of 190 mg (1.32 mmol) of *N*-formyl-L-proline[2] in 4 mL of acetic anhydride was added 0.45 mL (435 mg, 5 mmol) of 2-chloroacrylonitrile. The solution was heated at 80 °C for 24 h and evaporated, and the residue was chromatographed on 10 g of silica gel. The fraction eluted with chloroform gave 121 mg (70%) of **14**: mp 46–50 °C (methanol); IR (CCl_4) 3200 (broad), 2225 cm^{-1}; NMR ($CDCl_3$) δ 2.31–3.1 (m, 4, protons on C_1 and C_2), 3.95 (t, 2, C_3), 6.45 (AB quartet, 2, $\Delta\nu$ = 10 Hz, J = 3 Hz, olefinic protons).

Anal. Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.51; H, 5.90; N, 20.95.

5-Methyl-7-cyano-2,3-dihydro-1*H*-pyrrolizine (15). A solution of L-proline (115 mg, 1 mmol) in 4 mL of acetic anhydride and 0.9 mL (880 mg, 10 mmol) of 2-chloroacrylonitrile was heated at 80 °C for 24 h. Excess reagents were evaporated in vacuo, and the residue was chromatographed through a silica gel column. The fraction eluted with methylene chloride gave 95 mg (65%) of **15**: mp 58–62 °C; IR (CCl_4) 3200 (broad), 2225 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (s, 3, $-CCH_3$), 2.29–3.15 (m, 4, protons on C_1 and C_2), 3.87 (t, 2, protons on C_3), 6.10 (s, 1, olefinic proton).

Anal. Calcd for $C_9H_{10}N_2$: C, 73.97; H, 6.85; N, 19.18. Found: C, 73.85; H, 6.42; N, 18.92.

1-Cyano-5,6,7,8-tetrahydroindolizine (16) and 1-Cyano-2-acetyl-5,6,7,8-tetrahydroindolizine (19). A solution of *N*-formylpipecolic acid[3] (314 mg, 2 mmol) in 3 mL of acetic anhydride and 0.9 mL (880 mg, 10 mmol) of 2-chloroacrylonitrile was heated at 80 °C for 3 h. Excess reagents were evaporated in vacuo, and the residue was chromatographed on silica gel. The fraction eluted with benzene gave 224 mg (77%) of **16**: IR (CCl_4) 3100, 2990, 2225, 1565 cm^{-1}; NMR ($CDCl_3$) Δ 6.45 (AB quartet, 2, $\Delta\nu$ = 7 Hz, J = 3 Hz, olefinic protons), 3.95 (broad t, 2, protons on C_8), 2.90 (broad t, 2, protons on C_5), 1.90 (m, 4, protons on C_6 and C_7).

Anal. Calcd for $C_9H_{10}N_2$: C, 73.97; H, 6.85; N, 19.18. Found: C, 73.60; H, 7.20; N, 19.30.

The fraction eluted with benzene–chloroform (19:1) gave 54 mg (14%) of **19**: mp 105–106.5 °C; IR (KBr) 3100, 2950, 2925, 2225, 1660 cm^{-1}; NMR ($CDCl_3$) δ 7.12 (s, 1, olefinic proton), 4.35 (broad t, 2, protons on C_8), 2.91 (broad t, 2, protons on C_5), 2.37 (s, 3, CCH_3), 1.89 (m, 4, protons on C_6 and C_7); mass spectrum, m/e 188 (M^+).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.35; H, 6.61; N, 14.95.

1-Cyano-5,6,7,8-tetrahydroindolizine (16). The same reaction was carried out with a solution of *N*-formylpipecolic acid (314 mg, 2 mmol), acetic anhydride (3 mmol), 2-chloroacrylonitrile (1.8 mL, 1.74 g, 20 mmol), and 10 mL of methylene chloride stirred for 24 h at room temperature. Workup of the solution as previously described afforded 240 mg (82%) of **16** and a small quantity of **19** (detected by TLC).

5,6,7,8-Tetrahydroindolizine-1-carboxylic Acid (17). Alkaline Hydrolysis of 16. A 144-mg (1 mmol) sample of **16** in 4 mL of 1 N KOH solution in 2:1 methanol–water was heated for 4 h at reflux. Methanol was evaporated in vacuo and the solution acidified with HCl to pH 1. The precipitate was filtered and dried, giving 40 mg (25%) of **17**. The melting point and mixture melting point with an authentic sample were 151–153 °C dec (lit.[8] 151–153 °C); IR (KBr) 3600–3200 (broad), 2950, 1640 cm^{-1}; NMR ($CDCl_3$) δ 11.00 (broad s, 1, exchangeable with D_2O, $-COOH$), 6.68 (AB quartet, 2, $\Delta\nu$ = 10 Hz, J = 3 Hz, olefinic protons), 4.08 (broad t, 2, protons on C_8), 3.23 (broad t, 2, protons on C_5), 1.85 (m, 4, protons on C_6 and C_7).

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.45; H, 6.66; N, 8.48. Found: C, 65.30; H, 6.64; N, 8.40.

1-Cyano-3-methyl-5,6,7,8-tetrahydroindolizine (18) and 1-Cyano-2-acetyl-3-methyl-5,6,7,8-tetrahydroindolizine (20). A solution of pipecolic acid (387 mg, 3 mmol), 1.35 mL (1.3 g, 15 mmol) of 2-chloroacrylonitrile and 4 mL of acetic anhydride was refluxed and stirred for 2 h. Excess reagents were evaporated in vacuo, and the residue was dissolved in benzene and chromatographed on 20 g of silica gel. The fraction eluted with benzene–chloroform (1:1) gave 334 mg (70%) of **18**: mp 61–65 °C; IR (KBr) 3100, 2910, 2225, 1530 cm^{-1}; NMR ($CDCl_3$) δ 6.00 (s, 1, olefinic proton), 3.72 (broad t, 2, protons on C_8), 2.85 (broad t, 2, protons on C_5), 2.10 (s, 3, CCH_3), 1.85 (m, 4, protons on C_6 and C_7).

Anal. Calcd for $C_{10}H_{12}N_2$: C, 75.00; H, 7.50; N, 17.50. Found: C, 75.40; H, 7.94; N, 17.35.

The fraction eluted with benzene–chloroform (1:2) gave 30 mg (5%) of **20**: mp 166–169 °C; IR (KBr) 3100, 2950, 2925, 1660, 1540 cm^{-1}; NMR ($CDCl_3$) δ 3.80 (broad t, 2, protons on C_8), 2.90 (broad t, 2, protons on C_5), 2.55 and 2.45 (2s, 3, CCH_3), 1.95 (m, 4, protons on C_6 and C_7); mass spectrum m/e 202 (M^+).

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.35; H, 7.03; N, 13.50.

Preparation of 18 and 20 with Acetic Acid. The reaction was carried out as above, with the addition of 1 mL of acetic acid. The fraction eluted with benzene–chloroform (1:1) gave 150 mg (31%) of **18** and that eluted with benzene–chloroform (1:2) gave 280 mg (46%) of **20**.

1-Cyano-2-carboxy-3-methyl-5,6,7,8-tetrahydroindolizine (21). To a solution of **20** (74 mg, 0.37 mmol) in 2 mL of *p*-dioxane was added 4 mL of a 32% NaOH solution, and a iodine–iodide solution (316 mg of I_2, 632 mg of KI, 2.6 mL of water) was added dropwise with stirring. Water (10 mL) was added, the precipitated iodoform was centrifuged, and the solution was extracted (2 × 5 mL) with ether. After acidification (6 N HCl), the iodine was reduced with sodium bisulfite. The acid was extracted with ether (3 × 5 mL) and the ether evaporated to give 64 mg (84%) of **21**: mp 220–224 °C dec; IR (KBr) 3300 (broad), 2950, 2225, 1650, 1580, 1540 cm^{-1}; NMR (NaDO in D_2O) δ 4.2 (broad t, 2, protons on C_8), 3.30 (broad t, 2, protons on C_5) 2.60 (s, 3, $-CCH_3$), 2.15 (m, 4, protons on C_6 and C_7).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.30; H, 6.25; N, 13.60

Preparation of 18 from 21. The acid **21** was heated at 230 °C (bath temperature), 16 torr, giving **18** in 80% yield.

2-Phenyloxazolium 5-Oxide (2; R = C_6H_5, R_1 = H). A solution of 179 mg (1 mmol) of hippuric acid in 3 mL of acetic anhydride was refluxed for 30 min. The solution was evaporated to dryness, and the residue was chromatographed on 10 g of silica gel. The fraction eluted with chloroform gave 50 mg of **2** (R = C_6H_5, R_1 = H): NMR ($CDCl_3$) δ 8.00 (m, 2 H, protons on C_2' and C_6'), 7.45 (m, 3, protons on C_3', C_4' and C_5'), 4.40 (s, 2, protons on C_4). This compound is unstable and cannot be analyzed. By treating the oil with water, hippuric acid was isolated.

Registry No.—**2**, 30216-01-4; **6**, 26187-29-1; **9**, 52179-70-1; **10**, 67421-64-1; **11**, 67421-65-2; **12**, 67421-66-3; **13**, 3042-21-5; **14**, 67421-67-4; **15**, 67421-68-5; **16**, 67421-69-6; **17**, 61009-82-3; **18**, 67421-70-9; **19**, 67421-71-0; **20**, 67421-72-1; **21**, 67421-73-2; DL-alanine, 302-72-7; 2-chloroacrylonitrile, 920-37-6; *N*-formyl-C-phenylglycine, 67421-74-3; DL-α-phenylglycine, 2835-06-5; α-benzamidophenylacetic acid, 29670-63-1; 2,4-diphenyl-Δ^2-oxazolin-5-one, 28687-81-2; *N*-formyl-L-proline, 13200-83-4; L-proline, 147-85-3; *N*-formylpipecolic acid, 54966-20-0; pipecolic acid, 535-75-1; hippuric acid, 495-69-2.

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Synthesis of 2-Aryl-*cis*-3a,6a-octahydropyrrolo[2,3-*b*]pyrroles

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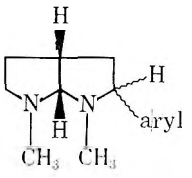
Received March 13, 1978

The synthesis of a series of 2-aryl-*cis*-3a,6a-octahydropyrrolo[2,3-*b*]pyrroles (**1**) via the reductive cyclization of 3-(2-aryl-2-aminoethyl)-1-methyl-2-pyrrolidones (**4**) using diisobutylaluminum hydride is described. The diastereomers of **1** were separated and structures assigned on the basis of NMR spectra. The products resulting from the reductive trapping of the ring opened iminium species **7** with sodium cyanoborohydride generated from **1** in acid solution are also identified.

In our search for new bioactive structures, the octahydropyrrolo[2,3-*b*]pyrrole ring system bearing an aryl substituent in the 2 position (**1**) appeared as a promising candidate. This



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relatively simple ring system has not previously been reported, although it does occur fused to an aromatic ring in the physostigmine-type alkaloids.

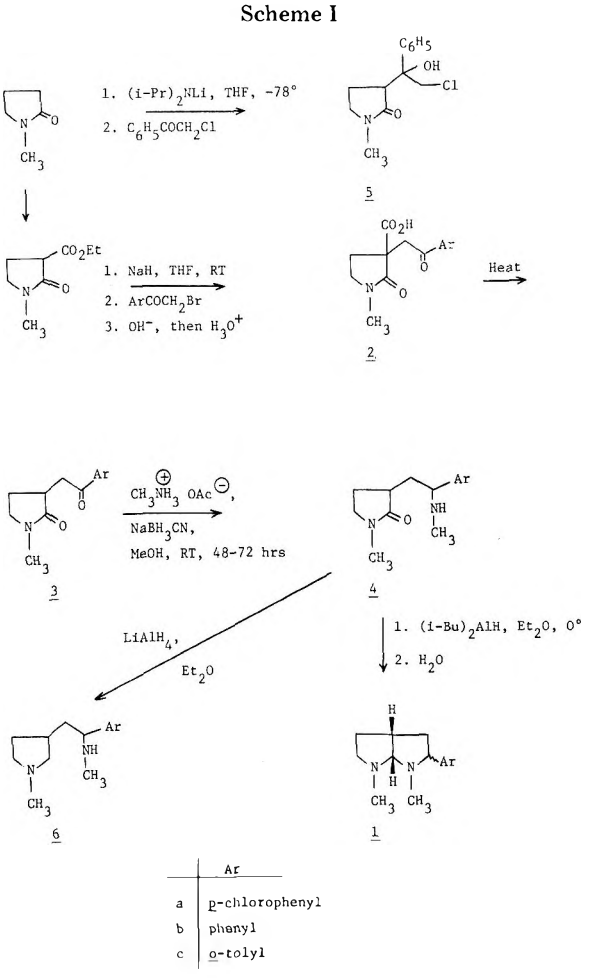
N-Methyl-2-pyrrolidone was chosen as the starting material for the synthesis of **1** since it was hoped that anion formation followed by alkylation with a phenacyl halide would lead to ketone **2**. Surprisingly, the only product which could be isolated from the alkylation reaction was the chloro alcohol **5** in 20–25% yield.

We then decided to alkylate the enolate of *N*-methyl-3-carbethoxy-2-pyrolidinone[1] since it was felt that this anion would be less reactive with respect to carbonyl addition. In the event, the desired alkylation proceeded cleanly and was followed by hydrolysis to afford the carboxylic acids **2**. Decarboxylation then gave the ketolactam **3**. The ketolactam **3** was then aminated using sodium cyanoborohydride[2] and methylammonium acetate to afford good yields of **4**.

Although the literature of the physostigmine alkaloids reports ring closures of the desired type (**4** to **1**) using lithium aluminum hydride,[3] in our hands this reagent gave only poor yields of **1**. The primary product from this reaction was the mixture of diastereomers **6**. Changing the order of addition, temperature, or using clarified solutions of lithium aluminum hydride in place of a suspension had little or no effect on the results. However, the use of diisobutylaluminum hydride, which has found utility in the generation of enamines from lactams,[4] afforded **1** in good yield accompanied by small amounts of **6** (Scheme I).

Chromatography of the reaction mixture on alumina cleanly separated the C-2 epimers of **1**. Table I lists examples of

Scheme I



	Ar
a	*p*-chlorophenyl
b	phenyl
c	*o*-tolyl

compounds prepared by this route. The yields are believed to represent the distribution of products from the reaction mixture since the epimers of **1** were found to be stable to base and to rechromatography on alumina. However, the dissolution of either isomer in acid and reisolation gave the same mixture of isomers observed in the reaction before chromatography, determined in both cases by NMR spectrometry.

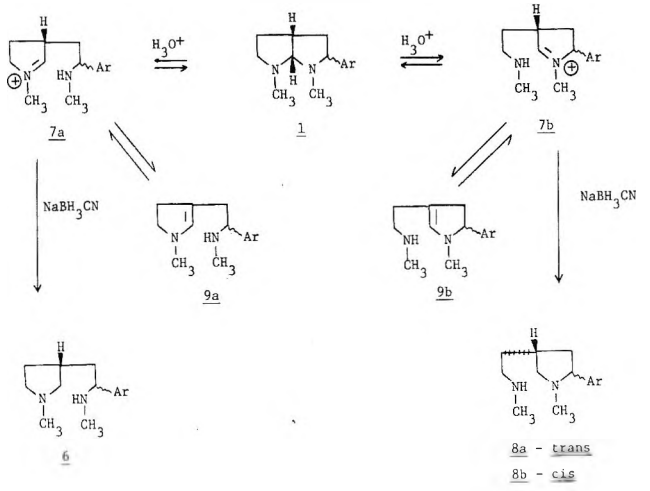
0022-3263/78/1943-4276$01.00/0

Table I. Product Distribution of 2-Aryl-*cis*-3a,6a-octahydropyrrolo[2,3-*b*]pyrroles

compd 1, Ar =	isomer[a] A	registry no.	δ_{H6a}	B	registry no.	δ_{H6a}
a. *p*-chlorophenyl	mp 69–70 °C (27%)	67505-89-9	3.9, J = 7 Hz	mp 56–57 °C (36%)	67529-75-3	3.6, J = 7 Hz
b. phenyl	mp 46–47 °C (29%)	67505-90-2	3.9, J = 7 Hz	bp 74–77 °C (0.01 mm) (42%)	67529-76-4	3.6, J = 7 Hz
c. *o*-tolyl	bp 79–81 °C (0.02 mm) (19%)	67505-91-3	3.9, J = 7 Hz	mp 48–50 °C (42%)	67529-77-5	3.6, J = 7 Hz

[a] Isomer A is the compound which eluted first from the column and isomer B eluted second. Numbers in parentheses are yields after purification.

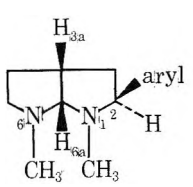
Scheme II



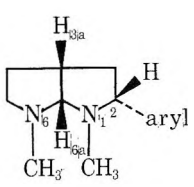
Because each of the epimers of 1 was readily equilibrated to the original mixture of diastereomers, we thought it would be desirable to determine how the ring system opened and reclosed. We also felt that this information could have biological significance. A priori, in acidic solution two modes of ring opening are possible to give the iminium species **7a** and **7b**. Both **7a** and **7b** could be trapped by sodium cyanoborohydride under the conditions of the reaction to give the amines **6** and/or **8**. Furthermore, both **6** and **8** could be produced as a mixture of diastereomers from a given epimer of **1** if equilibration through enamines **9a** and **9b** were to be faster than reduction. However, choice of a suitable pH for the trapping experiment could be expected to minimize enamine formation.

In the event, each epimer of **1b** gave rise to a single diastereomeric product when added to a solution of sodium cyanoborohydride initially at pH 4. If, however, each epimer of **1b** was first dissolved in acid (pH 4) and after several minutes treated with sodium cyanoborohydride, then a mixture of diastereomeric reduction products could be detected. Identification of the reduction product was straightforward since comparison of the NMR spectral data of the reduction product with that of the diastereomeric mixture **6** prepared by an independent route (vide supra) confirmed that **8** was indeed the compound isolated, no trace of **6** being detected (Scheme II). The stereochemistry of **8** will be commented on below.

Assignment of Structures. The two possible cis diastereomers of **1** are shown below (only one component of each racemic mixture is shown for clarity):



exo-1



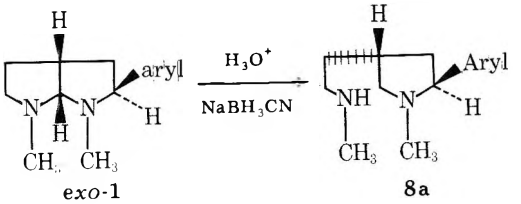
endo-1

The cis ring fusion is assigned on the basis of what is known concerning *cis*- and *trans*-bicyclo[3.3.0]octanes. On the basis of combustion data,[5,6] the cis hydrocarbon is ca. 6 kcal/mol more stable than the trans isomer. We expect that this preference should carry over to the octahydropyrrolo[2,3-*b*]pyrrole system. Further, our observed coupling constants for the bridgehead protons ($J_{3a,6a}$ = 7 Hz) are indicative of a cis ring fusion. A coupling constant of the same order (6.2 Hz) was reported[7] for the *cis*-tetrahydrofuro[2,3-*b*]furan[8] moiety present in clerodendrin A. Similar J values (6.0–6.7 Hz) have also been reported[9] for the bridgehead protons in *cis*-hexahydrofuro[2,3-*b*]imidazolones. Unfortunately, there do not appear to be any reports in the literature where the coupling constants between bridgehead protons in *trans*-[3.3.0]bicyclic systems have been observed, thus making a direct comparison impossible.

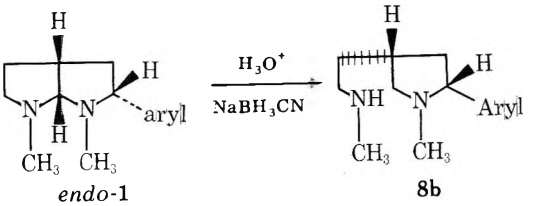
Examination of Dreiding models suggests that the N_1–CH_3 and the aryl substituent should prefer a trans relationship in both isomers. This observation is supported by recent NMR evidence[10] that the *N*-methyl group and pyridine ring of nicotine are trans in the most stable conformation. For both isomers examination of models predicts a pseudoequatorial assignment for N_6–CH_3. This leads to the conclusion that the 6a proton will be cis to N_6–CH_3 in both isomers. The 6a proton, however, is cis to N_1–CH_3 in the endo isomer and trans to N_1–CH_3 in the exo isomer when both isomers are in their most stable conformation.

Breuer and Melumad[11] have shown that protons attached to the α position of *N*-methylpyrrolidines are shielded when situated cis to the *N*-methyl group. Thus, for our case, the endo isomer should show more shielding of the 6a proton than the exo isomer due to the relationship between the 6a proton and N_1–CH_3. A distinct difference is observed, the 6a proton being more shielded in isomer B than in A (Table I). Therefore, on the basis of NMR data, isomer A can be assigned as *exo*-**1** and isomer B as *endo*-**1**.

Each epimer of **1** was shown to give a single diastereomeric product (**8**) upon reduction in acid solution. The structures of these products can now be assigned based on the structure of the starting epimer of **1** and are shown below (one component of the racemic mixture is shown for clarity):



exo-**1** **8a**



endo-**1** **8b**

Experimental Section

NMR spectra were run on a Varian T-60 spectrometer using $CDCl_3$ as solvent with tetramethylsilane as internal standard. All melting and boiling points are uncorrected. Elemental analyses were done by the analytical staff of MSDRL under the direction of Mr. Jack Gilbert. Tetrahydrofuran (THF) was distilled from sodium–benzophenone and ether was used from freshly opened cans.

Reaction between *N*-Methylpyrrolidone Anion and Phenacyl Chloride. To a cold (−60 °C) solution of lithium diisopropylamide (50 mmol) in THF–hexane (1:1, 50 mL) was added a solution of *N*-methyl-2-pyrrolidone (4.95 g, 50 mmol) in THF (25 mL) during 30 min followed by an additional 15 min of stirring. Phenacyl chloride (7.75 g, 50 mmol) in THF (125 mL) was added to the cold anion solution during 1 h followed by stirring at −60 °C for 4 h. The cooling bath was then removed and the reaction mixture allowed to reach room temperature after which it was poured into saturated sodium chloride solution (100 mL). The organic phase was separated, washed with brine, and dried over anhydrous Na_2SO_4. Filtration followed by concentration of the filtrate on the rotary evaporator left a yellow oil. Dissolution of the oil in ether followed by standing yielded a white crystalline solid (2.20 g). Recrystallization from CH_2Cl_2–ether gave white needles: mp 126–127 °C; NMR ($CDCl_3$) δ 7.30 (5 H), 4.56 (d, 1 H, J = 13 Hz), 4.47 (s, 1 H), 4.01 (d, 1 H, J = 13 Hz), 3.07 (m, 3 H), 2.73 (s, 3 H); MS, M^+, 235; base peak, 204.

Anal. Calcd for $C_{13}H_{16}ClNO_2$: C, 61.54; H, 6.32; N, 5.52. Found: C, 61.63; H, 6.18; N, 5.43.

1-Methyl-3-phenacyl-2-pyrrolidone-3-carboxylic Acid (2b). In a 1 L three-neck flask equipped with a dropping funnel, nitrogen bubbler, and an efficient mechanical stirrer was placed sodium hydride (2.75 g, 57% mineral oil dispersion, 65 mmol) which was then washed several times with pentane to remove oil and finally was suspended in THF (200 mL). 1-Methyl-3-carbethoxy-2-pyrrolidone[1] (10.0 g, 58.5 mmol) in THF (200 mL) was added during 1 h and the mixture stirred an additional 1.5 h, all at room temperature. Phenacyl bromide (11.7 g, 58.5 mmol) in THF (100 mL) was added during 1 h at room temperature and the resulting mixture stirred for 18–20 h. Water (10 mL) was then added and the mixture filtered. The filtrate was dried over $MgSO_4$ and concentrated to give the ketoester as a thick oil which was hydrolyzed directly to the ketoacid.

The crude ketoester (50 mmol) was dissolved in methanol (50 mL) and treated with a solution of sodium hydroxide (4.2 g) in water (100 mL). The mixture was kept at 60 °C for 30 min, then cooled to room temperature, diluted with water (150 mL), and washed with CH_2Cl_2. The aqueous phase was acidified with concentrated hydrochloric acid and the precipitated carboxylic acid was filtered and dried. The dried acid was triturated with pentane to remove yellow impurities. The acid was recrystallized from pentane–CH_2Cl_2: yield 9.53 g, 73%; mp 158–159 °C dec.

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.39; H, 5.74; N, 5.36. Found: C, 64.50; H, 5.96; N, 5.24.

1-Methyl-3-(*p*-chlorophenacyl)-2-pyrrolidone-3-carboxylic Acid (2a): 90% yield; mp 154–155 °C dec.

Anal. Calcd for $C_{14}H_{14}ClNO_4$: C, 56.88; H, 4.73; N, 4.73. Found: C, 56.99; H, 4.76; N, 4.67.

1-Methyl-3-(o-methylphenacyl)-2-pyrrolidone-3-carboxylic acid (2c): 86% yield; mp 143–144 °C.

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.47; H, 6.18; N, 5.09. Found: C, 65.47; H, 6.18; N, 4.99.

1-Methyl-3-phenacyl-2-pyrrolidone (3b). The acid **2b** (8.00 g, 30.6 mmol) was placed in a round-bottom flask and heated at 165 °C until CO_2 evolution ceased. The reaction mixture was cooled and the ketolactam **3b** purified by bulb-to-bulb distillation: bp 150 °C (50 μm); 5.78 g, 87%; NMR δ 8.0 (m, 2 H), 7.45 (m, 3 H), 3.0–4.0 (m, 5 H), 2.85 (s, 3 H), 1.5–2.9 (m, 2 H).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.90; H, 6.90; N, 6.45. Found: C, 71.63; H, 6.92; N, 6.53.

1-Methyl-3-(*p*-chlorophenacyl)-2-pyrrolidone (3a): 88% yield; mp 76–77 °C (ether–pentane); NMR δ 7.7 (4 H), 3.0–4.0 (m, 5 H), 2.85 (s, 3 H), 1.5–2.9 (m, 2 H).

Anal. Calcd for $C_{13}H_{14}ClNO_2$: C, 62.06; H, 5.56; N, 5.56. Found: C, 62.00; H, 5.25; N, 5.16.

1-Methyl-3-(*o*-methylphenacyl)-2-pyrrolidone (3c): 96% yield; isolated as a thick oil after chromatography on silica gel with 95:5 $CHCl_3$–2-propanol; NMR δ 7.2–7.8 (4 H), 3.0–4.0 (m, 5 H), 2.85 (s, 3 H), 2.50 (s, 3 H), 1.5–2.9 (m, 2 H).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.55; H, 7.41; N, 5.97.

3-(2-Phenyl-2-*N*-methylaminoethyl)-1-methyl-2-pyrrolidone (4b). To a solution of methylammonium acetate, prepared by mixing ice cold solutions of 6 M methanolic methylamine (45 mL, 0.27 mol) and acetic acid (16.2 g, 0.27 mol) in methanol (25 mL), was added **3b** (8.68 g, 40 mmol) and sodium cyanoborohydride (1.70 g, 27 mmol). The solution was stirred at room temperature for 48 h after which it was reduced in volume by ca. 50% on the rotary evaporator. Water (150 mL) was added and the pH adjusted to 1 by the addition of concentrated hydrochloric acid (**Caution:** HCN). After the evolution of gas ceased, the reaction mixture was washed with CH_2Cl_2. The aqueous layer was made basic and extracted with CH_2Cl_2. Drying (K_2CO_3) and concentration of the organic extracts afforded **4b** as a pale yellow oil: 8.16 g, 94%; NMR δ 7.3 (s, 5 H), 3.6 (m, 1 H), 3.2 (m, 2 H), 2.8 (s, 3 H), 2.25 (s, 3 H), 1.3–2.4 (m, 6 H).

3-(2-*p*-Chlorophenyl-2-*N*-methylaminoethyl)-1-methyl-2-pyrrolidone (4a): 87% yield; NMR δ 7.2 (s, 4 H), 3.7 (m, 1 H), 3.2 (m, 2 H), 2.8 (s, 3 H), 2.2 (s, 3 H), 1.2–2.5 (m, 6 H).

3-(2-*o*-Tolyl-2-*N*-methylaminoethyl)-1-methyl-2-pyrrolidone (4c): 75% yield; NMR δ 7.3 (m, 4 H), 4.1 (t, 1 H), 3.2 (q, 2 H), 2.8 (s, 3 H), 2.4 (s, 3 H), 2.25 (s, 3 H), 1.2–2.4 (m, 6 H).

1,6-Dimethyl-2-phenyl-*cis*-3a,6a-octahydropyrrolo[2,3-*b*]pyrrole (1b). To a 1 L three-neck flask equipped with a dropping funnel, thermometer, and a reflux condenser carrying a nitrogen bubbler was added a solution of **4b** (7.74 g, 33 mmol) in anhydrous ether (300 mL) which was then cooled to 0 °C with an ice–salt bath. The dropping funnel was charged with a heptane solution of diisobutylaluminum hydride (56 mL, 1.26 M, 70 mmol) diluted with ether (200 mL) which was added dropwise over a period of 3 h. After the addition was complete, the cooling bath was removed and the reaction mixture stirred an additional 20 h. The reaction was quenched by the very cautious addition of water (5 mL) during 20 min followed by 15% sodium hydroxide solution (5 mL). After a few minutes of additional stirring the mixture was filtered, the filter cake was washed with ether, and the combined filtrate and washings were concentrated. The crude product was chromatographed on neutral activity III Woelm alumina using 7:3 hexane–ether as eluent. Fractions were collected and examined by TLC for products. See Table I for mp/bp's and yields.

1,6-Dimethyl-2-phenyl-*cis*-3a,6a-octahydropyrrolo[2,3-*b*]pyrrole (1b). Isomer A (exo): NMR δ 7.3 (s, 5 H), 3.9 (d, 1 H), 3.7 (q, 1 H), 2.9 (m, 2 H), 2.5 (s, 3 H), 2.2 (s, 3 H), 1.4–2.2 (m, 5 H).

Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.79; H, 9.25; N, 12.95. Found: C, 78.00; H, 9.50; N, 12.93.

Isomer B (endo): NMR δ 7.3 (m, 5 H), 3.6 (d, 1 H), 3.4 (q, 1 H), 2.8 (m, 2 H), 2.5 (s, 3 H), 2.2 (s, 3 H), 1.2–2.4 (m, 5 H).

Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.79; H, 9.25; N, 12.95. Found: C, 78.04; H, 9.28; N, 12.86.

1,6-Dimethyl-2-*p*-chlorophenyl-*cis*-3a,6a-octahydropyrrolo[2,3-*b*]pyrrole (1a). Isomer A (exo): NMR δ 7.2 (s, 4 H), 3.9 (d, 1 H), 3.6 (q, 1 H), 2.9 (m, 2 H), 2.45 (s, 3 H), 2.2 (s, 3 H), 1.3–2.4 (m, 5 H).

Anal. Calcd for $C_{14}H_{19}ClN_2$: C, 67.09; H, 7.58; N, 11.17. Found: C, 66.97; H, 7.75; N, 11.01.

Isomer B (endo): NMR δ 7.3 (s, 4 H), 3.6 (d, 1 H), 3.4 (q, 1 H), 2.8 (m, 2 H), 2.5 (s, 3 H), 2.2 (s, 3 H), 1.1–2.4 (m, 5 H).

Anal. Calcd for $C_{14}H_{19}ClN_2$: C, 67.09; H, 7.58; N, 11.17. Found: C, 67.12; H, 7.77; N, 11.11.

1,6-Dimethyl-2-*o*-tolyl-*cis*-3a,6a-octahydropyrrolo[2,3-*b*]pyrrole (1c). Isomer A (exo): NMR δ 7.3 (m, 4 H), 3.9 (d, 1 H), 3.8–4.2 (m, 1 H), 3.0 (m, 2 H), 2.5 (s, 3 H), 2.4 (s, 3 H), 2.3 (s, 3 H), 1.2–2.3 (m, 5 H).

Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.28; H, 9.56; N, 12.16. Found: C, 78.58; H, 9.74; N, 12.16.

Isomer B (endo): NMR δ 7.7 (m, 1 H), 7.2 (m, 3 H), 3.6 (d, 1 H), 3.5–3.9 (m, 1 H), 2.8 (m, 2 H), 2.5 (s, 3 H), 2.3 (s, 3 H), 2.2 (s, 3 H), 1.0–2.5 (m, 5 H).

Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.28; H, 9.56; N, 12.16. Found: C, 78.36; H, 9.28; N, 12.00.

Attempted Ring Closure of 4b with Lithium Aluminum Hydride. A solution of **4b** (1.15 g, 4.9 mmol) in ether (25 mL) was added to a cold (5 °C) solution of lithium aluminum hydride (10.5 mmol) in ether (25 mL) during 15 min. The reaction was brought to room temperature and stirred an additional 20 h, then quenched, filtered, and concentrated to a clear gum (0.95 g). Chromatography on alumina prep plates (8:2 ether–hexane) afforded 3 identifiable products, **1b** (isomer A), 85 mg, 8% yield; **1b** (isomer B), 119 mg, 11% yield; 1-methyl-3-(2-phenyl-2-methylaminoethyl)pyrrolidine (**6**), 570 mg, 54% yield, as a mixture of diastereomers. NMR ($CDCl_3$, diastereomeric mixture): N–CH_3 signals, δ 2.21, 2.24, 2.28.

Anal. Calcd for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16; N, 12.83. Found: C, 77.16; H, 10.03; N, 13.05.

Reductive Ring Opening of 1b (Isomer A, exo) and 1b (Isomer B, endo) with Sodium Cyanoborohydride. Sodium cyanoborohydride (50 mg, 0.8 mmol) was dissolved in aqueous acetic acid (2.0 mL),

prepared by adding sodium acetate (1.50 g) to 1 M acetic acid (100 mL). The substrate (50 mg, 0.23 mmol) was then added followed by methanol (10 drops) to give a homogeneous mixture. After 3 h at room temperature, 15% sodium hydroxide (1 mL) was added followed by extraction with CH_2Cl_2 (2 × 3 mL) after which the extracts were dried and concentrated. The products were isolated as oils.

***trans*-1-Methyl-2-phenyl-4-(2-methylaminoethyl)pyrrolidine (8a):** bp 58–60 °C (0.005 mm) (bulb to bulb); NMR δ 7.2 (s, 5 H), 3.3 (d of d, 1 H), 3.1 (t, 1 H), 2.4 (s, 3 H), 2.2 (s, 3 H), 1.4–2.8 (m, 8 H), 1.1 (s, 1 H). Anal. Calcd for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16; N, 12.83. Found: C, 77.12; H, 10.42; N, 12.80.

***cis*-1-Methyl-2-phenyl-4-(2-*N*-methylaminoethyl)pyrrolidine (8b):** bp 55 °C (0.005 mm) (bulb to bulb); NMR δ 7.1 (s, 5 H), 2.8–3.3 (m, 2 H), 2.4 (s, 3 H), 2.1 (s, 3 H), 1.2–2.8 (m, 9 H). Anal. Calcd for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16; N, 12.83. Found: C, 76.88; H, 10.38; N, 12.87.

Registry No.—**2a,** 67505-92-4; **2b,** 67505-93-5; **2c,** 67505-94-6; **3a,** 67505-95-7; **3b,** 67505-96-8; **3c,** 67505-97-9; **4a,** 67505-98-0; **4b,** 67505-99-1; **4c,** 67506-00-7; **6b** isomer 1, 67506-01-8; **6b** isomer 2, 67506-02-9; **8a** (Ar = Ph), 67506-03-0; **8b** (Ar = Ph), 67506-04-1; 1-methyl-3-(2-chloro-1-hydroxy-1-phenylethyl)-2-pyrrolidone, 67506-05-2; *N*-methylpyrrolidone anion, 67506-06-3; *N*-methyl-2-pyrrolidone, 872-50-4; phenacyl chloride, 532-27-4; phenacyl bromide, 70-11-1; 1-methyl-3-carbethoxy-2-pyrrolidone, 30932-85-5; *p*-chlorophenacyl bromide, 536-38-9; o-methylphenacyl bromide, 51012-65-8; methylammonium acetate, 6998-30-7.

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2,2,6,6-Tetramethyl-4-oxo-1-(1,1-diphenylethoxy)piperidine: Synthesis and Thermal Stability[1]

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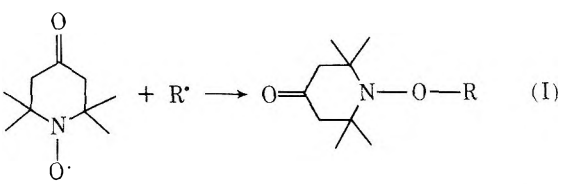
Received February 1, 1978

2,2,6,6-Tetramethyl-4-oxopiperidinyl-1-oxy reacts with the 1,1-diphenylethyl radical to give 2,2,6,6-tetramethyl-4-oxo-1-(1,1-diphenylethoxy)piperidine. In solution this ether appears to exist in equilibrium with the parent radicals with $\Delta H°_2 \sim -21.4$ kcal mol^{-1} and $\Delta S°_2 \sim -36$ cal deg^{-1} mol^{-1}. In degassed solution there is an irreversible first-order decay of this *O*-alkyl hydroxylamine to give 1,1-diphenylethylene and 1-hydroxy-2,2,6,6-tetramethylpiperidin-4-one with $\log (k_3/s^{-1}) = 14.8 - 6425/T$. Decomposition is significantly faster when the solution contains dissolved oxygen because 1,1-diphenylethyl radicals are rapidly converted to 1,1-diphenylethylperoxy radicals and $\log (k_{-2}/s^{-1}) = 14.8 - 5354/T$. The strength of the O–C bond in 2,2,6,6-tetramethyl-4-oxo-1-(1,1-diphenylethoxy)piperidine must be ~21 kcal mol^{-1}. 2,2,6,6-Tetramethyl-4-oxo-1-cumyloxypiperidine can be prepared from 2,2,6,6-tetramethyl-4-oxopiperidinyl-1-oxy and cumyl radicals and it is significantly more stable in degassed and oxygen-containing solutions than the *O*-1,1-diphenylethyl analogue.

Introduction

Cyclic di-*tert*-alkylnitroxides such as 2,2,6,6-tetramethyl-4-oxopiperidinyl-1-oxy, TMPO·, are efficient inhibitors for autoxidation because they can successfully compete with molecular oxygen for chain propagating alkyl radicals.[3,4] The mechanism for inhibition by this class of antioxidants involves a simple radical–radical combination reaction to give a stable ether,[3] e.g.



(I)

The stability of these ethers is pertinent to the use of nitroxides as antioxidants[3,4] and as radical scavengers in the determination of rates of initiation for homolytic reactions.[5] In this context we have recently discovered that several of these ethers, e.g., 2,2,6,6-tetramethyl-4-oxo-1-(1,1-diphenylethoxy)piperidine, are thermally unstable. This discovery prompted us to embark on a kinetic and product study of the decomposition of this *O*-alkyl hydroxylamine and the closely related *O*-cumyl derivative and the results of this work are reported here.

Results and Discussion

During an attempt to measure the rate of production of 1,1-diphenylethyl from thermolysis of 2,2,3,3-tetraphenylbutane (3.3 mM) in oxygen-free *tert*-butylbenzene at 50 °C by monitoring the disappearance of 2,2,6,6-tetramethyl-4-oxopiperidinyl-1-oxy, TMPO· (initial concentration = 0.031 mM), we found (i) that the rate of nitroxide disappearance did not follow the expected zero-order kinetics, (ii) that the initial rate of nitroxide disappearance was about one-half the expected rate based on the known rate constant for decomposition of TPB[6] and the efficiency of radical production,[7] and (iii) that the nitroxide reached an apparent steady-state concentration of 0.002 mM (see Figure 1).

Now it is generally accepted that reactive alkyl radicals add rapidly to nitroxides to give *O*-alkyl hydroxylamines.[3,9–12] The reaction of 1,1-diphenylethyl with TMPO· would, therefore, be expected to give 2,2,6,6-tetramethyl-4-oxo-1-(1,1-diphenylethoxy)piperidine, $TMPOR_1$, and in the presence of excess TPB all the nitroxide should have been consumed.

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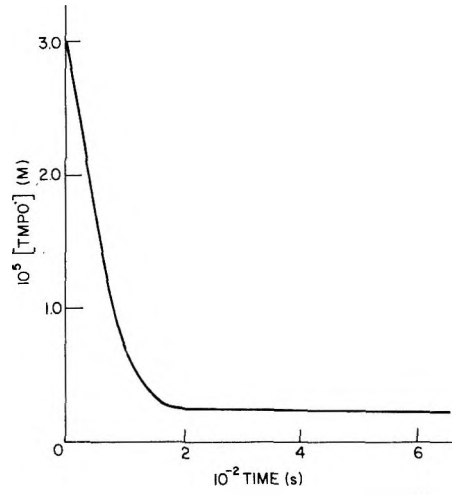
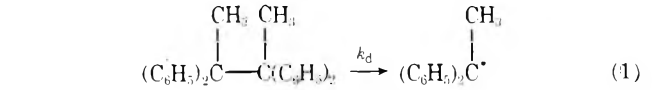
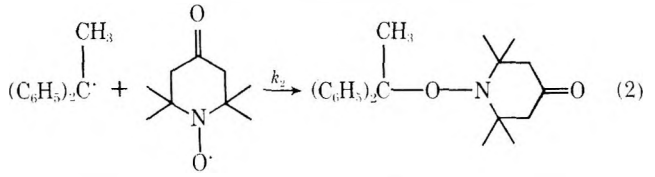
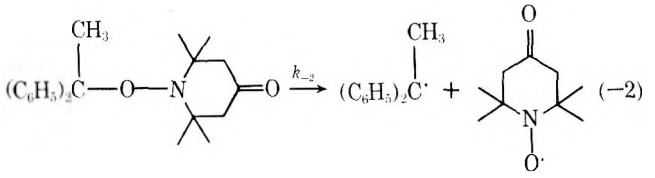


Figure 1. The concentration of TMPO· as a function of time in the presence of TPB (0.0033 M) in oxygen-free *tert*-butylbenzene at 50 °C.


(1)


(2)

We also discovered that the nitroxide concentration could be increased by raising the temperature and decreased by lowering the temperature with no apparent loss in nitroxide concentration, behavior that suggests that reaction 2 is reversible.[8]


(−2)

Over a period of several hours the nitroxide concentration did not increase or decrease irreversibly and the radical concentrations given in Table I were measured. Above 100 °C increasing the temperature had no effect on [TMPO·] and if it was assumed that $[TMPO\cdot]_{max}$ was equal to the concentration of $TMPOR_1$, the equilibrium constants K_2, given in the last column of Table I, could be calculated from

$$K_2 = \frac{[TMPOR_1]}{[(C_6H_5)_2\dot{C}CH_3][TMPO\cdot]} = \frac{[TMPOR_1]}{[TMPO\cdot]^2}$$

A van't Hoff plot of ln K_2 against $1/T$ yielded thermodynamic parameters $\Delta H°_2 = -21.4 \pm 1.5$ kcal mol^{-1} and $\Delta S°_2 = -36 \pm 4$ cal deg^{-1} mol^{-1}.

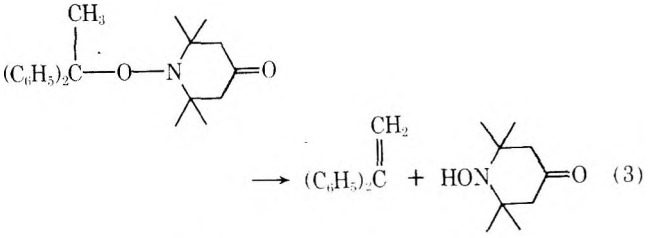
In aliphatic solvents, such as cyclohexane, the situation was somewhat different in that $-d[TMPO\cdot]/dt$ was independent of the radical concentration until about 90% of the radical had been consumed and was equal to twice the rate of decomposition of TPB. The rate then slowed down rapidly and stopped to leave a residual radical concentration equal to about 1% of the original concentration. This residual nitroxide concentration could be increased or decreased by raising or lowering the temperature between 100 and 20 °C.

An NMR study of the decomposition of TPB (0.053 M) in the presence of TMPO· (0.1 M) in $CDCl_3$ at 50 °C revealed

Table I. Steady-State Concentrations of 2,2,6,6-Tetramethyl-4-oxopiperidinyl-1-oxy in *tert*-Butylbenzene as a Function of Temperature after the Decomposition of Tetraphenylbutane (0.47 mM) in the Presence of TMPO· (0.031 mM) at 50 °C

temp, °C	10^6 [TMPO·], M	10^{-6} K_2, M^{-1}
38	0.81	8.2
60	1.5	2.4
80	3.4	0.47
70	2.4	0.94
90	4.4	0.28
60	1.7	1.87
50	1.0	5.4
38	0.74	9.86
90	4.26	0.30
100	5.0	0.22
112	5.4	
122	5.2	

that TPB disappeared exponentially with a first-order rate constant k_d equal, within experimental error, to the literature value,[6] and $TMPOR_1$ was formed initially at close to twice the rate of disappearance of TPB. The ether did, however, reach a maximum concentration of ca. 0.07 M while 1,1-diphenylethylene and 1-hydroxy-2,2,6,6-tetramethylpiperidin-4-one, TMPOH, became major reaction products. On allowing air into the system the hydroxylamine was *slowly* oxidized to TMPO· ($\tau_{1/2} \sim 12$ h at 30 °C).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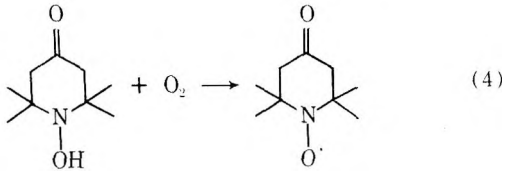

(4)

Decomposition of $TMPOR_1$. 2,2,6,6-Tetramethyl-4-oxo-1-(1,1-diphenylethoxy)piperidine was isolated and found to decompose in degassed $CDCl_3$ at 51.5 °C to give quantitative yields of 1-hydroxy-2,2,6,6-tetramethylpiperidin-4-one and 1,1-diphenylethylene. There was no evidence for the formation of 1,1-diphenylethane. The kinetics of the decomposition at this temperature strictly obeyed the rate expressions

$$\frac{-d[TMPOR_1]}{dt} = \frac{d[TMPOH]}{dt} = \frac{d[(C_6H_5)_2C{=}CH_2]}{dt} = k_3[TMPOR_1]$$

with $k_3 = 1.1 \times 10^{-5}$ s^{-1}. Values of k_3 were obtained from 50 to 90 °C and an Arrhenius plot yielded the activation parameters $E_3 = 29.4 \pm 0.8$ kcal mol^{-1} and log (A_3/s^{-1}) = 14.8 ± 0.5 (Table II). Decomposition in C_6D_6 appeared slightly slower with $k_3 = 5.6 \times 10^{-6}$ s^{-1} at 51.5 °C.

Decomposition of $TMPOR_1$ in the Presence of Oxygen. $TMPOR_1$ was very unstable in solvents containing dissolved oxygen and had a half-life of 43 s in oxygen-saturated chlorobenzene at 50 °C. A kinetic study of this oxidation revealed that the rate of oxygen absorption was proportional to the

Table II. Rate Constants for Thermal Decomposition of 2,2,6,6-Tetramethyl-4-oxo-1-(1,1-diphenylethoxy)-piperidine

solvent	temp, °C	$10^4 k_3/s^{-1}$
$CDCl_3$	51.5	0.11
	62.5	0.4
	74.2	1.9
	91.3	15
C_6D_6	51.5	0.056

concentration of $TMPOR_1$ to the first power and equal to the rate of formation of TMPO·, i.e.

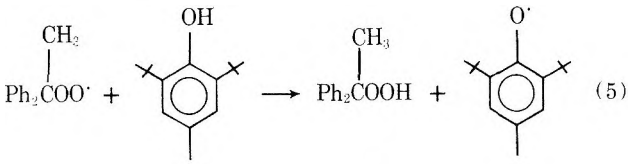
$$\frac{-d[O_2]}{dt} = \frac{d[TMPO\cdot]}{dt} = k_{-2}[TMPOR_1]$$

where k_{-2} is the first-order rate constant for decomposition of $TMPOR_1$. Values of k_{-2} were determined from 20 to 50 °C (Table III) and obey the Arrhenius equation

$$\log (k_{-2}/s^{-1}) = 14.8 \pm 0.6 - (5348 \pm 180)/T$$

Atmospheric oxidation gave almost quantitative yields of TMPO· along with somewhat lower yields of acetophenone, benzophenone, and 1,1-diphenylethanol (Table III). These ketones and alcohol suggest the intermediacy of 1,1-diphenylethylperoxy radicals and/or 1,1-diphenylethoxy radicals although it should be noted that the yields were significantly greater than were obtained from decomposition of tetraphenylbutane in the presence of oxygen.[13,14]

Rates of decomposition in the presence of oxygen were not influenced by the free-radical scavenger 2,6-di-*tert*-butyl-4-methylphenol. In this case the principal products were TMPO·, 1,1-diphenylethyl hydroperoxide, and 2,6-di-*tert*-butyl-4-methyl-4-(1,1-diphenylethylperoxy)-2,5-cyclohexadien-1-one, proving that $TMPOR_1$ does indeed decompose at the C–O bond to give TMPO· and 1,1-diphenylethyl. In the presence of oxygen the latter radicals were rapidly converted into 1,1-diphenylethylperoxy, which in the presence of a good hydrogen atom donor such as 2,6-di-*tert*-butyl-4-methylphenol was reduced to the hydroperoxide and trapped by the phenoxy radical according to reactions 5 and 6.[15]



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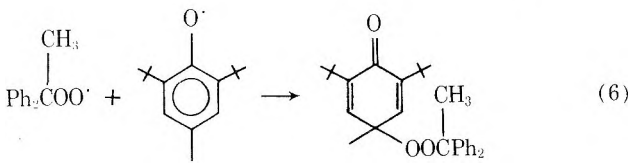
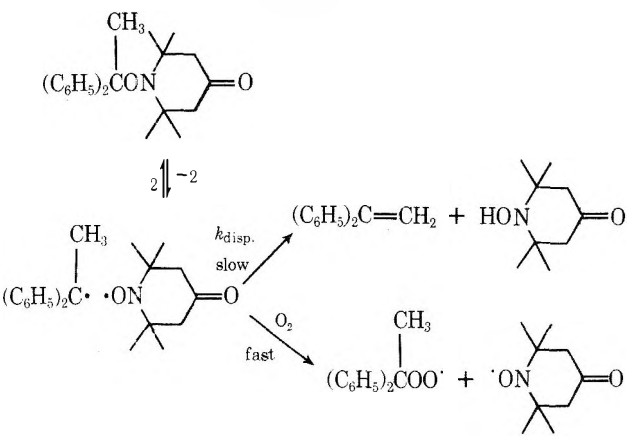


(6)

Scheme I



2,2,6,6-Tetramethyl-4-oxo-1-cumyloxypiperidine. The stability of *O*-alkyl hydroxylamines is quite sensitive to the nature of the alkyl moiety attached to oxygen as indicated by the fact that 2,2,6,6-tetramethyl-4-oxo-1-cumyloxypiperidine ($TMPOR_2$) is very much more stable than the *O*-1,1-diphenylethyl derivative. Thus the rate of disappearance of TMPO· in degassed *tert*-butylbenzene was equal to the rate of generation of cumyl radicals from thermolysis of azocumene at 50 °C. Furthermore, the reaction was zero order with respect to TMPO· and the nitroxide was completely destroyed by excess azocumene. An NMR study of the decomposition of $TMPOR_2$ indicated that it had a half-life of 1.3×10^4 s at 100 °C (cf. $\tau_{1/2}$ = 460 s for $TMPOR_1$ at 91.3 °C).

Decomposition of $TMPOR_2$ was much faster in the presence of oxygen. For instance, a 0.012 M solution in chlorobenzene absorbed oxygen (0.011 M) with an initial rate of 1.0×10^{-6} M s^{-1} at 60 °C to give TMPO· (0.012 M), acetophenone (0.006 M), and α-cumyl alcohol (0.005 M) as major reaction products. This ratio of acetophenone to cumyl alcohol (1.2) is similar to the ratio obtained from the decomposition of azocumene in oxygen saturated chlorobenzene[14] and is indicative of the intermediacy of cumylperoxy radicals.

The rate of oxidation of $TMPOR_2$ was not influenced by 2,6-di-*tert*-butyl-4-methylphenol. In this case α-cumyl hydroperoxide and 2,6-di-*tert*-butyl-4-methyl-4-cumylperoxy-2,5-cyclohexadien-1-one were the major reaction products.

Conclusions

It would appear that the kinetics and products for decomposition of 2,2,6,6-tetramethyl-4-oxo-1-(1,1-diphenylethoxy)piperidine in the absence and presence of oxygen can best be rationalized on the basis of the mechanism given in Scheme I.

The thermodynamic parameters for the equilibrium process (2) have been estimated to be $\Delta H°_2 = -21.4$ kcal mol^{-1} and $\Delta S°_2 = -36$ cal deg^{-1} mol^{-1}, which are not unreasonable when

Table III. Product and Kinetic Data for Decomposition of $TMPOR_1$ in Oxygen-Saturated Chlorobenzene

temp, °C	$[TMPOR_1]$, mM	$[O_2]_{abs}$,[a] mM	[TMPO·], mM	$[C_6H_5COCH_3]$, mM	$[(C_6H_5)_2CO]$, mM	$[(C_6H_5)_2CCH_3OH]$, mM	$10^3 k_{-2}$, s^{-1}
21	6.0	6.0	5.4	2.1	1.3	2.2	0.37
30	6.3	6.4	5.5	1.0	0.15	1.1	1.5
30	6.0[b]	4.1	3.6	—	—	1.8[c]	1.6
40	6.2	5.3	5.2	1.3	0.3	1.2	5.4
50	3.4	1.7	2.7	0.94	0.3	1.2	16
50	5.5[d]	12	—	1.5	0.2	0.3	—

[a] Concentrations of oxygen absorbed at the higher temperatures are low probably because of oxidation before the sample reached reaction temperature. [b] In the presence of 2,6-di-*tert*-butyl-4-methylphenol (0.09 M). [c] After reduction with Ph_3P (8 mM). [d] TPB (i.e., R_1–R_1).

compared with parameters for other radical–metastable dimer equilibria.[8,16-19] It should be pointed out, however, that the steady-state concentration of TMPO· may be influenced by reaction of TMPOH with 1,1-diphenylethyl or other reactive radicals in the system.

Decomposition is very fast in the presence of oxygen because 1,1-diphenylethyl radicals are efficiently scavenged by oxygen. The Arrhenius parameters for oxidation should be equal to the parameters for reaction −2; i.e., $\log (A_{-2}/s^{-1}) = 14.8$ and $E_{-2} = 24.5$ kcal mol^{-1}. Now the thermodynamic parameters for 2 indicate that

$$\log \frac{k_2}{k_{-2}} = \log \frac{A_2}{A_{-2}} + \frac{E_{-2} - E_2}{2.303RT} = -7.87 + \frac{21\,400}{2.303RT}$$

from which we can calculate that $\log (k_2/M^{-1}\ s^{-1}) = 6.93 - 3100/2.303RT$. This expression gives a rate constant for combination of TMPO· with 1,1-diphenylethyl = 5×10^4 M^{-1} s^{-1} at 30 °C, which is rather low when compared with the rate constants of ~10^8 M^{-1} s^{-1} reported by Ingold and Schmid[12] for addition of alkyl radicals to nitroxides. There may, however, be considerable steric hindrance to addition of 1,1-diphenylethyl to TMPO·.

The enthalpy change for reaction 2 (21.4 kcal mol^{-1}) is equivalent to the strength of the O–C bond in $TMPOR_1$ and is consistent with the activation energy for oxidation (24.5 kcal mol^{-1}) and a small activation energy for the radical recombination reaction.

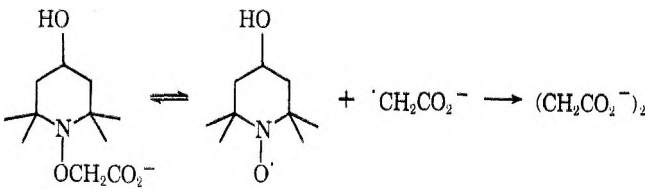
2,2,6,6-Tetramethyl-4-oxo-1-cumyloxypiperidine is ca. 10^{-3} times as reactive to oxidation at 60 °C as the *O*-1,1-diphenylethyl derivative, which means that the entropies of activation for reaction −2 must be very different because $\Delta\Delta H^{\ddagger}_{-2}$ should not be greater than about 2 kcal mol^{-1}.

Rate constants for the decomposition of $TMPOR_1$ in the absence of oxygen are described by $\log (k_3/s^{-1}) = 14.8 - 6425/T$, which according to Scheme I is equivalent to $k_{disp.}/K_2$. We can therefore calculate $\log (k_{disp.}/M^{-1}\ s^{-1}) = 6.9 - 1746/T$, which implies that the disproportionation reaction between TMPO· and 1,1-diphenylethyl is much slower than combination because of a substantial activation energy ($E_{disp.} = 8$ kcal mol^{-1}).

Finally, we would like to comment on three reports in the literature concerning the chemistry of *O*-alkyl derivatives of TMPO· and related compounds. First we could find no evidence for reaction of alkylperoxy radicals ROO· with TMPOR via an S_H2 mechanism[20] to give TMPO· and ROOR.

Secondly, Hook and Saville[21] found that TMPO· had no effect on the amount of oxygen absorbed by TPB in the presence of 2,6-di-*tert*-butyl-4-methylphenol and concluded that the nitroxide, even in 50-fold excess, did not compete with oxygen for the 1,1-diphenylethyl radical. It is, however, clear from our work that even if reaction of TMPO· with 1,1-diphenylethyl in the presence of oxygen is very efficient, almost quantitative amounts of oxygen would be absorbed because of oxidation of $TMPOR_1$.

Thirdly, Sheats and McConnell[22] have noted that 2,2,6,6-tetramethyl-4-hydroxy-1-carboxymethoxypiperidine slowly decomposes to the nitroxide. In this case the carboxymethyl radicals probably undergo self-reaction.



Experimental Section

Materials. 2,2,3,3-Tetraphenylbutane (TPB) was generously provided by Dr. L. R. Mahoney (Ford Motor Co., Dearborn). Azocumene was prepared by the method of Bartlett and Nelsen.[23] 2,2,6,6-Tetramethyl-4-oxopiperidinyl-1-oxy was purified by sublimation: mp 40 °C.

2,2,6,6-Tetramethyl-4-oxo-1-(1,1-diphenylethoxy)piperidine. A mixture of 2,2,6,6-tetramethyl-4-oxopiperidinyl-1-oxy (0.138 g, 0.8 mmol) and 2,2,3,3-tetraphenylbutane (0.165 g, 0.45 mmol) was dissolved in hexane, thoroughly degassed, and heated for 10 h at 60 °C. The final reaction mixture was colorless and a white crystalline product crystallized out of solution upon cooling. These crystals were recrystallized from deoxygenated hexane: mp 112–114 °C; ^{1}H NMR δ (in CCl_4) 0.89 (6 H, ax CH_3), 1.29 (6 H, eq CH_3), 2.15 (3 H, CH_3C, A_2B_2 quartet, J = 12 Hz), 2.66, 2.47, 2.20, 1.97 (4 H, br m), 7–7.6 (10 H, $C(C_6H_5)_2$). Anal. Calcd for $C_{23}H_{29}O_2N$: C, 78.63; H, 8.26; N, 3.99. Found: C, 77.7; H, 8.06; N, 3.91. Interestingly catalytic reduction gave the hydroxylamine and 1,1-diphenylethane rather than the amine and carbinol.[3]

2,2,6,6-Tetramethyl-4-oxo-1-cumyloxypiperidine. A mixture of 2,2,6,6-tetramethyl-4-oxopiperidinyl-1-oxy (0.0414 g, 0.24 mmol) and azocumene (0.0363 g, 0.14 mmol) was heated at 60 °C in deoxygenated hexane for 10 h. A crude crystalline material was obtained when the solvent was removed. Recrystallization from oxygen-free hexane gave an analytically pure sample: mp 93–94 °C; ^{1}H NMR δ (in CCl_4) 0.99 (6 H, ax CH_3), 1.14 (6 H, eq CH_3), 1.67 (6 H, $(CH_3)_2CO$, A_2B_2 quartet, J = 12 Hz), 1.9, 2.1, 2.33, 2.53 (4 H, br m), 7–7.6 (5 H, $C(C_6H_5)$). Anal. Calcd for $C_{18}H_{27}O_2N$: C, 74.74; H, 9.34; N, 4.84. Found: C, 74.81; H, 9.53; N, 4.97. Both $TMPOR_1$ and $TMPOR_2$ contained traces of TMPO· which we were not able to remove by repeated recrystallization.

Kinetic Procedures. Rates of disappearance and appearance and absolute concentrations of TMPO· were determined by EPR spectroscopic techniques. Autoxidations were conducted in the automatic gas absorption apparatus described previously.[24] In a typical experiment $TMPOR_1$ (0.011 g, 6.3 mmol) in chlorobenzene (4 mL) was shaken with oxygen (720 torr) at 30 °C. The initial rate of oxygen absorption was 7.1×10^{-6} M s^{-1} and 6.4 mmol was absorbed. The yields of the principal reaction products were determined by standard GLC techniques using a Varian 2800 chromatograph equipped with a 12-ft 12% OV-101 on Chromosorb W column.

Rates of decomposition of $TMPOR_1$ and rates of formation of 1,1-diphenylethylene and TMPOH in the absence of oxygen were determined by NMR spectroscopy with a Varian XL 100 spectrometer. Relative concentrations of $TMPOR_1$, TMPOH, and $(C_6H_5)_2C{=}CH_2$ were determined from absorptions at δ 0.887, 1.223, 5.457, respectively. Oxidation of TMPOH to TMPO· was followed by ESR spectroscopy.

The products from oxidation of $TMPOR_1$ in the presence of 2,6-di-*tert*-butyl-4-methylphenol were identified and their approximate yields estimated by means of thin-layer chromatography on silica gel (Baker-flex 1B2-F). Authentic 1,1-diphenylethyl hydroperoxide and 2,6-di-*tert*-butyl-4-methyl-4-(1,1-diphenylethylperoxy)cyclohexa-1,4-dien-1-one were prepared from tetraphenylbutane by the method of Bickel and Kooyman.[15]

Acknowledgment. We would like to thank a referee for helpful comments and Mr. J. Bornais for performing the NMR experiments.

Registry No.—2,2,6,6-Tetramethyl-4-oxo-1-(1,1-diphenylethoxy)piperidine, 67478-83-5; 2,2,6,6-tetramethyl-4-oxopiperidinyl-1-oxy, 2896-70-0; 2,2,3,3-tetraphenylbutane, 10496-82-9; 2,2,6,6-tetramethyl-4-oxo-1-cumyloxypiperidine, 67478-84-6; azocumene, 5676-79-9.

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Metal–Ammonia Reduction and Reductive Alkylation of Polycyclic Aromatic Compounds: Nature of the Anionic Intermediates

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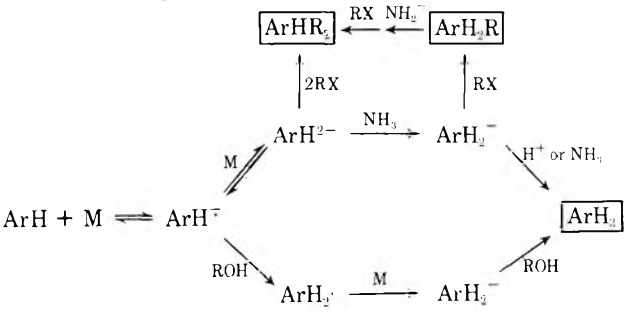
Received July 28, 1978

A scheme of metal–ammonia reduction is presented which categorizes the behavior of aromatic and polynuclear aromatic compounds according to the nature of the intermediate radical anions, monoanions, and dianions. It is found that the outcome of many reductions and reductive alkylations is, in fact, a result of secondary reactions that occur during the quenching process, and a dramatic difference is found in many cases by the introduction of an inverse quench procedure. That is, the ammonia solution is poured into the quenching agent, which may be a proton source (water, saturated ammonium chloride) or an alkyl halide solution. The results of a series of such experiments are presented and indicate that common hydrocarbons such as anthracene and naphthalene react with Li or Na in ammonia to form dianions which are quickly protonated by ammonia to form dianions which are quickly protonated by ammonia to form monoanions. The alkylation of these monoanions is studied under a variety of conditions, and both monoalkylation and dialkylation (via a subsequent reaction) can occur. This behavior is contrasted to dibenzocyclooctatetraene, which is shown to form a dianion resistant to protonation by ammonia.

The reduction of polycyclic aromatic compounds by solutions of alkali metals in liquid ammonia has received considerable attention,[1] and a wide variety of experimental procedures have been developed. For example, the metals employed are usually lithium or sodium, but also include potassium and calcium. Protonating agents range from moderately acidic, such as ammonium chloride and water, to weakly acidic, like ethanol and 2-methyl-2-propanol. A wide range of cosolvents is also employed (usually but not always ethers), and iron salts are sometimes added to limit reduction. In addition, polynuclear compounds often lead to stable anionic intermediates which can be alkylated by suitable alkylating agents, but once again the results are variable, leading to the incorporation of zero to three alkyl groups depending on the compound reduced as well as reaction conditions such as choice of metal and/or cosolvent.

Thus, it has become generally concluded that this reaction must be carried out with meticulous care, since it has been shown that the selection of reaction conditions can afford a wide range of results. For example, the reduction of anthracene[1c] can result in dihydro, tetrahydro, or further reduced products depending on the level of alkali metal employed, cosolvents, and the presence of iron impurities. To our surprise, however, we have found that anthracene can be reduced quantitatively to 9,10-dihydroanthracene (in 10 min) with no prior purification of ammonia or cosolvents, and with a wide variation in alkali metal concentration as well as stoichiometry (1.2–5 equiv of metal). These results were accomplished by inverse quenching (i.e., hydrocarbon/metal/ammonia solution poured into a large volume of water) and, although not applicable to all polycyclic hydrocarbons, should be useful in many cases. Of greater importance, however, are the mechanistic implications of this result and the fact that the quenching procedure is by far the most significant factor in this particular reaction.

Scheme I



Thus, a general understanding of the overall reaction mechanism should allow for predictions concerning which experimental variables should be of greatest importance. With this in mind, we would like to present Scheme I for reduction and reductive alkylation and catagorize aromatic compounds according to their particular position within this system.

a. Only Radical Anions Generated. In this case, the initial equilibrium usually lies to the left and $ArH^{-}\cdot$ is the only anionic species present. In order to effect reduction, a proton source must be added to shift the equilibrium by protonation of the radical anion, which then accepts another electron, resulting in a monoanion which is protonated to form the reduced product, ArH_3. It is important that the proton source not be too strong, or metal will be destroyed rapidly, shifting the equilibrium back to the left. Alcohols are most commonly used for this purpose, and this method represents the procedure known as the Birch reduction. Monobenzenoid compounds most frequently fall into this category, and reductive alkylation is not possible due to the low nucleophilicity of radical anions and the much more rapid electron-transfer reaction.[4]

b. Dianions Resistant to Protonation by Ammonia. In

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the case where dianions (ArH^{2-}) are formed which are resistant to protonation by ammonia (probably very few polyaromatic compounds fit into this category; see discussion below), simple reduction is best accomplished by rapid quench with a strong proton source such as ammonium chloride or water. It should be noted, however, that in this case alcohols *should not be used* as a quenching agent (a common error), since the metal is not rapidly consumed under these conditions, and any excess metal/ammonia/alcohol can reduce ArH_3 as it is formed, leading to overreduction of the original compound (the exception is when ArH_3 is nonreactive). Alkylation is expected to give $ArHR_2$ *provided* $ArHR^-$ is not protonated by ammonia before the second alkylation takes place.

c. Monoanions Resistant to Protonation by Ammonia. In this case we envision the major anionic species to be the monoanion (ArH_2^-) resulting from protonation of the more basic dianion (ArH^{2-}) by ammonia, and probably a number of polyaromatic compounds fall into this category. Methods of reduction in these cases are identical with those discussed above for dianion formation for the same reasons. Although reductive alkylation may provide good yields of ArH_2R under certain conditions, $ArHR_2$ as well as ArR_3 (see below) can also be formed and have often complicated reaction mixtures in the past.

d. Neutral Compounds Produced by Complete Protonation by Ammonia. In some cases, the monoanions produced by protonation of dianions by ammonia may be sufficiently basic themselves so as also to be protonated by the ammonia. This can lead to two results: (1) the compound produced (ArH_3) is resistant to further reduction; or (2) the compound may be reduced by any of the pathways described previously. It is the latter case in which removal of surplus metal becomes important, and we would like to examine the use of ferric chloride to limit reduction in light of Scheme I.

For example, although the first efficient reduction of anthracene to 9,10-dihydroanthracene involved the use of added ferric chloride with extended reaction periods,[1c] the importance of rapid quenching has since been realized for several polycyclic systems.[5] It is evident from alkylation behavior (see below) that anthracene forms monoanions[6] (Scheme I) and that overreduction occurs during the quenching process. That is, excess metal[7] reacts with the product as it is formed, and the iron simply consumes this surplus metal.[8] However, the use of ferric chloride involves relatively long reaction times and is unnecessary in cases where monoanions are formed. As mentioned above, anthracene can be reduced quantitatively under almost any conditions provided the quenching process is rapid with a strong proton source (H_2O, NH_4Cl). With small quantities (1–2 g) and a controlled amount of metal (1.3 equiv) this can be done conveniently by simply adding saturated ammonium chloride as fast as possible, whereas with larger amounts (e.g., 10 g) quantitative results can still be obtained by pouring the ammonia solution into a large volume of saturated ammonium chloride. In either case, the anions are protonated and excess metal is destroyed at such a rate as to make overreduction impossible.

The use of iron is necessary in some cases, however, and according to Scheme I it is evident that surplus metal will be an important factor when the product ArH_3 is generated by protonation from ammonia (i.e., metal not yet quenched) and is *itself* reducible. A notable example of this situation is found

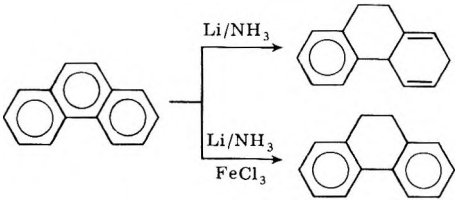


Table I. Metal–Ammonia Reduction of Naphthalene[a]

metal	temp, °C	quench[b]	1,2,3,4-tetrahydronaphthalene[c]	1,4-dihydronaphthalene[c]	naphthalene[c]
Na	−33	normal	17	83	
Na	−33	inverse	18	72	10
Na	−78	normal	2	98[d]	
Li	−78	normal	14	81	5
Li	−33	inverse	55	40	5

[a] Metal added to naphthalene in NH_3/ether (2:1), and reaction stirred for ~15 min. [b] Either excess aqueous ammonium chloride solution added rapidly (normal), or ammonia solution poured into excess ammonium chloride (inverse). [c] By GLC on a 6 ft × 1/8 in W-98 (silicon) column, corroborated by relative NMR integrations. [d] Examination on a 4; 15% Carbowax column indicated a very small shoulder, and (coupled with NMR) this suggests the presence of the 1,2-dihydro isomer (1–2%).

with the reduction of phenanthrene,[9] which proceeds smoothly to the tetrahydro stage with adequate metal concentration, but can be limited to the formation of 9,10-dihydrophenanthrene by the use of less metal and added ferric chloride.

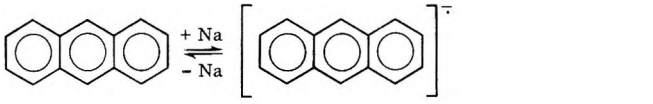
Another case of single-stage reduction that deserves special attention is naphthalene. Quite to our surprise, although a considerable amount of work has been reported on the reduction of naphthalene derivatives,[1c] a perusal of the literature has not uncovered an efficient synthesis of 1,4-dihydronaphthalene by metal/ammonia reduction of the parent hydrocarbon. As it turns out, the metal/ammonia reduction of naphthalene is quite sensitive to reaction conditions as is indicated by the data in Table I. Although reduction is essentially quantitative with the use of sodium metal at −78 °C followed by a *rapid* quench with ammonium chloride solution, the use of lithium metal results in significant overreduction. Since overreduction occurs even with an inverse quench procedure, we conclude that naphthalene leads to a monoanion according to Scheme I, which itself undergoes significant protonation by ammonia at either higher temperatures, or when lithium is the counterion. These results seem reasonable, however, since radical anions formed from lithium are more easily protonated than those from sodium, and the more easily protonated tight ion pairs are expected to be more abundant at higher temperatures.[4]

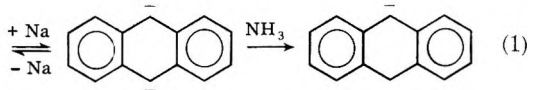
Reductive Alkylation. The formation of stable dianions from the reaction of anthracene and other polycyclic hydrocarbons with alkali metals in liquid ammonia had been accepted for over 30 years in accordance with Wooster's rule[1b] (see also ref 8 and references therein), and the presence of such intermediates seemed to be confirmed by the fact that dialkyl derivatives are produced by the addition of alkyl halides to alkali metal solutions of these hydrocarbons in anhydrous ammonia.[1,9] However, it has since been recognized[5] that dialkylated products could also arise by alkylation of a monoanion followed by reaction with amide (formed from protonation of the dianion by ammonia) to generate a second monoanion, which is in turn alkylated.[11]

$$ArH_2^- \xrightarrow{RX} ArH_2R \xrightarrow{NH_2^-} ArHR^- \xrightarrow{RX} ArHR_2$$

Harvey et al. concluded that this is indeed the case with biphenyl[5] and suggested that this process should be examined for anthracene as well as other polynuclear systems. They also suggested that in the reduction of anthracene, dianions are indeed formed and are protonated rapidly in the case of lithium or calcium, but more slowly with sodium. Our results, however, indicate that protonation is rapid with both lithium

and sodium, and that both systems result in essentially irreversible monoanion formation. This can be demonstrated in the following manner. Equation 1 depicts our proposal that the anthracene radical anion accepts a second electron, resulting in the reversible formation of a dianion. However, we





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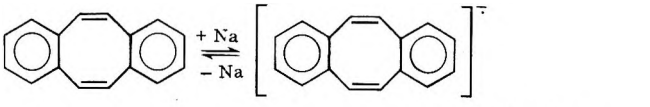
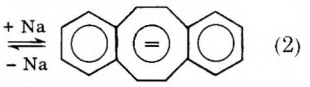
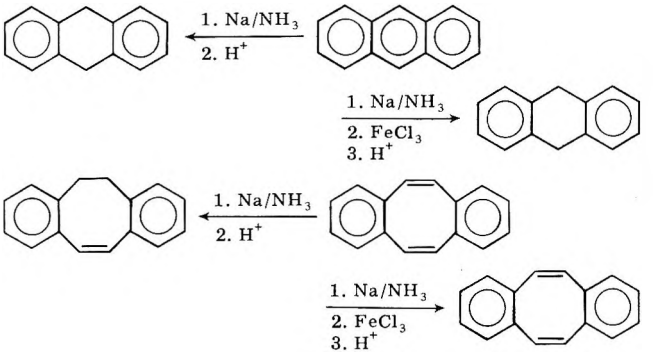




(2)

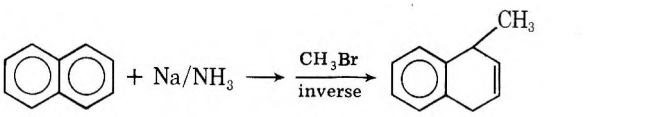
$$Na + NH_3 + FeCl_3 \longrightarrow NaNH_2 + H_2 \quad (3)$$

suggest that this dianion is rapidly protonated by ammonia to form a monoanion and amide ion. In an effort to detect this chemically, we sought a model system for comparison that would form a stabilized dianion. Hence, we selected *sym*-dibenzocyclooctatetraene, since the addition of two electrons (eq 2) would result in an aromatic dianion which we felt may be resistant to protonation by ammonia. Thus, the validity of eq 1 and 2 can be tested by taking into account the effect of added iron salts. As indicated in eq 3, ferric chloride catalyzes the reaction of sodium with ammonia (resulting in amide and hydrogen), which effectively removes the metal from metal–ammonia solutions. It is expected that removal of metal (i.e., $FeCl_3$ addition) from the *sym*-dibenzocyclooctatetraene dianion solution would shift the equilibrium back to the hydrocarbon (it is well established that dianions exist in equilibrium with their radical anions[4a]), whereas, according to eq 1, there would be no effect in the anthracene case. In fact,



when metal–ammonia solutions of both hydrocarbons are generated, protonation of aliquots after 10 min gives reduction products in both cases. However, if ferric chloride is then added and the reactions quenched with water after 2 h, anthracene still gives the reduction product exclusively, whereas *sym*-dibenzocyclooctatetraene is *itself* recovered from the latter reaction.

A similar contrast in behavior is noted with reductive alkylations. Thus, all three systems, naphthalene, anthracene, and *sym*-dibenzocyclooctatetraene, provide good yields of dialkylated, dihydro products when alkyl halides are added to their metal–ammonia solutions, but only *sym*-dibenzocyclooctatetraene produces dimethylation (see eq 4–6) upon inverse addition to an ethereal solution (or neat) of methyl bromide or iodide. Thus, this rapid quenching process is able to "trap" the dianion in the latter case, but does not allow



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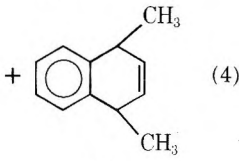

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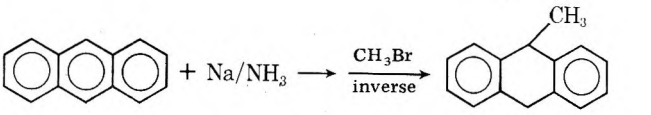

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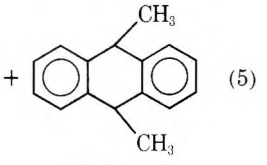

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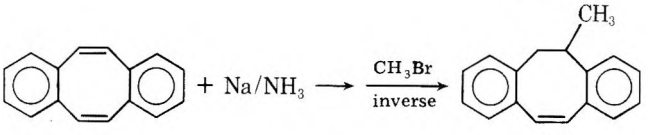

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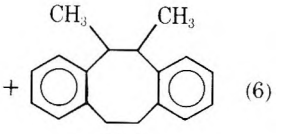

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enough time for secondary reactions, and the monoanions that result in the first two cases result in monomethylation.

A more detailed description of the reductive alkylation behavior of naphthalene[13] and anthracene is presented in Tables II–IV. Thus, in contrast to *sym*-dibenzocyclooctatetraene, naphthalene and anthracene provide monoalkylation as the chief product in most cases involving a reverse quench procedure (in many cases >90%), and, as mentioned previously, these results support the intermediacy of monoanions. The possibility that the anthracene/Na/NH_3 system results in dianions that are slowly protonated[5] was examined by inverse quenching of several samples over a period of 30 min (Table III). Our results show very little variation in dialkylation with time and do not support this possibility. Thus, we conclude that the dialkylated products are due to the back reaction with amide even under inverse quench conditions. That this back reaction *can* occur with inverse quench procedures is demonstrated by the use of added sodium amide (1 equiv) during reduction followed by an inverse quench. As indicated in Table III, dialkylation goes up to 94% with added amide ion as compared to 42% in its absence. These results are in substantial agreement with previous studies on the reductive alkylation of biphenyl and anthracene[5] and a clear pattern now emerges. Conditions which result in a slower quenching process (i.e., lower vs. higher temperatures, gaseous vs. liquid methyl bromide, alkyl bromides vs. alkyl iodides, and ethyl vs. methyl bromide) lead to a greater proportion of di- and trialkylated products. This is, of course, consistent with our hypothesis that the amide back reaction is responsible for di- and trialkylation, since slowing the quench allows time for this reaction to occur.

We should also note that our results show a substantial

Table II. Reductive Methylation of Anthracene (ArH)

R–X	metal	temp, °C	quench procedure	% composition[a] ArH_2R[b]	% composition[a] $ArHR_2$[c]
MeBr	Na	−78	inverse[d]	88	12
MeBr	Na	−78	normal[e]	15[f]	80[f]
MeBr (liq)	Na	−33	inverse	89	11
MeBr (liq)	Na	−33	normal	6	85
MeI	Na	−33	inverse	95	5
MeI	Na	−33	normal	14[g]	64[g]
MeI	Li	−78	inverse	97	3
MeI	Li	−78	normal	58	42

[a] By relative NMR integrations and/or GLC on a 6 ft W-98 (silicon) column at 165 °C. [b] 9-Methyl-9,10-dihydroanthracene. [c] 9,10-Dimethyl-9,10-dihydroanthracene. [d] Metal added to anthracene in NH_3/ether (2:1), and reaction mixture pumped under inert gas into alkyl halide under inert gas (MeBr was condensed to a liquid for inverse quenches and added as a gas for normal quenches). [e] As above except after the time period (~15 min) the alkyl halide was added to the reaction mixture. [f] ~5% ArR_3. [g] ~23% ArR_3.

Table III. Reductive Ethylation of Anthracene (ArH)

metal	temp, °C	quench procedure	time	temp of EtBr, °C	% composition[a] ArH_2R[b]	% composition[a] $ArHR_2$[c]
Li	−33	inverse[d]	10	ambient	97	3
Li	−33	normal[e]	10	ambient	40	60
Li	−78	inverse	10	ambient	81	9
Li	−78	normal	10	ambient	32	68
Na	−33	inverse	10	ambient	82	18
Na	−33	normal	10	ambient		80[f]
Na	−78	inverse	10	−78	40	60
Na	−78	inverse	10	ambient	60	40
Na	−78	inverse	20	−78	48	52
Na	−78	inverse	20	ambient	58	42
Na	−78	inverse	30	−78	37	63
Na	−78	inverse	30	ambient	63	37
Na	−78	normal	30	ambient	27	75
Na (+$NaNH_2$)	−78	inverse	20	ambient	6	94

[a] Relative amounts determined by NMR integration and corroborated in many cases by GLC on a 6 ft × ⅛ in. W-98 (silicon) column at 165 °C. [b] 9-Ethyl-9,10-dihydroanthracene. [c] *cis*-9,10-Diethyl-9,10-dihydroanthracene. [d] See footnote *d*, Table II. [e] See footnote *e*, Table II. [f] ~15% ArR_3. In substantial agreement with previous results: R. G. Harvey and L. Arzadon, *Tetrahedron*, **25**, 4887 (1969).

Table IV. Reductive Alkylation of Naphthalene (ArH)[a]

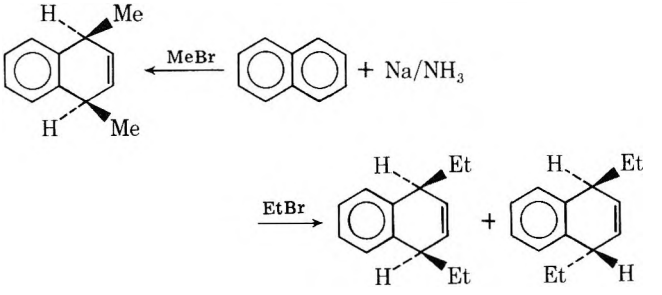
R–X	temp, °C	quench procedure	% composition[b] ArH_2R[c]	% composition[b] $ArHR_2$[d]
EtBr	−78	inverse[e]	90	9
EtBr	−78	normal[f]	25	75
MeI	−78	inverse[g]	82[h]	
MeI	−78	normal	33[h]	51[h]
MeI	−33	inverse	85[i]	1[i]
MeI	−33	normal	18[i]	55[i]
MeBr (liq)	−78	inverse	90[h]	
MeBr (liq)	−78	normal	20	80
MeBr (gas)	−78	normal		85[j]

[a] Reaction with Na in NH_3/THF (2:1). [b] By GLC on a 6 ft × ⅛ in. W-98 (silicon) column, corroborated by NMR peak intensities. [c] 1-Alkyl-1,4-dihydronaphthalene. [d] *cis*-1,4-Dimethyl-1,4-dihydronaphthalene (in the case of MeX), or a mixture of *cis*- and *trans*-1,4-diethyl-1,4-dihydronaphthalene (in the case of EtX). [e] See footnote *d*, Table II. [f] See footnote *e*, Table II. [g] A change in MeI temperature from ambient to −78 °C produced no significant change in results. [h] Contained some overreduction products and naphthalene. [i] Contained overreduction products. [j] In agreement with data of ref 14.

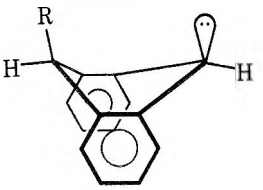
difference between lithium and sodium. This effect has been noted previously[5,14] and the increased amount of dialkylation with sodium has been attributed to the greater solubility of sodium amide in ammonia.[5]

It should be noted that the earlier observation[14] that reductive methylation of naphthalene with sodium and methyl bromide gas gives dimethylation exclusively, whereas the use of lithium provides monomethylation, is quite dependent on the choice of alkyl halide in that these results are not general for all alkyl halides. In fact, these results are dependent on the use of a gaseous alkyl halide which leads to a relatively slow quench. When the sodium/naphthalene solution is quenched inversely into liquid methyl bromide at −78 °C under inert gas, only monomethylation results (see Table III). However, a normal quench with liquid methyl bromide produces a considerable amount of dimethylation, whereas the use of methyl bromide gas gives dimethylation exclusively (as previously reported[14]). This is, of course, all quite consistent with the scheme provided herein, since once again the back reaction with amide ion is expected to be more efficient with slower quenching. This reaction appears to be of little importance when lithium is used due to the limited solubility of lithium amide in ammonia.[5]

An even more curious feature of the reaction is the fact that



reductive methylation of naphthalene leads only to cis products, whereas reductive ethylation provides a mixture of both cis and trans products. These results are quite significant, since it has always been puzzling as to why the reductive alkylation of naphthalene should be more stereoselective than anthracene. The arguments presented for the stereochemical outcome in anthracene[15] suggest that "peri" interactions in



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the anion 1 force a pseudoaxial position for the substituent with the electron pair also pseudoaxial (for maximum overlap with aromatic rings). Thus, the second alkylation occurs from the same side, resulting in overall cis dialkylation. However, although this reaction is stereospecific for many R groups, it is not for methyl, presumably due to its smaller size. We should also note that isomerization of alkylated dihydroanthracenes and dihydronaphthalenes has never been observed by ammonia. Thus, the alkylation behavior of naphthalene warrants further study and is currently under investigation.

Experimental Section

General Procedures. (1) Preparation of Metal–Ammonia Solutions. The hydrocarbon was added to a solution of 1 part dry THF (or anhydrous ether where specified) in 2 parts ammonia at −78 °C (or −33 °C where specified), followed by the addition of 1.25 equiv of sodium or lithium metal, and stirred under helium for 20 min. **(2) Reduction/Normal Quench.** Saturated ammonium chloride solution was added as rapidly as possible to discharge the deep color.[16] **(3) Reduction/Inverse Quench.** The reaction mixture was pumped (helium pressure) through a glass tube into a large volume of saturated ammonium chloride solution (**Caution:** some spattering occurs).[16,17] **(4) Reductive Alkylation/Normal Quench.** An excess of alkyl halide dissolved in dry THF was added from a dropping funnel (or in the case of CH_3Br introduced as the gas) at a reasonable rate until the discharge of the deep color. This was followed immediately by the addition of saturated ammonium chloride solution.[16] **(5) Reductive Alkylation/Inverse Quench.** The reaction mixture was pumped (helium pressure) through a glass tube which was immersed in a large excess of alkyl halide (under helium) which was cooled to the same temperature as the reaction mixture (**Caution:** this must be done carefully to avoid frothing).[16,17]

Anthracenes. All of the reduced products from anthracene (see Table II) are known compounds and were compared with authentic spectral data.[15,18] 9,10-Dihydroanthracene can be prepared from anthracene in essentially quantitative yield by either procedure 2 or 3. As mentioned previously, procedure 3 is much less sensitive to experimental conditions and precautions.

Naphthalenes. The reduction products of naphthalene are known compounds, although to the best of our knowledge the data in Table I represent the only efficient (98%) preparation of 1,4-dihydronaphthalene from naphthalene via metal–ammonia reduction. 1-Methyl-1,4-dihydronaphthalene and *cis*-1,4-dimethyl-1,4-dihydronaphthalene are known compounds and identification was made by comparison with authentic spectral data.[14]

1-Ethyl-1,4-dihydronaphthalene was obtained as a colorless liquid by the above procedures followed by spinning band distillation (bp 79 °C): NMR (CCl_4) δ 7.0 (m, 4 H), 5.8 (complex d, 2), 3.3 (m, 3), 1.6 (complex q, 2), 0.8 (t, 3).

Anal. Calcd for $C_{12}H_{14}$: C, 91.14; H, 8.86. Found, C, 91.27; H, 8.82.

***cis*-1,4-Diethyl-1,4-dihydronaphthalene**[19] was prepared according to the above procedures and trapped off GLC (5 ft, 7% DEGS at 135 °C, retention time 7.8 min) to yield a colorless oil: NMR (CCl_4) δ 7.1 (s, 4 H), 5.9 (complex d, 2), 3.4 (bm, 2), 1.7 (complex q, 4), 0.9 (t, 6).

Anal. Calcd for $C_{14}H_{18}$: C, 90.32; H, 9.68. Found, 89.32 H, 9.95.[19b]

***trans*-1,4-Diethyl-1,4-dihydronaphthalene**[19] was isolated in the same fashion as the cis isomer (retention time 6.2 min): NMR (CCl_4) δ 7.1 (bs, 4 H), 5.8 (d, 2), 3.4 (bm, 2), 1.8 (m, 4), 0.75 (t, 6).

Anal. Calcd for $C_{14}H_{18}$: C, 90.32; H, 9.68. Found, C, 89.56; H, 9.71.[19b]

Dibenzo[*a,e*]cyclooctatetraenes. The reduced hydrocarbon is a known compound and is easily identified by its NMR spectrum.[20] The presence of small amounts of monomethylated reduced hydrocarbon was suggested by GLC and NMR results for the alkylation experiments, and no attempt was made to isolate this compound.

11,12-Dimethyldibenzo[*a,e*]cyclooctatriene[21] was prepared by the above inverse quench procedure and led to a nearly quantitative yield. Recrystallization from aqueous ethanol produced white crystals: mp 69–70 °C; NMR (CCl_4) δ 7.0 (m, 8 H), 6.9 (s, 2), 3.0 (m, 2), and 1.3 (cd, 6).

Anal. Calcd for $C_{18}H_{18}$: C, 92.26; H, 7.74. Found: C, 92.21; H, 8.00.

Acknowledgment is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We would also like to thank Professor Ronald G. Harvey for helpful comments.

Registry No.—Naphthalene, 91-20-3; 1,2,3,4-tetrahydronaphthalene, 119-64-2; 1,4-dihydronaphthalene, 612-17-9; anthracene, 120-12-7; 9-methyl-9,10-dihydroanthracene, 17239-99-5; 9,10-dimethyl-9,10-dihydroanthracene, 22566-43-4; 9-ethyl-9,10-dihydroanthracene, 605-82-3; *cis*-9,10-diethyl-9,10-dihydroanthracene, 20826-55-5; 1-ethyl-1,4-dihydronaphthalene, 36789-17-0; 1-methyl-1,4-dihydronaphthalene, 21564-70-5; *cis*-1,4-dimethyl-1,4-dihydronaphthalene, 21947-40-0; *cis*-1,4-diethyl-1,4-dihydronaphthalene, 67542-20-5; *trans*-1,4-diethyl-1,4-dihydronaphthalene, 67542-21-6; dibenzo[*a,e*]cyclooctatetraene, 262-89-5; 11,12-dimethyldibenzo[*a,e*]cyclooctatriene, 67542-22-7; ammonia, 7664-41-7; sodium, 7440-23-5; lithium, 7439-93-2.

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(2) In experiments using excess metal and short reaction times, it is not unexpected that trace iron impurities do not affect results.[3]
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(5) D. F. Lindow, C. N. Cortez, and R. G. Harvey, *J. Am. Chem. Soc.*, **94**, 5406 (1972).
(6) For example, compounds which only form radical anions in ammonia do not furnish reduction products on quenching with water (due to rapid reaction of water with metal) and normally undergo extensive electron transfer with alkyl halides.
(7) Performing reduction without a slight excess of metal generally leads to poor results.
(8) As has been noted previously.[3] See also ref 9.
(9) P. W. Rabideau and R. G. Harvey, *J. Org. Chem.*, **35**, 25 (1970).
(10) R. G. Harvey and L. Arzadon, *Tetrahedron*, **25**, 4887 (1969).
(11) For additional discussion concerning the exclusion of radical anions as intermediates in reductive alkylation (as well as protonation by ammonia in scheme I) see ref 5.
(12) It is well established that dianions exist in equilibrium with their radical anions. See ref 4.
(13) Sodium metal was used exclusively in the naphthalene reductive alkylations, since simple reduction of this system with lithium consistently gave over-reduction products (cf. previous discussion).
(14) P. W. Rabideau and R. G. Harvey, *Tetrahedron Lett.*, 4139 (1970).
(15) P. P. Fu, R. G. Harvey, J. W. Paschal, and P. W. Rabideau, *J. Am. Chem. Soc.*, **97**, 1146 (1975).
(16) In each case, the crude product was isolated by ether extraction and then purified by distillation, recrystallization, or GLC.
(17) Although we recommend that inverse quenches be carried out with caution, our experience has been that this technique does not provide any serious safety hazard when carried out in an efficient hood.
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(19) (a) Isomer assignment is tentative (based on comparison with dihydroanthracenes[15]) and is currently being investigated in more detail. (b) Both of these compounds appeared somewhat unstable and several samples were submitted for microanalysis with variable results. VPC/MS was accom-

panied by substantial decomposition, but indicated strong *m/e* 186 peaks. In addition, ^{13}C and off-resonance proton decoupled ^{13}C NMR results were quite consistent.

(20) T. J. Katz, M. Yoshida, and L. C. Siew, *J. Am. Chem. Soc.*, **87**, 4516 (1965).

(21) Both the relatively sharp melting point and NMR spectrum suggest that we have produced a single isomer. Inspection of the models with regard to steric preferences for the first methyl group incorporated together with maximum overlap of the monocarbanion suggests that this is probably the trans isomer.

Halocyclization of *N*-Allylbenzamide Derivatives. Effects of Halogenating Agent, Alkene Substitution, and Medium

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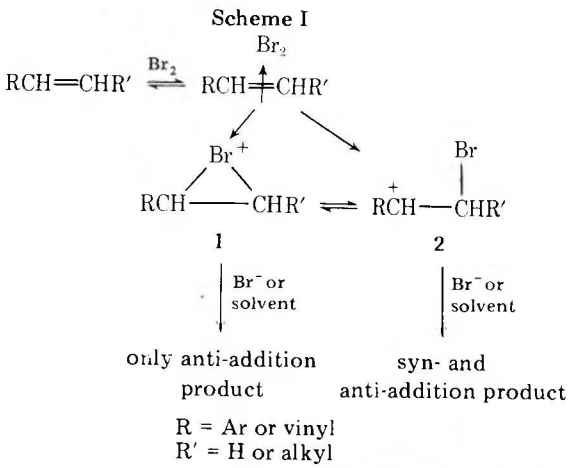
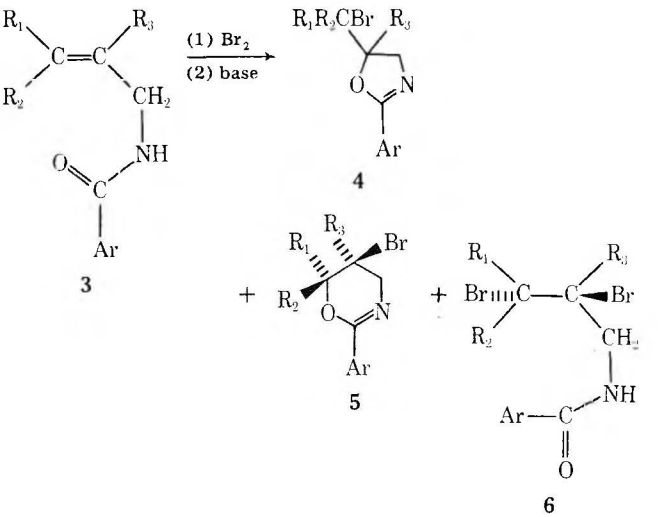
Received February 27, 1978

Halogenation of *N*-allylamide derivatives produces ring-closure products and addition products in varying amounts depending on the halogenating agent, the alkene structure, and the solvent. Concerted addition–cyclization does not occur in these systems when the alkene is activated by attached groups which aid in the delocalization of transition state charge. Instead, the results from the studies of these systems are best explained by invoking carbocation intermediates or carbocation-like product-forming steps. Equilibria between halonium ions and haloalkyl carbocations are probably not established in these reactions owing to the high reactivity of the carbocations in the presence of good nucleophiles. There remains the possibility that **3c–e**, like **3a** and **3b**, are brominated via a bromonium ion intermediate as the product-forming species. If this mechanism is operative, these reactions provide a rare example of fused mode cyclization in such circumstances.

Since first postulated by Roberts and Kimball,[1] cyclic bromonium ions have been considered important intermediates in the electrophilic bromination of most alkenes.[2] Evidence for ethylenebromonium ion intermediates and bromination mechanisms incorporating them seems well justified when the alkene is nonconjugated.[3-10] Conjugated alkenes such as styrene derivatives[3,11] and dienes[12] often behave differently.[13,14] The mechanistic change, which is revealed by the study of product stereochemistry and the application of linear free-energy relationships, arises because the resonance stabilized substituted β-bromoethyl cation **2** has an energy similar to that of its isomeric bromonium ion, Scheme I.

We began the present work with the goal of ascertaining whether or not ions **1** and **2** were both important product-forming intermediates. We chose to compare results of halogenation studies of the series of amides **3a–e** because of the neighboring amide group which should participate in these reactions thus aiding in assigning a structure to the intermediates. At the outset we assumed that there is a strong tendency of ring opening–ring closures of substances like bromonium ions to strongly prefer the spiro mode over fused mode cyclizations,[15-19] eq 1. Thus, one predicts that five-membered ring bromocylization products would arise from





3–10a, $R_1 = R_2 = R_3 = H$; Ar = phenyl
b, $R_1 = R_2 = H$; $R_3 = Me$; Ar = phenyl
c, $R_1 = Me$; $R_2 = R_3 = H$; Ar = *p*-nitrophenyl
d, $R_1 = R_2 = Me$; $R_3 = H$; Ar = *p*-nitrophenyl
e, $R_1 = Ph$; $R_2 = R_3 = H$; Ar = *p*-nitrophenyl

3a–e when the substrates react via amide attack on the bromonium ion, e.g., structure **7**, eq 2. However, the favored carbocation intermediates from **3d** and **3e** should be the tertiary cation **8d** and the benzylic cation **8e**, respectively, and these would cyclize only to the six-membered rings **5d** and **5e**, respectively, eq 3.[20] We have also investigated the effect of the medium on these addition–cyclization reactions.

Results and Discussion

The *p*-nitrobenzamides **3c–e** (Ar = *p*-nitrophenyl) were prepared and brominated in acetic acid and in carbon tetrachloride giving bromocyclization products and dibromides.[21] In each case, these products were isolated and their structures determined by the use of elemental analysis, IR, NMR, and mass spectroscopy. The stereochemistry of the dibromides isolated from the bromination of **3c** and **3e** was consistent with

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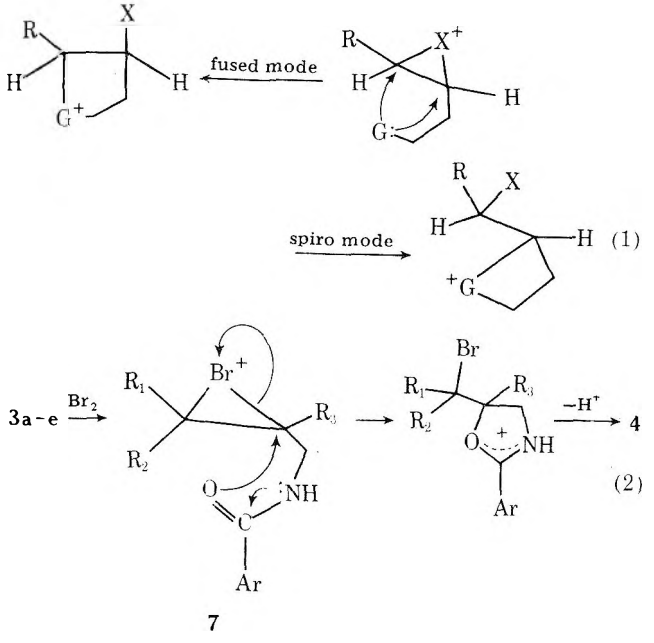
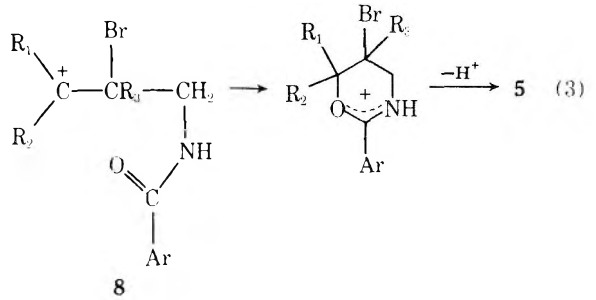
Table I. Halogenation of N-Allylbenzamide Derivatives

alkene	halogenation agent	solvent	react temp, °C	% yield[a] of halocyclization products(s)	cyclization ratio O-5:O-5	% yield[a] of dihalide	ratio of cyclization to addition
CH_2=$CHCH_2NHCOPh$ (**3a**)	Br_2[b]	$CHCl_3$	0	42	100:0	55	43:57
	Br_2[b]	AcOH	15	45	100:0	49	48:52
CH_2=$C(CH_3)CH_2NHCOPh$ (**3b**)	Br_2[c]	MeOH	−78	63	100:0	*d*	*d*
	Cl_2[c]	MeOH	−78	47	100:0	*d*	*d*
	F_2[c]	MeOH	−78	21	100:0	*d*	*d*
t-CH_3CH=$CHCH_2NHCO$-*p*-$NO_2C_6H_4$ (**3c**)	Br_2	CCl_4	25–30	36	48:52[e]	58	36:64
	Br_2	AcOH	16–18	61	21:79[e]	30	67:33
	NRS	AcOH	26	71	34:66[e]	*f*	*f*
	Cl_2	AcOH	25–28	30[e]	40:50[e]	23	57:43
$(CH_3)_2C$=$CHCH_2NHCO$-*p*-$NO_2C_6H_4$ (**3d**)	Br_2	CCl_4	16–18	61[e]	0:100	22[e]	73:27
	Br_2	AcOH	16	82[e]	0:100	16[e]	84:16
	Br_2[g]	AcOH	16	95	0:100	5[e]	95:5
t-$PhCH$=$CHCH_2NHCO$-*p*-$NO_2C_6H_4$ (**3e**)	Br_2	CCl_4	25	36	0:100	64	36:64
	Br_2	AcOH	18	76	0:100	22	77:23

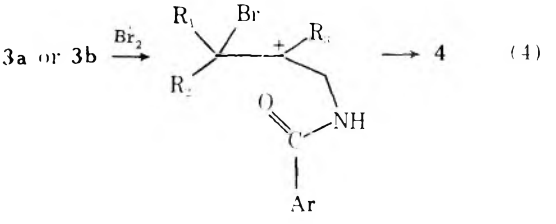
[a] Isolated yields unless otherwise stated; balance in some cases is unreacted amide, see Experimental Section. [b] Reference 22. [c] Reference 23. [d] NMR analysis indicated the presence of dihalides and halo ether products; however, these products were not isolated; reference 22. [e] Determined by gas chromatography. [g] Dihalide cannot form and acetoxy halide was not sought. [g] A molar excess of Br_2 was used in this run.

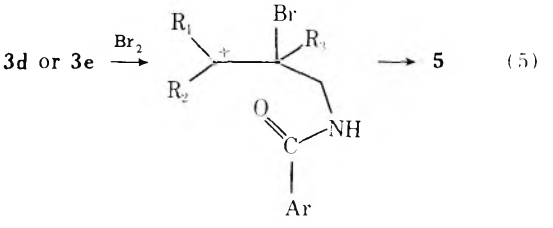




anti addition of bromine. Likewise, the dihydrooxazine derivatives obtained from bromocyclization of **3c** and **3e** were found to contain the ring bromine and methyl (from **3c**) or phenyl (from **3e**) in a trans arrangement. In one case, **3c**, chlorination in acetic acid was also carried out. The products, their relative ratios, and yields are given in Table I along with some comparative data of other reactions. Through control experiments **6d** was found to be solvolytically unstable; the product data shown have thus been confirmed by gas chromatography in questionable cases.

Cyclization Mode. Significantly, we observed a change in the mode of cyclization as the hydrogens about the vinyl system are replaced with a methyl or phenyl group. Goodman and Winstein[22] and Merritt[23] have studied halocyclization of the terminally unsubstituted N-allylamides **3a** and **3b**. The five-membered ring (an oxazoline), and not the six-membered ring (a dihydrooxazine), is the only cyclic product. This is consistent with cyclization via intermediate **9** or Markovnikov-like cyclization of intermediate **7**. The amides **3d** and **3e** would give a similar bromonium ion (**7**) as **3a** or **3b** but would give the respective tertiary or benzylic carbocations **10d** or **10e** and not the secondary cations **9d** or **9e**. According to our assumption that the spiro cyclization mode would preferentially occur, intermediates **7d** and **7e** would yield oxazoline derivatives **4** while **9d** and **9e** could only give the dihydrooxazine derivatives **5d** and **5e**, respectively. Since only the latter form in this instance either carbocations are involved or fused mode cyclization is occurring.[24]





The more symmetrically substituted amide **3c** provides an interesting contrast to what appears as limiting behavior of the other amides under all conditions; a mixture of the five- and six-membered ring products was formed. Formation of a six-membered ring product by amide group attack on the bromonium ion from **3c** would require fused mode cyclization

(spiro route highly favored); alternatively, these results are accommodated by amide group attack on the open secondary carbocation **10c**.

Either of the explanations above are unsatisfying based on the conventional view of fused vs. spiro cyclizations[15] or of simple disubstituted alkene brominations.[2,5] The stereochemical studies of Rolston and Yates,[3] for example, showed considerable differences between the behavior of the isomeric 2-butenes when compared to isomeric 1-phenypropenes. While >99% anti addition was observed for the butenes under a variety of conditions, significant amounts of syn addition were noted for the 1-phenylpropenes. A reasonable conclusion was that the benzyl-like carbocation in the latter case allowed for a different mechanism.[5] It is of course possible to extend the carbocation mechanism to trisubstituted alkenes where tertiary alkyl carbocations form (e.g., **3d**), but secondary carbocations in these processes have not been strongly indicated by other evidence. Since the possibility of fused mode cyclization, albeit unfavorable, has not been shown to be impossible, this alternative seems the better choice until more proof exists to favor the secondary carbocations.

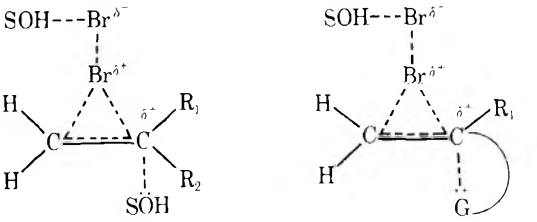
Halogenation Agent. Although the halonium ion mechanism is advocated for chlorination as well as for bromination of alkyl substituted alkenes,[2] it is well known that, relative to their open carbocation isomers, chloronium ions do not enjoy the stability of bromonium ions.[10,25] Thus, when analyzing the results of halocyclization studies, this stability trend should be evident if the stability–selectivity principle[26] is followed. We believe such a trend is indeed evident from the results compiled in Table I. Merritt[23] found a steady decrease in the halocyclization fraction as the halogen was varied from bromine to fluorine in the halogenation of **3b** in methanol. We found a smaller amount of cyclic product when **3c** was chlorinated than when it was brominated in acetic acid.

There is probably little or no bridging in fluorination reactions.[2b,25] Therefore, if all of the halogenations of **3b** occurred at equal rates (which, of course, they do not) ca. 20% cyclization product could be expected. That is, the neighboring amide group will capture a rather constant percentage of the carbocationic intermediates because the energy of that process regardless of the halogen is nearly a constant. Likewise halide ion and solvent trapped product should be nearly a constant.

Now let us consider halonium ion intermediates. Despite its attractiveness, the cyclization trend is not explained by invoking the intermediacy of a greater amount of halonium ion as the size of the halogen is increased. The problem with that rationale can be seen by considering the stability–selectivity relationships of the various halonium ion–halide systems. Assuming the halonium ion stability order bromonium > chloronium > fluoronium, the nucleophilicity order $Br^- > Cl^- > F^-$ > amide group, and operation of the stability–selectivity principle, one would predict that the bromonium ion is more likely to react with the bromide ion rather than the amide group while the less stable (less selective) chloronium ion would react relatively better with amide group as compared to the chloride ion. Thus the wrong cyclization trend is predicted.

A plausible explanation comes from the consideration of the different halogenation mechanisms, their rates, i.e., F_2–alkene > Cl_2–alkene > Br_2–alkene, and the Hammond postulate.[27] The charge developed in the transition state upon halogenation increases in the order: fluorination < chlorination < bromination. The charge at carbon upon bromination could be large enough to allow for nucleophilic solvation of the transition state.[28–32] The solvent or a nucleophilic neighboring group, e.g., the amide group, could fulfill this role by solvation of the backside of the carbon as shown in Scheme II. It follows from established principles that the later the transition state

Scheme II



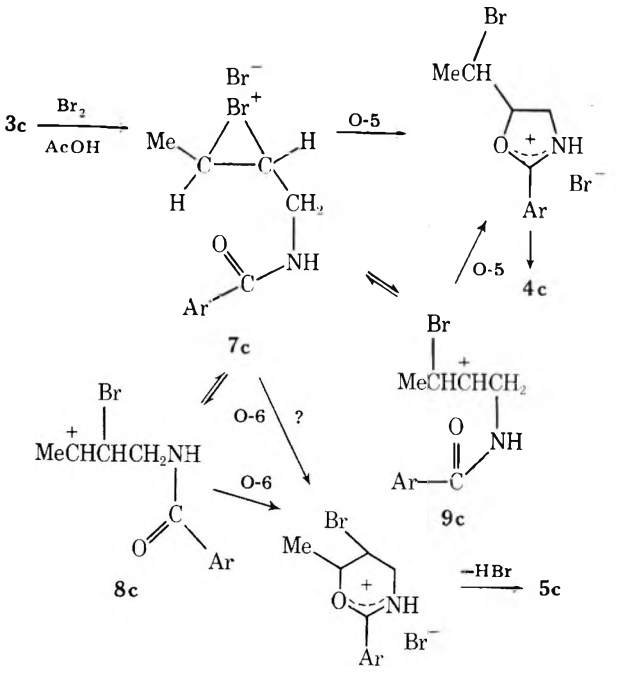
the more important structures like those in Scheme II become. Obviously, the halogen, solvent, and neighboring group can affect the importance of them.[33] Because of the entropy loss involved in ordering a neighboring group-solvated transition state, bromination and, to a lesser extent, chlorination may give such highly structured transition states with the extent depending on alkene structure and solvent.[34] *N*-Bromosuccinimide (NBS), which in some solvents reacts by rate-limiting nucleophilic attack on a bromonium-like species,[35] may best illustrate the concepts proposed to explain the effect of the halogenation agent, Table I. Using the reagent with **3c**, the amount of cyclization product increased (as compared to Br_2) and the five-membered ring product (O-5 cyclization) increased relative to the six-membered ring product (O-6 cyclization).

Solvent Effects. While we have considered some general solvent effects above, it is interesting to consider solvent effects on product composition,[36] Table I. Acetic acid, which is more polar and nucleophilic than carbon tetrachloride, allows for a larger fraction of cyclization than carbon tetrachloride or chloroform. This trend is consistent with the proposal above, Scheme II, as the charge developed in the transition state would be greater in the more polar solvent despite the higher rate.[34] This trend is also consistent with what one would expect if the competitive attack on a bromonium ion by bromide and the neighboring group is considered. As the charge developed at carbon is less, the better nucleophile, bromide ion, should fare better. This alone does not account for all of our observations, however, since the six-membered ring products, even from **3c**, may be formed from amide attack on a carbocation and not a bromonium ion.

If we examine the data from bromination of **3c** in acetic acid and in carbon tetrachloride the trend expected from the intermediacy of the carbocation **8c** and the bromonium ion **7c** is present.[37–39] Of the two carbocations, substituent effects favor **8c** over **9c**, Scheme III. Carbocation **9c** may also be a product-forming intermediate, but the data do not allow for a decision as to whether it or the bromonium ion **7c** leads to the five-membered ring product. In carbon tetrachloride there is more product formation via the bromonium ion **7c** and hence the greater proportion of cyclic product is the O-5 cyclization product. Also, there is a significant amount of dibromide (only anti addition) consistent with the theory that the better nucleophile reacts faster with the bromonium ion. In the better ionizing solvent, acetic acid, the amount of dibromide decreased and the O-6 cyclization fraction increased. The actual amount of O-5 cyclic product remained nearly constant.

Reaction Stereochemistry. The observation that only anti addition products are formed is generally consistent with bromonium ion intermediates.[2] Thus, since the dihydrooxazine formed from **3c** and **3e** is the one with the bromine and methyl or phenyl group trans, it is consistent with stereospecific ring closure and not with the intermediacy of carbocations. The reasons for this need to be discussed. A possible stereospecific pathway to the dihydrooxazines has been mentioned and eliminated.[24] While it is possible that the trans isomer forms from the carbocation because it is the more stable one,[40] it is highly probable that the carbocations are

Scheme III

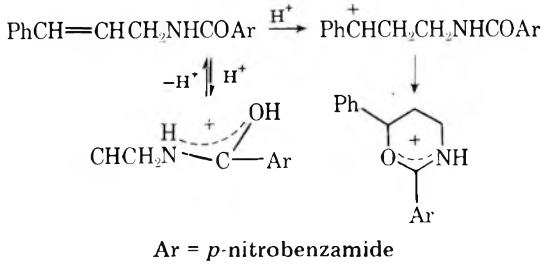


captured by bromide ion or the neighboring group before a significant amount of rotation can occur. In fact, it is entirely possible for there to be a merger of mechanisms as the solvent stabilization of the intermediates and cation stabilities vary. For example, cation 8 is not expected to be very stable in carbon tetrachloride; therefore it is probable that under these conditions 8 is never fully formed. Instead partially formed 8 is intercepted along the reaction coordinate to 8 to give product. A number of investigations lend support to this nonlimiting view of the mechanism.[41]

Comparison with Other Studies. McManus et al.[42] have reported the acid-catalyzed cyclization of N-allylamides and similar compounds. The results of these studies, which were carried out in 50–96% aqueous sulfuric acid, were consistent with cyclization via carbocation formation. For example, N-allyl-*p*-nitrobenzamide gave only oxazolinium product by an O-5 route while *N*-cinnamyl-*p*-nitrobenzamide gave exclusively the O-6 product via the more stable benzylic carbocation, Scheme IV. Nakai et al.[43,44] have observed similar protonation results with dithiocarbamates and have also studied the cyclization of the dithiocarbamate **11** which can undergo competitive O-5 and O-6 cyclization, Scheme V. Both O-5 and O-6 cyclization products were obtained with the relative ratios of five- and six-membered ring cations varying with the acid catalyst.[45] That these results parallel our bromination results is taken as strong evidence for the carbocationic nature of the product-forming intermediates in our bromination studies.

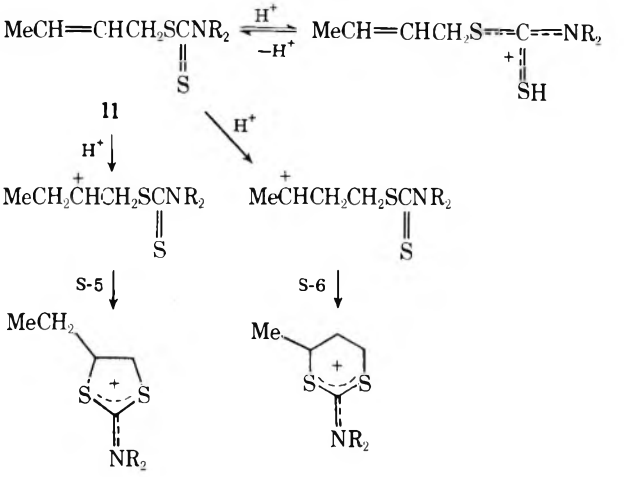
In stark contrast to our studies, Nakai et al.[44] have found that, regardless of the substitution pattern, bromination (in carbon tetrachloride) of N-allyl dithiocarbanate derivatives (i.e., **12 a–e**) leads only to five-membered ring products of

Scheme IV



Ar = *p*-nitrobenzamide

Scheme V

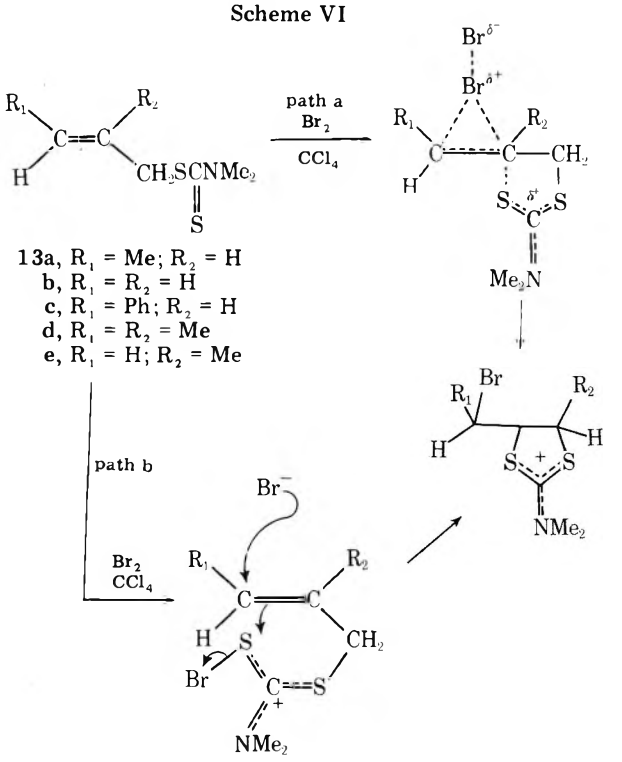


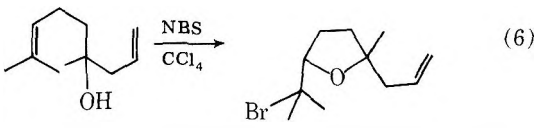
bromocyclization. There are two reasonable rationales for the differences between our results and those of Nakai et al., the reactions could proceed solely by an anchimerically assisted route (path a, Scheme VI), or electrophilic attack could initially occur at sulfur with subsequent bromide ion (or tribromide ion) attack at carbon to give the observed cyclic product (path b). The latter mechanism (path b) is attractive because of the high nucleophilicity of the sulfur and the similarity with brominations thought to proceed by initial electrophilic attack other than at carbon.[14] Nevertheless, because the cyclic salts are said to immediately precipitate from solution,[44] path a is assumed to be preferred.

Our bromocyclization results are also different from those of Klein et al.[46] who report exclusive O-5 ring closure upon NBS treatment of linalool, eq 6. This reaction is obviously anchimerically assisted since the expected product (cf. eq 2) from that route and not from the route involving carbocations is formed.

Conclusions. Numerous factors are shown to affect the amount of halocyclization and dihalide fractions upon halogenation of alkenes bearing a proximate nucleophilic neighboring group. Because of the way the product fractions are

Scheme VI





(6)

varied we conclude that nucleophilic solvent or neighboring group assistance may be important in the rate-determining and product-determining step. In anchimerically assisted addition–cyclizations, the neighboring group fulfills the role solvent may otherwise fulfill and the rate-determining and product-determining steps are the same. When polar solvents are employed or when carbocation stabilizing substituents are attached to the alkene carbons, there is a tendency to form carbocations and halonium ion intermediates. Because of the difference in reactivity of these intermediates, the products in such cases can largely be accounted for by excluding significant participation of the halonium ion as an important product-forming intermediate. The product stereochemistry, however, suggests that the carbocationic intermediates are most often trapped before significant rotation can occur, hence the halonium ion ring opening tends to merge with nucleophilic attack on carbocation to give a spectrum of product-forming reactions from S_N1-like on the one end to S_N2-like on the other.

Experimental Section

General. Melting points were taken in capillaries with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded of films or KBr disks with a Beckman Acculab I, a Beckman IR-5A, or Beckman IR-10 spectrometer. Proton nuclear magnetic resonance spectra were obtained with a Bruker HFX-10 90 MHz spectrometer equipped with a spin decoupler or with a Varian *EM-360 60-MHz* spectrometer. Unless otherwise stated, internal tetramethylsilane (Me_4Si) was used as an internal reference standard ($\delta = 0$). The mass spectra were recorded with a CEC 21-110 mass spectrometer. Elemental analyses were determined by Gailbraith Laboratories, Inc., Knoxville, Tenn. Gas chromatographic analyses were obtained using a Hewlett-Packard Series 5750 gas chromatograph equipped with a flame ionization detector and a Model 3370A electronic integrator and printout. Owing to decomposition of the halogenated compound by metal columns, glass columns with on column injection were used throughout. Analysis of the halogenation mixtures was performed using a 6-ft glass column packed with 6% OV-210 on Gas Chromosorb Q (80–100 mesh). Freshly opened reagent grade solvents and reagents were used as obtained. Other solvents and reagents were purified by recrystallization or distillation and drying. *N*-Cinnamylamine was prepared in best yields by use of *the Delepine* reaction[47] and was converted to *its p*-nitrobenzamide as previously described.[43] The other amines were prepared from commercially available purified chlorides or bromides using a modification of the Gabriel synthesis[48] described for the crotyl derivative by Roberts and Mazur.[49]

***N*-Crotyl-*p*-nitrobenzamide (*N*-(*trans*-2-buten-1-yl)-*p*-nitrobenzamide) (3c).** Freshly distilled crotyl chloride (bp 83–84 °C) (45.5 g, 0.5 mol) and potassium phthalimide (93.0 g, 0.5 mol) were dissolved in 500 mL of dimethyl sulfoxide in a 1000-mL round-bottom flask fitted with a reflux condenser and the resulting solution was heated to mild reflux (190 °C) for 2 h. The solution was cooled and poured into 500 mL of an ice and water mixture. The phthalimide, which precipitated, was vacuum filtered, washed with water while on the funnel, and dried in air at room temperature to yield 87.0 g (86.6%) of crude *N*-crotylphthalimide. This material was used without purification or characterization in the *next step*.

The crude *N*-crotylphthalimide (87.0 g, 0.43 mol) was added to 400 mL of ethylene glycol in a 100-mL round-bottom flask fitted with a reflux condenser. Hydrazine hydrate (19.0 g of 64% solution, 0.38 mol) was added and the solution was heated to reflux for 2 h. A distillation head and condenser were then fitted to the reaction flask, and the solution was distilled to a head temperature of 190 °C at atmospheric pressure. The residue, consisting of ethylene glycol and phthalhydrazide, was discarded. The distillate containing water and *N*-crotylamine was added to 5.0 g of potassium hydroxide, which resulted in two liquid phases. The water-miscible bottom phase was discarded. The top phase, consisting of *N*-crotylamine, residual water, and ethylene glycol, was fractionally distilled yielding 16.3 g (46.6%) of *N*-crotylamine, bp 82–86% (lit.[49] bp 81–82 °).

N-Crotylamine (15.9 g, 0.22 mol) was dissolved in 100 mL of ether in a 250-mL round-bottom flask. Pyridine (45 mL) and freshly recrystallized p-nitrobenzoyl chloride (35.0 g, 0.19 mol) were added to the flask and the contents were swirled for several minutes. Removal of volatile material in vacuo resulted in a light yellow solid which was extracted with 150 mL of methanol. The methanol insoluble material had a melting point in excess of 160 °C. Methanol was removed in vacuo from the dissolved solids to give a light yellow solid. Recrystallization from methanol yielded 12.1 g (29%) of *N*-crotyl-*p*-nitrobenzamide (**3c**): mp 108–110 °C; IR (KBr) 3340 (s), 1650 (s), 1500 (s), 1550 (s), 1530 (s), 1490 (m), 1350 (s), 1240 (m), 1110 (m), 970 (m), 870 (m), 720 (m), 680 cm^{-1} (m); NMR (Me_4Si, $CDCl_3$) δ 1.67 (d, 3 H, J = 6 Hz, CH_3), 3.98 (t, 2 H, J = 5 Hz, CH_2), 5.60 (m, 2 H, nonequivalent vinyl protons), 7.19 (5, br, 1 H, NH), 7.97 (d, 2 H, J = 9 Hz, equivalent aryl protons), 8.22 (d, 2 H, J = 9 Hz, equivalent aryl protons).

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49. Found: C, 59.81; H, 5.35.

***N*-(3-Methyl-2-buten-1-yl)-*p*-nitrobenzamide (3d).** Following the procedure for the preparation of **3c**, freshly distilled 1-chloro-3-methyl-2-butene was converted to **3d** in 16% overall yield; after recrystallization from methanol: mp 106–108 °C; IR (KBr) 3300 (s), 1650 (s), 1560 (s), 1530 (s), 1350 (s), 1200 (m), 1120 (m), 975 (m), 850 (m), 700 cm^{-1} (m); NMR (Me_4Si, $CDCl_3$) δ 1.69 (s, 6 H, CH_3), 4.01 (t, 2 H, J = 5 Hz, CH_2), 5.26 (t, 1 H, J = 5 Hz, CH), 8.17 (d, 2 H, J = 9 Hz, equivalent aryl protons).

Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.54; H, 5.98. Found: C, 61.75, H, 5.96.

Bromination of 3c, 3d, and 3e. General Procedure in Acetic Acid. Bromine in acetic acid (ca. 0.5–1 mmol/mL) was slowly added by glass syringe to a well-stirred solution of the allylic amide in acetic acid (ca. 0.05–2 mmol/mL). Precipitation of the bromocyclic salt(s) occurred over the course of the addition. Diethyl ether was added to double the volume and precipitate the remaining dissolved bromocyclic salt(s). The salt(s) were filtered, washed with ether, dried, and treated with an excess of anhydrous triethylamine. The resulting solution was diluted with ether (*ca.* 20-fold excess) and extracted twice with water. The ethereal solution was then dried (Na_2SO_4) and evaporated in vacuo to give the free base (oxazoline or oxazine or mixture). The filtrate from the salt filtration contained the dibromide.

Bromination of 3c in Acetic Acid. Following the general procedure above, **3c** (1.0 g., 4.5 mmol) reacted with bromine (0.73 g, 4.5 mmol) to give 1.06 g (61%) of a mixture of *trans*-2-*p*-nitrophenyl-5-bromo-6-methyl-5,6-dihydro-4*H*-oxazinium bromide (**5c·HBr**) and 2-*p*-nitrophenyl-5-(1-bromoethyl)oxazolinium bromide (**4c·HBr**): IR (KBr) 3200–2400 (s), 1730 (m), 1675 (s), 1600 (m), 1525 (s), 1480 (m), 1350 (s), 1270 (s), 1150 (m), 1010 (m), 850 (s), 700 cm^{-1} (s). After treatment with triethylamine, the residue from the ether solution was 0.82 g (60% overall) of a mixture of *trans*-2-*p*-nitrophenyl-5-bromo-6-methyl-5,6-dihydro-4*H*-oxazine (**5c**) and 2-*p*-nitrophenyl-5-(1-bromoethyl)-2-oxazoline (**4c**) (mp 89–105 °C): IR (KBr) 1650 (s), 1600 (s), 1520 (s), 1340 (s), 1260 (s), 1100 (s), 1070 (m), 860 (m), 840 (m), 790 cm^{-1} (s); NMR (Me_4Si, $CHCl_3$) 1.62 (d, 3 H, J = 6 Hz, CH_3), 1.78 (d, 3 H, J = 6 Hz, CH_3), 3.78–4.89 (m, CH and CH_2), 7.78–8.84 (m, aryl protons). The ratio of methyl protons by NMR integration of δ 1.62 vs. those at δ 1.78 was 79:21. Gas chromatographic analysis gave an 80:20 ratio.

Anal. Calcd for $C_{11}H_{11}N_2O_3Br$: C, 44.17; H, 3.71. Found: C, 44.24; H, 3.75.

The oxazine and oxazoline mixture (0.78 g) was dissolved in 20 mL of benzene and poured onto a column (2.4 × 20.0 cm) of Flurosil (80 g) prepared in benzene. Elution with benzene/ether (75/25 v/v) gave 0.15 g of pure **5c** free of its isomer which came off with the remainder of the oxazine: NMR (Me_4Si, $CDCl_3$) δ 1.62 (d, 3 H, J = 6 Hz, CH_3), 3.98 (m, 3 H, CHBr and CH_2), 4.43 (m, 1 H, HC-CH_3), 8.04 (d, 2 H, J = 9 Hz, equivalent aryl protons), 8.10 (d, 2 H, J = 9 Hz, equivalent aryl *protons*); mass spectrum (70 eV) *m/e* (*rel* intensity) 300, 298 (3, M^+), 219 (5, M^+ − Br), 191 (10, $ArC(O^+)=NCH=CH_2$), 179 (15, $HO^+CArN=CH_2$), 150 (30, $ArC\equiv O^+$), 41 (100, $N^+CH=CH_2$).

The filtrate from filtering the bromocyclic salt mixture yielded an oily reddish brown residue when dried. The residue was triturated with water (100 mL) to yield 0.52 g (30%) of N-(*erythro*-2,3-dibromobutyl)-*p*-nitrobenzamide (**6c**), mp 128–133 °C, from the trans addition of bromine. Recrystallization from methanol gave the pure amide: mp 135–138 °C; IR (KBr) 3300 (s), 1640 (s), 1590 (m), 1530 (s), 1510 (s), 1340 (s), 1320 (s), 1300 (s), 1240 (m), 1150 (m), 950 (m), 860 (m) 810 (m), 700 (m), 670 (m), 650 cm^{-1} (m); NMR (Me_4Si, $CDCl_3$) δ 1.96 (d, 3 H, (J = 6 Hz, CH_3), 3.67–4.89 (m, 4 H, NCH_2 and CHBr), 5.67 (br s, NH), 8.13 (d, 2 H, J = 8 Hz, aryl protons), 8.35 (d, 2 H, J = 8 Hz, aryl protons).

Anal. Calcd for $C_{11}H_{12}N_2O_3Br_2$: C, 34.76: H, 3.18. Found C, 34.84; H, 3.14.

In a separate experiment, *N*-bromosuccinimide (0.41 g, 2.3 mmol) was added with stirring over a 5-min period to **3c** (0.50 g, 2.3 mmol) in 25 mL of acetic acid. Precipitation of the oxazinum and oxazolinium salts (acetates) did not occur either in the reaction sequence or with the addition of ether (50 mL) to the solution. After the solvents were removed in vacuo, ether (50 mL) and pyridine (6 g) were added to the resulting air-dried precipitate. the **5c/6c** ratio in the resulting solution was determined by GLC analysis to be 34:66. This solution, neglecting the solvent, contained *N*-crotyl-*p*-nitrobenzamide (**3c**) (11%), the oxazine **5c** (47%), the oxazoline **4c** (24%), and an unidentified product (18%) that may be the result of elimination (pyridine present) or it may be the bromo acetate addition product.

Bromination of 3d in Acetic Acid. Following the general procedure given above, bromine (0.68 g, 4.3 mmol) was reacted with **3d** (1.0 g, 4.3 mmol) to yield 1.25 g (75%) of 2-*p*-nitrophenyl-5-bromo-6,6-dimethyl-5,6-dihydro-4*H*-oxazinium bromide (**5d·HBr**): IR (KBr) 3200–2400 (s), 1730 (m), 1675 (s), 1600 (m), 1525 (s), 1480 (m), 1370 (m), 1350 (s), 1300 (m), 1150 (m), 1110 (s), 1010 (m), 850 (s), 775 (m), 700 cm^{-1} (s). This salt subsequently gave 0.97 g (72%) of 2-*p*-nitrophenyl-5-bromo-6,6-dimethyl-5,6-dihydro-4*H*-oxazine (**5d**): mp 112–113 °C (from methanol); IR (KBr) 1650 (s), 1600 (s), 1520 (s), 1430 (m), 1340 (s), 1280 (s), 1180 (m), 1090 (s), 1070 (m), 850 (s), 690 cm^{-1} (m); NMR (Me_4Si, $CHCl_3$) δ 1.56 (s, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 3.98 (m, 3 H, CHBr and CH_2), 8.08 (d, 2 H, J = 9 Hz, equivalent aryl protons), 8.12 (d, 2 H, J = 9 Hz, equivalent aryl protons).

Anal. Calcd for $C_{12}H_{13}N_2O_3Br$: C, 46.02; H, 4.19. Found: C, 46.00, H, 4.13.

The filtrate from filtration of the oxazinium salt yielded only a brown tar when evaporated on a rotary evaporator at 21 °C. The tar was not characterized but was assumed to arise, at least in part, from decomposition of the dibromide addition product **6d.** Since isolation of the dibromide from this reaction mixture proved unlikely, a reaction mixture was prepared in the same molar ratios given above. The solution, which contained a white precipitate of the oxazinium salt, was treated with sufficient anhydrous triethylamine to neutralize the acetic acid and liberate **5d.** Excess triethylamine in the reaction mixture produced a two-phase liquid system which was reduced to a single liquid phase with the addition of an equal volume of acetone. A GLC analysis of the resulting solution revealed 82% **5d,** 16% *N*-(2,3-dibromo-3-methylbutyl)-*p*-nitrobenzamide (**6d**), and 2% of the starting amide **3d.** Based on mass response factors from GLC analysis of known amounts of the pure components, a complete mass balance was achieved.

In a reaction sequence similar to that above, a 100% molar excess of bromine was used. A GLC analysis of the reaction products indicated a 95% yield of **5d** and 5% **6d.**

Bromination of 3e in Acetic Acid. Following the general procedure given above, bromine (0.52 g, 3.3 mmol) was reacted with **3e** (0.93 g, 3.3 mmol) to give 1.10 g (76%) of *trans*-2-*p*-nitrophenyl-5-bromo-6-phenyl-5,6-dihydro-4*H*-oxazinium bromide (**5e·HBr**): mp 182.5–183.5 °C (from acetone/ether); IR (KBr) 3050–2850 (s), 1725 (s), 1600 (m), 1525 (s), 1490 (m), 1340 (m), 1315 (m), 1265 (s), 1110 (m), 1080 (s), 1005 (m), 705 (s), 690 cm^{-1} (m); NMR (Me_4Si, CF_3CO_2H) δ 8.56 (s, 4, *p*-nitrophenyl protons); 7.57 (s, 5, phenyl protons), 5.40 (m, 1, CHPh), 4.46 (m. 2, CH_2), 3.82 (m, 1, CHBr). After treatment with triethylamine, the oxazinium salt (1.0 g, 2.3 mmol) gave 0.66 g (81%) of *trans*-2-*p*-nitrophenyl-5-bromo-6-phenyl-5,6-dihydro-4*H*-oxazine (**5e**): mp 141–143 °C (from ethyl acetate); IR (KBr) 1660 (s), 1605 (s), 1520 (s), 1340 (s), 1260 (s), 1100 (s), 1020 (m), 865 (m), 855 (s), 770 (m), 750 (m), 695 cm^{-1} (s); NMR ($CDCl_3$) 3.88 (m, 2, CH_2), 4.23 (m, 1, CHBr), 5.34 (d, 1, J = 7.2 Hz, CHPh), 7.27 (s, 5, phenyl ring protons), 8.00 (m, 4, *p*-nitrophenyl ring protons).

Anal. Calcd for $C_{16}H_{13}N_2O_3Br$: C, 53.21; H, 3.60. Found: C, 53.10; H, 3.58.

Upon standing, the filtrate from the oxazinium salt filtration yielded 0.23 g of precipitate (mp 171–172 °C). Evaporation of this filtrate and recrystallization from ethanol yielded an additional 0.09 g for a total of 0.32 g (22%) of *erythro*-2,3-dibromo-3-phenylpropyl-*p*-nitrobenzamide (**6e**) resulting from trans addition of bromine: IR (KBr) 3350 (s), 1650 (s), 1605 (s), 1555 (s), 1525 (s), 1455 (m), 1425 (m), 1350 (s), 1325 (s), 1315 (s), 1050 (m), 965 (m), 870 (s), 765 (m), 720 (m), 710 (m), 645 (s), 690 (m), 650 cm^{-1} (m); NMR (Me_4Si, CF_3CO_2H) δ 8.21 (d, 2, J = 8.2 Hz, *p*-nitrophenyl ring protons), 7.90 (d, 2, J = 8.2 Hz, *p*-nitrophenyl ring protons), 7.18 (s, 5, phenyl ring protons), 4.95 (d. 1, J = 9.5 Hz, PhCHBr), 4.34 (m, 1, CHBr), 3.90 (m, 2, CH_2).

Anal. Calcd for $C_{16}H_{14}N_2O_3Br_2$: C, 43.66; H, 3.16. Found: C, 43.49; H, 3.28.

General Procedure in Carbon Tetrachloride. Owing to the relative insolubility of the amides in carbon tetrachloride the solvent volume was greater than for similar reactions in acetic acid. Thus, bromine in carbon tetrachloride (ca. 0.5–1 mmol/mL) was added by syringe to the amide in carbon tetrachloride (ca. 1 mmol/100 mL). The Br_2/CCl_4 solution was added over a 0.25–1-h period to an Al-foil-wrapped flask containing the alkene solution. The precipitate of the oxazinium/oxazolinum salts was filtered and the precipitate was washed with anhydrous diethyl ether and air dried. The free bases were generated from the salts by the same procedure given above for the acetic acid reactions. The ether and carbon tetrachloride filtrates from the salt filtration and washings were concentrated in vacuo to yield the dibromide addition products.

Bromination of 3c in Carbon Tetrachloride. Following the general procedure above, bromine (0.36 g, 2.3 mmol) was reacted with **3c** (0.5 g, 2.3 mmol) yielding 0.31 g (36%) of a mixture of the bromocyclic salts which in turn gave 0.22 g (33% overall) of a mixture of the bromooxazoline **4c** and the bromooxazine **5c** in a ratio of 48:52, respectively (by NMR integration of the methyl peaks at δ 1.62 and 1.78). The ether and carbon tetrachloride filtrates yielded 0.59 g (58%) of the dibromide **6c,** mp 135–138 °C. All products proved to be identical with those from the acetic acid run by NMR, IR, mmp, and GLC analysis.

Bromination of 3d in Carbon Tetrachloride. Bromine (0.775 g 4.72 mmol) was reacted with **3d** (1.10 g, 4.70 mmol) to give an immediate reddish precipitate. Owing to the lability of dibromide **6d** and its low solubility in carbon tetrachloride, the solvent was evaporated with a nitrogen jet, and the residue was extracted (soxhlet) with hexane to separate **6d** from **5d·HBr.** The hexane was evaporated with a nitrogen jet to yield 0.41 g of a mixture of unreacted starting material (**3d**) and the dibromide **6d.** Recrystallization from benzene/hexane (25/75) gave 0.04 g (2% overall) of pure *N*-(2,3-dibromo-3-methylbutyl)-*p*-nitrobenzamide (**6d**) (mp 122–123 °C): (KBr) 3300 (s), 1665 (m), 1650 (s), 1610 (m), 1560 (s), 1530 (s), 1370 (m), 1350 (s), 1330 (m), 1300 (m), 1190 (m), 1100 (m). 870 (m), 710 (m), 690 (m); NMR (Me_4Si, $CDCl_3$) 1.90 (s, 3 H, CH_3), 2.02 (s, 3 H. CH_3), 3.67 (m, 1 H, CHBr), 4.56 (m, 2 H, NCH_2), 6.87 (br, s, 7 H, NH), 8.00 (d, 2 H, J = 8 Hz. aryl protons), 8.33 (d, 2 H, J = 8 Hz, aryl protons).

Anal. Calcd for $C_{12}H_{14}N_2O_3Br_2$: C, 36.57; H, 3.56: N, 7.11. Found: C, 36.73; H, 3.48, N. 7.34.

The bromocyclic salt **5d** remaining in the extraction thimble was shown to be identical with that from the acetic acid run by IR. The product ratios, however, were determined by GLC from a separate reaction mixture analyzed immediately after reaction and with triethylamine. Analysis by GLC revealed a composition of 61% of the oxazine **5d,** 22% of the dibromide **6d,** and 15% unreacted amide **3d.**

Bromination of 3e in Carbon Tetrachloride. Following the general procedure, bromine (0.18 g, 1.1 mmol) was reacted with **3e** (0.30 g, 1.1 mmol) giving a quantitative precipitate of the oxazinium salt **5e·HBr** along with the dibromide **6e.** Quantitative IR analysis (empirical ratio method) of the solid mixture revealed the composition to be 36% **5e·**HBr and 64% **6e.** Recrystallization from acetone/ether gave material identified by IR and NMR comparisons as the bromooxazinium salt **5e·**HBr. Recrystallation of the residue from ethanol/water gave the dibromide **6e,** mp 165 °C, which had an IR identical with that from bromination of **3e** in acetic acid.

Chlorination of 3c in Acetic Acid. *N*-Crotyl-*p*-nitrobenzamide (**3c**) (1.0 g, 4.3 mmol) was added over a 5-min period with stirring to a solution of chlorine (0.32 g, 4.6 mmol) in acetic acid (22 mL) in a 100-mL round-bottom flask at a temperature of 25–28 °C. The solution changed from a moderate to a light yellow color with addition. An additional 33 mL of acetic acid was added to the solution. Triethylamine (7.2 g, 71 mmol) was added to 10 mL of this solution without the formation of a precipitate, and the solution was analyzed by GLC. The elution pattern obtained was identical to that of the bromination products. Analysis by GLC allowed the following assignments: chlorooxazoline (12%), chlorooxazine (18%), chlorine addition product (23%), and unreacted starting amide **3c** (47%).

Product Stability Studies. Stability of 6e. A sample of **6e** was dissolved in trifluoroacetic acid (TFA) in an NMR tube. The ^1H NMR of the solution was recorded immediately and at intervals of approximately 1 h for several hours and then after standing overnight. The initial spectrum was that of the amide **6e** (or its N-protonated form). The spectra obtained subsequently had chemical shifts and multiplicities similar to those from **5e.** It was therefore assumed that in protic solvents **6e** cyclizes to **5e** or its cis isomer with a half-life of several hours at room temperature. In CCl_4 **6e** was sparingly soluble but indefinitely stable.

Stability of 6c. The stability of **6c** in acetic acid and CCl_4 was confirmed by dissolution of samples of **6c** in these solvents and recovering them after 2 h or more. Like **6e, 6c** showed some tendency

to slowly solvolyze probably by cyclization to **4c** or **5c** (or its cis isomer).

Stability of 6d. The absence of **6d** as a product from the bromination of **3d** suggests that **6d** may be solvolytically unstable rapidly forming **5d.** This was confirmed by demonstrating that **6d** was formed as a product in the bromination reaction (GLC analysis, see above) and by showing that **6d** rapidly deteriorates upon dissolution in acetic acid.

Stability of 4c·HX and 5c·HX. The composition of a particular mixture of **4c** and **5c,** isolated from a bromination reaction of **3c,** was determined by integration of the methyl protons in its ^1H NMR ($CDCl_3$) to be 47/53 **4c/5c,** respectively. A separate sample of this mixture dissolved in TFA and held at room temperature for 2 h contained the same composition as determined by NMR.

Acknowledgments. This work was supported in part by the donors of the Petroleum Research Fund, administered by the American Chemical Society. We also kindly acknowledge the assistance of Joan MacDairmid, Janet Foutch, Pat Allen, and Peter Grohse in devising procedures for and preparing some of the starting materials. The 3M Company provided tuition assistance to D.W.W. and R.A.H. who kindly acknowledge the support.

Registry No.—**3c,** 67393-51-5; **3d,** 55289-73-1; **3e,** 34562-10-2; **4c,** 67393-52-6; **4c·HBr,** 55289-78-6; **5c,** 67393-53-7; **5c·HBr,** 67393-54-8; **5d,** 67393-55-9; **5d·HBr,** 67393-56-0; **5e,** 51979-14-7; **5e·HBr,** 52246-91-0; **6c,** 67393-57-1; **6d,** 55289-77-5; **6e,** 51979-15-8; crotyl chloride, 4894-61-5; potassium phthalimide, 1074-82-4; *N*-crotylphthalimide, 67393-58-2; *N*-crotylamine, 56930-04-2; *p*-nitrobenzoyl chloride, 122-04-3; 1-chloro-3-methyl-2-butene, 503-60-6.

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(10) (a) G. A. Olah, P. Schilling, P. W. Westerman, and H. C. Lin, *J. Am. Chem. Soc.*, **96** 3581 (1974); (b) G. A. Olah and T. R. Hockswender, Jr., *ibid.*, **96,** 3565 (1974).
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(13) Other conjugated systems may react by initial attack at an atom other than an olefinic carbon, cf. ref 14.
(14) H. Weiss, *J. Am. Chem. Soc.*, **99,** 1670 (1977).
(15) Halolactonization reactions have been shown (ref 16) to proceed by the spiro route. Some systems, e.g., acrylate and crotonate, which would undergo halolactionization to give highly strained systems via the spiro route are unreactive (ref 17). Selenolactonization (ref 18) and other ring closure reactions (ref 19) seem to verify the strong preference for the spiro mode. There are exceptions (ref 19) which appear to be of stereochemical origin. Since halolactonizations are now known to favor reversibly forming the thermodynamic product, those exceptions for halolactonizations (ref 16) need to be reinvestigated.
(16) W. E. Barnett and W. H. Sohn, *Chem. Commun.*, 472 (1972); *Tetrahedron Lett.*, 1777 (1972). For a review of the older literature with exceptions, see V. I. Staninets and E. A. Shilov, *Russ. Chem. Rev. (Engl. Transl.),* **40,** 272 (1971).
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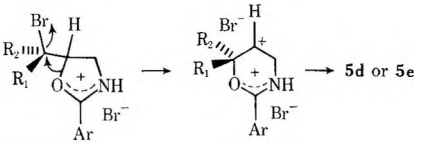
(20) The possibility that an anchimerically assisted addition–cyclization process might occur (e.g., D. L. H. Williams, E. Bienvenue-Goetz, and J. E. Dubois, *J. Chem. Soc. B,* 517 (1969), but see S. R. Hooley and D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2,* 503 (1975), and ref 15, pp 177–181) was considered. That **5d** and **5e** are the sole products of bromocyclization of **3d** and **3e,** respectively, effectively eliminates the anchimerically assisted route from consideration since the spiro mode product (the five-membered rings) is the expected product of a concerted addition–cyclization, cf. ref 15.
(21) A portion of this work has been reported in preliminary form: S. P. McManus and R. A. Hames, *Tetrahedron Lett.*, 4549 (1973); S. P. McManus and D. W. Ware, ibid., 4271 (1974).
(22) L. Goodman and S. Winstein, *J. Am. Chem. Soc.*, **79,** 4788 (1957).
(23) R. F. Merritt, unpublished results; we thank Dr. Merritt for providing us with a summary of his work.
(24) The possibility that **5d** and **5e** are thermodynamic products formed by rearrangement of the oxazolinum ions i and ii can be eliminated since the



i, $R_1 = R_2 = Me$
ii, $R_1 = Ph$; $R_2 = H$

cyclic salts generally were insoluble in the reaction medium and immediately precipitated. Furthermore, we were unable to detect any equilibration of oxazolinium cations under reaction conditions (see Experimental Section.)
(25) G. A. Olah, "Halonium Ions", Wiley, New York, N.Y., 1975.
(26) (a) J. M. Harris and C. C. Wamser, "Fundamental or Organic Reaction Mechanisms", Wiley, New York, N.Y., 1976, pp 123 and 124; (b) J. March, "Advanced Organic Chemistry", 2nd ed, McGraw-Hill, New York, N.Y., 1977, p 470.
(27) G. S. Hammond, *J. Am. Chem. Soc.*, **77,** 334 (1955); D. Farcasiu, *J. Chem. Educ.*, **52,** 76 (1975).
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(29) M. F. Ruasse and J. E. Dubois, *J. Org. Chem.*, **42,** 2689 (1977).
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(31) A. Modro, G. H. Schmid, and K. Yates, *J. Org. Chem.* 42, 3673 (1977).
(32) S. P. McManus and S. D. Worley, *Tetrahedron Lett.*, 555 (1977).
(33) The highly useful iodolactionization, cf., ref 16, and selenolactonization, cf. ref. 18, reactions probably owe their unusual facility to this concept.
(34) Although we eliminated the possibility of the concerted (anchimerically assisted) addition-cyclization for bromination of **3d** and **3e** and for a great portion of **3c,** cf. footnote 20, this possibility cannot be eliminated for **3a, 3b** and as a competing process in **3c** since the neighboring group assisted transition state shown in Scheme II could indeed lead directly to the observed cyclic product. In retrospect, it would have been useful to study chlorocyclization of **3d** and **3e** for comparison purposes.
(35) G. Bellucci, G. Berti, G. Ingrosso, and E. Mastrorilli, *Tetrahedron Lett.*, 3911 (1973); P. L. Barilli, G. Bellucci, F. Marioni, I. Morelli, and V. Scartoni, *J. Org. Chem.*, **37,** 4353 (1972).
(36) Solvent effects on rates have been thoroughly treated in recent articles, cf. ref. 29 and 31.
(37) Because of the presence of good nucleophiles it is unlikely that halonium ion-haloalkyl carbocation equilibria (cf. ref 38, 39) are established here.
(38) P. M. Henrichs and P. E. Peterson, *J. Am. Chem. Soc.*, **95,** 7449 (1973); *J. Org. Chem.*, **41,** 362 (1976).
(39) S. D. Beatty, S. D. Worley, and S. P. McManus; *J. Am. Chem. Soc.*, **100,** 4254 (1978); W. L. Jorgensen, *ibid.*; **100,** 1049 (1978).
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(42) S. P. McManus, J. T. Carroll, and C. U. Pittman, Jr., *J. Org. Chem.*, **35,** 3768 (1970); S. P. McManus, C. U. Pittman. Jr., and P. E. Fanta, *ibid.*, **37,** 2353 (1972).
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(45) Dr. Nakai has suggested (private communication) that this indicates initial protonation of the C=S bond as we have previously observed, cf. S. P. McManus, K. Y. Lee, and C. U. Pittman, Jr., *J. Org. Chem.*, **39,** 3041 (1974).
(46) E. Klein, H. Farnow, and W. Rojahn, *Tetrahedron Lett.*, 1109 (1963).
(47) A. T. Bottini, V. Derv, and J. Klinck, "Organic Synthesis", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 121.
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Preparation and Properties of Monosulfoxides of Dithioethers

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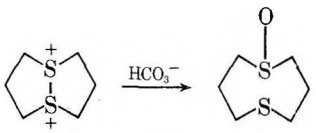
Received June 30, 1978

A study of the synthesis and properties of a series of acyclic and mesocyclic monosulfoxides of dithioethers with various oxidizing agents (MCPA, $NaIO_4$, Me_2SO) is reported. The results of this study are compared with monosulfoxide formation by the hydrolysis of dithioether dications. ^{13}C and ^1H NMR are used to identify the monosulfoxides. ^{13}C NMR is especially useful in confirming the structure of 2,5-dithiahexane monosulfoxide, where the ^1H NMR spectrum in $CDCl_3$ shows three singlets. Although $NaIO_4$ is the reagent of choice, small amounts of the disulfoxide (3–4%) are always present even though 1 equiv of oxidizing agent is used. Likewise with MCPA small amounts of disulfoxides are always present, and in certain compounds (1,4-dithiacycloheptane, 2,4-dithiahexane, and 2,7-dithiaoctane) the disulfoxide is formed in 25% yield. The influence of the S–O dipole on the reactivity of the remaining thioether group is discussed.

We recently reported that dithioether dications react with aqueous bicarbonate to give high yields of monosulfoxides, uncontaminated by sulfones and disulfoxides.[1] To confirm the identity of these monosulfoxides, we felt that it was necessary to synthesize authentic samples of monosulfoxides of dithioethers by another route. However, there were no established procedures in the literature for preparing these monosulfoxides, so a study of this reaction was initiated. The names and abbreviations of the dithioethers are as follows: 1,4-dithiane (1,4-DT); 1,4-dithiacycloheptane (1,4-DTCH); 1,5-dithiacyclooctane (1,5-DTCO); 1,5-dithiacyclononane (1,5-DTCN); 1,6-dithiacyclodecane (1,6-DTCD); 2,5-dithiahexane (2,5-DTH); 2,6-dithiaheptane (2,6-DTHP); and 2,7-dithiaoctane (2,7-DTO).



Background. In devising methods for the preparation of sulfoxides, the usual problem is overoxidation to sulfones. Several methods for the preparation of sulfoxides which have been used successfully include hydrogen peroxide in acetic acid in the presence of a catalytic amount of strong acid,[2] sodium periodate,[3] *m*-chloroperbenzoic acid, and oxygen exchange with dimethyl sulfoxide.[4] However, in the oxidation of dithioethers to monosulfoxides, not only overoxidation to sulfone but also formation of disulfoxide must be avoided. Attempts to oxidize dithioethers to monosulfoxides often result in the formation of one or both of the isomeric disulfoxides even though 1 equiv of oxidizing agent is used. An example of this problem is found in the oxidation of 1,4-dithiane with hydrogen peroxide. Although 1,4-dithiane 1-oxide would be expected in the reaction, only 1,4-dithiane and 1,4-dithiane 1,4-dioxide were detected in equal amounts.[5] 1,4-Dithiane 1-oxide can be prepared by treatment of 1,4-dithiane with 0.5 equiv of hydrogen peroxide.[6]

Even though hydrogen peroxide can cause difficulties, this reagent is still used extensively in the oxidation of dithioethers. Ogura and Tsuchihashi oxidized 2,4-dithiapentane and its derivatives using from 1 to 3 equiv of hydrogen peroxide and only reported monosulfoxide formation.[7] However, these dithioethers are thioacetals and may behave quite differently from the dithioethers under investigation. 3,6-Dithiaoctane was oxidized to the disulfoxide using slightly more than 2 equiv of hydrogen peroxide. The monosulfoxide of 3,6-dithiaoctane had to be synthesized in an unusual manner. Ethyl 2-chloroethyl sulfide was oxidized with hydrogen peroxide to make the sulfoxide, which was then treated with sodium ethanethiolate. No attempt was made to oxidize 3,6-dithiaoctane directly to the monosulfoxide.[8]

Sodium periodate has become well known as the reagent of choice to oxidize monothioethers to sulfoxides.[3] Isolated yields greater than 90% are reported. The disulfoxides of 2,4-dithiapentane and 2,5-dithiahexane have been synthesized using 2 equiv of sodium periodate. Louw and co-workers reported the synthesis of 2,5-dithiahexane 2-oxide using sodium periodate, but no synthetic details or physical properties were given.[9] Apparently, disulfoxide was also formed in the reaction, and, as expected, the monosulfoxide was hard to separate from the disulfoxide. In 1968, Kleinar prepared 1,5-dithiacyclooctane 1-oxide and 2,6-dithiaheptane 2-oxide using sodium periodate, but this research has not been published.[10]

The only study of the electronic effects which lead to sulfoxide formation in a system with two interacting thioether groups was carried out on substituted 1,3-dithianes.[11] In 1,3-dithiane, where the two sulfur atoms are separated by only one methylene group, there is a strong interaction between the two sulfur atoms. The lone pair orbitals can combine to give filled bonding and antibonding orbitals. The filled σ^* orbital possesses electron density localized away from the sulfur atoms and interacts with electrophilic oxidizing agents. This interaction leads to the formation of a sulfoxide which contains an equatorial oxygen. In the reaction of 4,6-dimethyl-1,3-dithiane with hydrogen peroxide, a nucleophilic attack on the peroxide oxygen by the thioether gives the monosulfoxide(s) having equatorial oxygen to axial oxygen in a ratio of 98:2.[11]

Although the mechanism for the oxidation by sodium periodate is unknown,[12] it has been proposed to proceed via a cyclic intermediate.[13] Due to the proximity of the two sulfur atoms in 1,3-dithiane, the lone pair on the thioether is polarized toward the positively charged sulfur in the periodate complex. In the oxidation of 2-*tert*-butyl-1,3-dithiane with sodium periodate, the monosulfoxide with equatorial oxygen was found to be the most favored product of kinetic control by a ratio of 90:10 and of thermodynamic control by 70:30.[14]

m-Chloroperbenzoic acid (MCPA) is also used to oxidize thioethers to sulfoxides. When thiiranes were oxidized with MCPA,[15] higher yields and purer sulfoxides were obtained than when either sodium periodate[16] or hydrogen peroxide[17] was used.

Another method for making disulfoxides from dithioethers involves oxygen exchange with dimethyl sulfoxide (Me_2SO). Since a large excess of Me_2SO must be used in the reaction, it is not possible to synthesize monosulfoxides of dithioethers by this method.[4]

Results and Discussion

When this study began, there were no detailed procedures in the literature for the synthesis of monosulfoxides of di-

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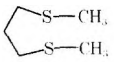
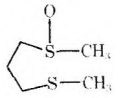
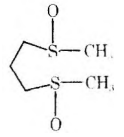
Table I. ^{1}H NMR Data for 2,6-Dithiaheptane, 2,6-Dithiaheptane 2-Oxide, and 2,6-Dithiaheptane 2,6-Dioxide[a,b]

	2.3 (m, 4, $-CH_2-S$) 1.8 (s, 6, CH_3-S) 1.6 (m, 2, $-CH_2-$)
	2.6 (m, 2, $-CH_2-SO$) 2.4 (m, 2, $-CH_2-S$) 2.3 (s, 3, CH_3-SO) 1.8 (s, 3, CH_3-S) 1.8 (m, 2, $-CH_2-$)
	2.6 (m, 4, $-CH_2-SO$) 2.3 (s, 6, CH_3-SO) 2.0 (m, 2, $-CH_2-$)

[a] Spectra were obtained in $CDCl_3$. [b] In parts per million (δ) relative to Me_4Si (multiplicity, number of hydrogens, assignment).

thioethers. In our laboratory, Gorewit synthesized 1,5-dithiacyclooctane 1-oxide in a straightforward reaction by combining equal molar amounts of 1,5-dithiacyclooctane and MCPA.[18] The products consisted of 89% 1,5-dithiacyclooctane 1-oxide and 3% 1,5-dithiacyclooctane 1,5-dioxide.

Since 1,5-dithiacyclooctane 1-oxide had been synthesized in good yield using 1 equiv of MCPA, no problems were anticipated in the synthesis of other monosulfoxides. However, when 1,4-dithiacycloheptane was treated with MCPA under the same conditions, only unreacted 1,4-dithiacycloheptane and small amounts of several other products, apparently the isomeric disulfoxides, were found in the reaction mixture. Thus, it appears that 1,4-dithiacycloheptane 1-oxide is oxidized more rapidly than the dithioether itself.

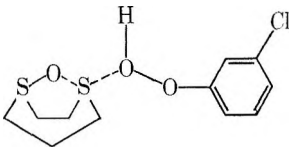
Because of this difficulty with MCPA, the oxidation of 1,4-dithiacycloheptane was carried out using 1 equiv of $NaIO_4$. With this reagent, a 58% yield of the monosulfoxide was obtained with only a small amount (~4%) of the disulfoxide.

In all of the reactions using either sodium periodate or MCPA as the oxidizing agent, at least 2–4% of the disulfoxide is always formed in addition to the desired monosulfoxide. In several of the oxidations with MCPA (1,4-dithiacycloheptane, 2,5-dithiahexane, 2,7-dithiaoctane), a larger amount, approximately 25%, of the disulfoxide and an equal amount of unreacted dithioether are obtained along with the monosulfoxide. Therefore, of the literature procedures, sodium periodate is the reagent of choice. However, monosulfoxides of the dithioethers are obtained by hydrolysis of the dithioether dications[1] in high yield and free from *all* traces of disulfoxide.

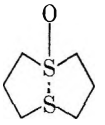
A comparison of the reactivity of the various dithioethers with MCPA shows that little disulfoxide is formed when a trimethylene chain spans the two sulfur atoms. However, except for 1,4-dithiane, an appreciable amount of disulfoxide always forms when two or four methylene groups separate the two sulfur atoms. These observations can be explained by a consideration of the structure of the monosulfoxides and the transition state leading to disulfoxide formation.

The mechanism of the oxidation of thioethers by MCPA involves a nucleophilic attack on the peroxide oxygen by the thioether.[20] Little steric effect should be observed in this reaction, and the charge distribution in the activated complex depends on the polarization of the thioether lone pair by the electrophile. Thus, in the oxidation of a monosulfoxide to a disulfoxide the relative orientation of the polar S–O group of the sulfoxide with respect to the thioether group will influence the course of the reaction.

If the S–O dipole of the sulfoxide can be aligned with the forming S–O dipole in the activated complex, disulfoxide



formation would be more favorable than monosulfoxide formation. This interaction should be most important when a five-membered ring can form, and it would account for the high yield of disulfoxide formation in 1,4-dithiacycloheptane and 2,5-dithiahexane. However, in cases where three methylene groups separate the thioether from the sulfoxide groups, a *sulfur–sulfur* interaction in the ground state reduces the



nucleophilicity of the thioether group and prevents disulfoxide formation. This interaction would account for dominant monosulfoxide formation in 1,5-dithiacyclooctane, 1,5-dithiacyclononane, and 2,6-dithiaheptane.

In cases where more than three methylenes separate the thioether and sulfoxide groups, such as in 2,7-dithiooctane, the groups should function independently and disulfoxide formation should compete favorably with monosulfoxide formation. 1,4-Dithiane is a special case where through-bond rather than through-space interactions occur. In this situation the nucleophilicity of the free thioether group is reduced in the monosulfoxide, and disulfoxide formation becomes unfavorable.

NMR Spectra of Monosulfoxides. In an acyclic monosulfoxide the NMR spectrum was expected to look like a combination of the spectrum of the dithioether and the disulfoxide, and perhaps the spectrum of the monosulfoxide would be difficult to distinguish from a mixture of dithioether and disulfoxide. To test this potential problem, an equal molar amount of 2,6-dithiaheptane and 2,6-dithiaheptane 2,6-dioxide was mixed, and the NMR spectrum was compared to that of authentic 2,6-dithiaheptane 1-oxide.

In 2,6-dithiaheptane the methyl group is a singlet at δ 1.8, whereas in 2,6-dithiaheptane 2,6-dioxide the methyl group is shifted downfield to δ 2.3. Since the monosulfoxide has one methyl group α to a thioether and the other methyl group α to a sulfoxide, its NMR spectrum shows two methyl singlets, which are in the same locations as those of 2,6-dithiaheptane and 2,6-dithiaheptane 2,6-dioxide. The main difference between the spectrum of 2,6-dithiaheptane 2-oxide and the spectrum of an equal molar mixture of 2,6-dithiaheptane and 2,6-dithiaheptane 2,6-dioxide occurs in the α methylene region. In the mixture, the resonance due to the α methylenes of 2,6-dithiaheptane 2,6-dioxide occurs at δ 2.6 and is a triplet. The triplet due to the α methylenes of 2,6-dithiaheptane is at δ 2.3 and is partly overlapped by the methyl singlet of the disulfoxide. The monosulfoxide has peaks between δ 2.3 and 2.7 as well; however, they form a complex multiplet which is quite distinct from the peaks of the mixture. Hence, a comparison of the NMR spectrum in the δ 2.3–2.7 region indicates whether the monosulfoxide or a mixture containing dithioether and disulfoxide is present (Table I). The spectra of 2,7-dithiaoctane and its mono- and disulfoxides are similar to those of 2,6-dithiaheptane and its sulfoxides, except that the additional β methylene group in the 2,7-dithiaoctane compounds increases the intensity in that δ region. However, the region in the NMR due to the β methylene is not as indicative of whether a monosulfoxide or a mixture is present.

The NMR spectra of all monosulfoxides, except 2,5-dithiahexane 2-oxide, were as expected. The spectrum of 2,5-dithiahexane 2-oxide in deuterated chloroform has three singlets

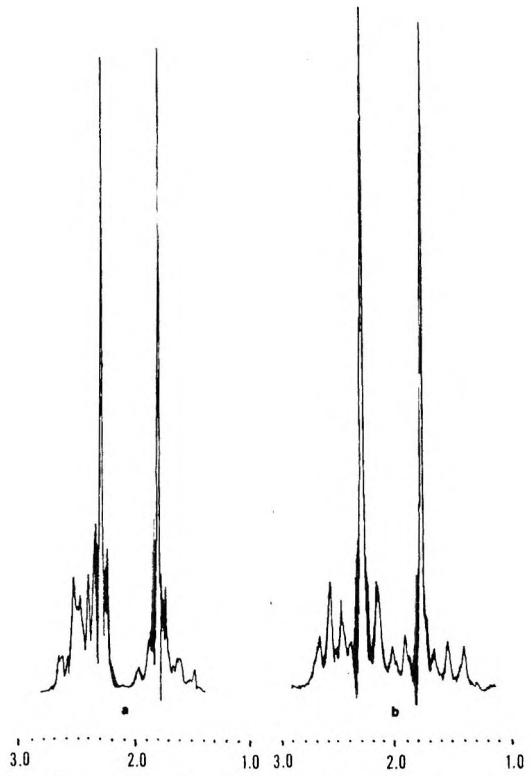


Figure 1. ^{1}H NMR spectra of (a) 2,6-dithiaheptane monosulfoxide and (b) an equal molar mixture of 2,6-dithiaheptane and 2,6-dithiaheptane disulfoxide.

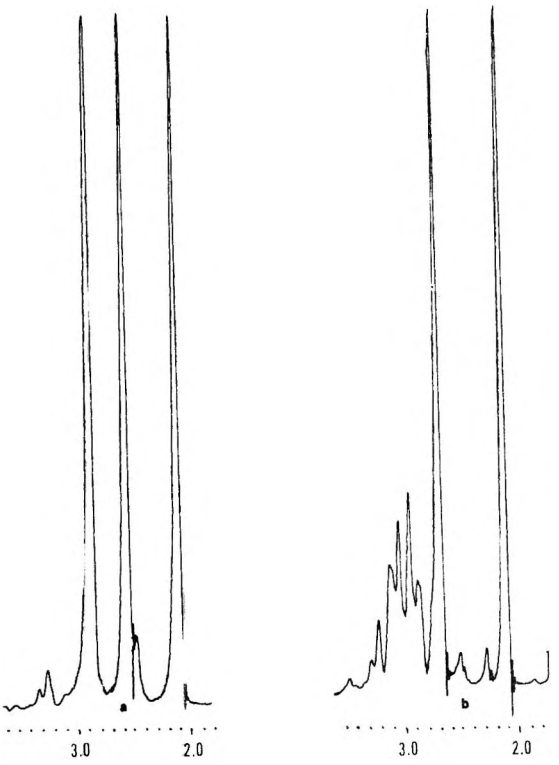
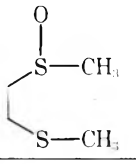


Figure 2. ^{1}H NMR spectra of 2,5-dithiahexane monosulfoxide (a) in deuterated chloroform and (b) in deuterium oxide.

at δ 2.9, 2.6, and 2.1 which integrate to 4:3:3. It appears that the methylene protons α to the sulfoxide and those α to the thioether coincidentally occur at the same frequency. When the NMR spectrum of 2,5-dithiahexane 2-oxide is obtained in deuterium oxide, the singlet at δ 2.9 is split into multiplets because the methylene protons α to the sulfoxide shift downfield slightly. The ^{13}C NMR spectrum of 2,5-dithiahexane 2-oxide in deuterated chloroform shows four different carbons. Off-resonance decoupling identifies the carbon at 25.6 ppm as the methylene α to the thioether and the carbon at 52.8 ppm as the methylene α to the sulfoxide. Both methylenes have hydrogen absorptions at δ 2.9, as shown in Table II.

Table II. ^{13}C and ^{1}H NMR Data for 2,5-Dithiahexane 2-Oxide[a]



^{13}C NMR, δ	assignment	^{1}H NMR, δ
52.8	CH_2 α to S–O	2.9
37.4	CH_3 α to S–O	2.6
25.4	CH_2 α to S	2.9
14.6	CH_3 α to S	2.1

[a] Spectrum was taken in $CDCl_3$; in parts per million (δ) relative to Me_4Si.

Summary

The synthesis of monosulfoxides of dithioethers using *m*-chloroperbenzoic acid and sodium periodate results in variable yields of monosulfoxide which are always contaminated by at least small amounts of disulfoxides. With MCPA, often a large fraction of the product is the disulfoxide. Oxygen exchange between dithioethers and Me_2SO would seem to be the favored method for synthesis of disulfoxides.

It appears that the best method for synthesizing pure monosulfoxides of dithioethers involves treatment of the dithioether dications with water. The monosulfoxides are formed in greater than 70% yield, and no disulfoxides or sulfones can be impurities. The major limitation of the method is that the dithioether dications must have the two dicationic sulfur atoms in close proximity to one another so that one group influences the other. When the two positively charged atoms are isolated from one another, a mixture of dithioether, monosulfoxide, and disulfoxide would be expected.

Experimental Section

Physical Measurements. Melting points are uncorrected and were determined on a Thomas-Hoover Unimelt. ^{1}H NMR spectra were measured on a Varian Model EM-360 spectrometer; ^{13}C NMR spectra were measured at 25.14 MHz on a Nicolet TT-23 spectrometer. Ultraviolet and visible spectra were determined on a Cary-17 recording spectrometer. Infrared spectra were measured on a Beckman IR8 or IR12 infrared spectrometer. Gas chromatograms were obtained on a Varian Aerograph Model 90-P chromatograph. Thin-layer chromatograms were run on Eastman Kodak silica gel TLC plates or Merck silica gel TLC plates. Column chromatography was run on Merck silica gel. Microanalyses were performed by the Microanalytical Laboratory operated by the College of Chemistry, University of California, Berkeley, Calif.

One analytical procedure is described for a typical synthesis of a monosulfoxide of a dithioether. The yield and experimental data for other monosulfoxides prepared by the same procedure are then listed.

Use of MCPA. The sulfoxides were synthesized by a modification of the procedure of Kondo.[15] To a rapidly stirring solution of 2.63 g (17.7 mmol) of 1,5-dithiacyclooctane in 100 mL of chloroform maintained at −20 °C under nitrogen was added 3.59 g (17.7 mmol) of 85% *m*-chloroperbenzoic acid in 90 mL of chloroform over 30 min. The solution was stirred for 30 min longer at −20 °C and then allowed to warm to room temperature over 45 min. Anhydrous ammonia was bubbled into the reaction mixture. Immediately the mixture became cloudy and ammonium *m*-chlorobenzoate precipitated. The mixture was filtered through a bed of Celite and treated once more with ammonia. The filtrate was concentrated to a yellow oil under vacuum. The oil was dissolved in 1:1 ethanol–ether and cooled overnight. Fil-

tration of the white crystals gave 66.2 mg (2%) of **1,5-dithiacyclooctane 1,5-dioxide:** mp 150–151 °C; IR (CH_2Cl_2) 1020 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ 3.33 (m, 8, $-CH_2S{=}O$), 2.60 (m, 4, $-CH_2-$).

The remaining oil was dissolved in ether–dichloromethane (5:1) and cooled overnight. The flask containing the crystals and supernatant liquid was placed in liquid nitrogen and transferred to a dry-box. The crystals were filtered rapidly and then dried under vacuum to give 1.78 g (62%) of very hygroscopic **1,5-dithiacyclooctane 1-oxide:** mp 27–29 °C; IR (CH_2Cl_2) 1010 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ 3.12 (m, 4, $CH_2S{=}O$), 2.64 (m, 4, CH_2S), 2.29 (m, 4, $-CH_2-$); ^{13}C NMR ($CDCl_3$) δ 56.6, 30.2, 23.7; mass spectrum (70 eV), *m/e* (relative intensity) 164 (10), 148 (40), 106 (78), 45 (100). Precise mass for $C_6H_{12}S_2O$: found, 164.0357 and 164.0327.[18]

2,6-Dithiaheptane 2-Oxide: 2.95 g (96%);[23] IR (CH_2Cl_2) 1052 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.6 (m, 2, $-CH_2SO$), 2.4 (m, 2, CH_2S), 2.3 (s, 3, CH_3SO), 1.8 (s, 3, CH_3S), 1.8 (m, 2, CH_2); ^{13}C NMR ($CDCl_3$) δ 54.2, 37.8, 32.1, 21.0, 14.3; mass spectrum (70 eV), *m/e* (relative intensity) 136 (83), 121 (82), 73 (79), 61 (100), 45 (87). Anal. Calcd for $C_5H_{12}OS_2$: C, 39.44; H, 7.94. Found: C, 39.43; H, 7.83.

1,4-Dithiane 1-Oxide: 0.55 g (68%); mp 119–122 °C (lit.[16] mp 125 °C); IR (Nujol) 1050 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ 2.1–3.7 (m, 8); mass spectrum (70 eV), *m/e* (relative intensity) 120 (100), 84 (95), 61 (76), 46 (71).

1,5-Dithiacyclononane 1-Oxide: 0.40 g (83%); mp 65–70 °C; IR (Nujol) 1010 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ 3.2 (m, 4, $-CH_2SO$), 2.7 (m, 4, $-CH_2S$), 2.0 (m, 6, $-CH_2-$); ^{13}C NMR ($CDCl_3$) δ 47.8, 46.5, 31.8, 29.4, 26.5, 19.3, 17.4; mass spectrum (70 eV), *m/e* (relative intensity) 162 (53), 161 (21), 120 (31), 88 (60), 87 (93), 55 (100). Anal. Calcd for $C_7H_{14}OS_2$: C, 47.15; H, 7.91. Found: C, 46.92; H, 7.66.

1,4-Dithiacycloheptane 1,4-Dioxide: 38.2 mg;[24,25] mp 143–145 °C; IR (Nujol) 1040 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ 3.3 (broad s, 4, CH_2SO), 2.5 (m, 2, CH_2); mass spectrum (70 eV), *m/e* (relative intensity) 138 (39), 89 (88), 76 (65), 63 (74), 45 (69), 41 (100). Anal. Calcd for $C_5H_{10}O_2S_2$: C, 36.12; H, 6.06. Found: C, 36.10; H, 6.05.

2,7-Dithiaoctane 2-Oxide: 1.50 g (23%);[24] IR (neat) 1020 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ 2.3–2.8 (m, 4, CH_2S and CH_2SO), 2.4 (s, 3, CH_3SO), 2.0 (s, 3, CH_3S), 1.7 (m, 4, CH_2); ^{13}C NMR ($CDCl_3$) δ 52.6, 37.2, 32.4, 26.9, 20.5, 14.2; mass spectrum (70 eV), *m/e* (relative intensity) 166 (12), 150 (10), 103 (30), 61 (82), 55 (100). Anal. Calcd for $C_6H_{14}OS_2$: C, 43.33; H, 8.49. Found: C, 43.44; H, 8.28.

2,5-Dithiahexane 2,5-Dioxide: 0.42 g (25%); α mp 169–171 °C (lit. mp 169–170[4] and 163–164 °C[19]); α and β mmp 136–142 °C (lit.[21] 128–130 °C); IR (Nujol) 1040 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ 3.1 (m, 4, CH_2SO), 2.6 (s, 6, CH_3SO); mass spectrum (70 eV), *m/e* (relative intensity) 139 (8), 126 (5), 91 (50), 64 (35), 63 (100).

Use of Sodium Periodate. Sulfoxides were synthesized by a modification of the procedure of Leonard and Johnson[3] and Carlson and Helquist.[22] To a solution of 1.20 g (10.0 mmol) of 2,5-dithiahexane in 125 mL of methyl alcohol was added 2.25 g (10.5 mmol) of sodium periodate in 50 mL of water at room temperature over 30 min. The mixture was stirred for 20 h. The resulting mixture was filtered to remove sodium iodate. The filtrate was concentrated under vacuum to a yellow oil containing a white solid. The mixture was treated with water and extracted three times with chloroform. The combined organic phase was washed with aqueous sodium thiosulfate, dried over Na_2SO_4, filtered, and concentrated under vacuum to give 0.67 g (42%) of **2,5-dithiahexane 2-oxide:** IR (CH_2Cl_2) 1052 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ 2.9 (s, 4, $-CH_2-$), 2.5 (s, 3, CH_3SO), 2.1 (s, 3, CH_3S); ^{13}C NMR ($CDCl_3$) δ 52.8, 37.4, 25.6, 14.6; mass spectrum (70 eV), *m/e* (relative intensity) 138 (11), 126 (6), 122 (2), 91 (70), 64 (72), 63 (100). Anal. Calcd for $C_4H_{10}OS_2$: C, 35.01; H, 7.29. Found: C, 35.14; H, 7.14.

2,7-Dithiaoctane 2-Oxide: 1.60 g (32%).

1,4-Dithiacycloheptane 1-Oxide: 3.47 g (58%); IR (CH_2Cl_2) 1040 cm^{-1} (S→O); ^1H NMR ($CDCl_3$) δ 3.0–3.5 (m, 4, $CH_2S(-O)CH_3$), 2.5–2.9 (m, 4, CH_2SCH_3), 1.8–2.4 (m, 2, CH_2); ^{13}C NMR ($CDCl_3$) δ 55.5, 48.7, 31.9, 24.7, 21.2; mass spectrum (70 eV), *m/e* (relative intensity) 150 (65), 133 (15), 106 (10), 90 (42), 87 (23), 45 (100). Anal. Calcd for $C_5H_{10}OS_2$: C, 39.97; H, 6.71. Found: C, 39.82; H, 6.68.

1,5-Dithiacyclooctane 1-Oxide: 1.67 g (85%).

1,5-Dithiacyclononane 1-Oxide: 0.20 g (72%).

1,6-Dithiacyclodecane 1-Oxide: 0.19 g (85%); ^1H NMR ($CDCl_3$) δ 2.7–3.7 (m, 4, CH_2SO), 2.4–2.7 (m, 4, CH_2S), 1.4–2.2 (m, 8, CH_2).

2,6-Dithiaheptane 2-Oxide: 0.64 g (40%).

Use of Me_2SO. 2,7-Dithiaoctane 2,7-dioxide was synthesized by the method of Hull and Bargar.[4] To 3.00 g (20 mmol) of 2,7-dithiaoctane was added 4.5 mL of Me_2SO and 14.5 μL of 12 N hydrochloric acid. The mixture was heated overnight on a steam bath. Upon cooling to room temperature, white crystals precipitated. The crystals were collected by suction filtration and recrystallized from ethyl acetate to give 2.51 g (69%) of **2,7-dithiaoctane 2,7-dioxide:** mp 100–105 °C (lit.[4] mp 110–111 and 120–122 °C); IR (Nujol) 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.8 (m, 4, CH_2SO), 2.5 (s, 6, CH_3SO), 1.8 (m, 4, CH_2); mass spectrum (70 eV), *m/e* (relative intensity) 167 (52), 149 (12), 119 (38), 103 (43), 63 (70), 61 (50), 55 (100).

2,6-Dithiaheptane 2,6-Dioxide: 2.46 g (74%) recrystallized from tetrahydrofuran; mp 109–111 °C (lit.[4] mp 117–118 °C); IR (CH_2Cl_2) 1054 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.7 (t, 4, CH_2SO), 2.4 (s, 6, CH_3SO), 2.2 (m, 2, CH_2); mass spectrum (70 eV), *m/e* (relative intensity) 153 (44), 105 (50), 89 (78), 77 (64), 63 (100).

Acknowledgment. We wish to thank the University of California for a Faculty Research Grant and the Eastman Kodak Co. for a fellowship to P.B.R.

Registry No.—1,5-DTCO, 6572-95-8; 1,5-DTCO 1,5-dioxide, 67463-83-6; 1,5-DTCO 1-oxide, 61358-15-4; 2,6-DTHP, 24949-35-7; 2,6-DTHP 2-oxide, 67217-05-4; 1,4-DT, 505-29-3; 1,4-DT 1-oxide, 19087-70-8; 1,5-DTCN, 6573-48-4; 1,5-DTCN 1-oxide, 67463-84-7; 1,4-DTCH, 6008-55-5; 1,4-DTCH 1,4-dioxide, 67463-85-8; 2,7-DTO, 15394-33-9; 2,7-DTO 2-oxide, 67463-86-9; 2,5-DTH, 6628-18-8; 2,5-DTH 2,5-dioxide, 10349-04-9; 2,5-DTH 2-oxide, 67463-87-0; 1,4-DTCH 1-oxide, 67463-88-1; 1,6-DTCD, 51472-64-1; 1,6-DTCD 1-oxide, 67463-89-2; 2,7-DTO 2,7-dioxide, 56348-36-8; 2,6-DTHP 2,6-dioxide, 56348-35-7.

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(24) Purified by column chromatography on silica gel with chloroform as eluent.
(25) Recrystallized from dichloromethane–heptane.

Quantitative Treatment of Micellar Catalysis of Reactions Involving Hydrogen Ions[1]

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Received May 16, 1978

At concentrations of sodium lauryl sulfate (NaLS) greater than 10^{-2} M the acid benzidine rearrangement of 1,2-diphenylhydrazine (**1**) is second order in micellar bound hydrogen ions and first order in bound substrate, whereas the acid hydrolysis of *p*-nitrobenzaldehyde diethyl acetal (**4**) is first order with respect to each micellar bound reactant. The kinetic binding constant of **1** to the micelle agrees with that determined spectrophotometrically. Although the pseudophase distribution model is successful at moderately high concentrations of NaLS, it fails at very low concentrations probably because of the formation of submicellar aggregates.

Micellar catalysis of reactions in aqueous solution is generally explained in terms of a distribution of reactants between water and the micelles, with reactions occurring in both environments.[3] It should be possible therefore to treat the rate–surfactant profiles in terms of the concentrations of reactants in the aqueous and micellar pseudophases and the rate constants in each pseudophase. This approach has been applied to micellar catalyzed reactions of nonionic substrates with nonionic nucleophiles[8,9] and to reactions of hydrophobic anionic nucleophiles by estimating nucleophile concentrations in the micellar pseudophase.[8]

Except for reactions involving the hydrogen ion, this experimental approach has not been used for reactions of hydrophilic ions, although Romsted has shown how rate–surfactant profiles can be rationalized in terms of such a model[10] and a similar model has been used to treat micellar catalysis of nucleophilic addition to carbocations.[11]

The distribution of hydrogen ions between water and anionic micelles of sodium lauryl sulfate (NaLS) has been determined by several independent methods,[12] and under conditions in which the substrate was extensively micellar bound the rate–surfactant profiles for acetal hydrolysis depend on the concentrations of micellar bound hydrogen ions rather than on total concentration or activity.[13] The rate–surfactant profiles for the acid hydration of dihydropyridines in aqueous NaLS have also been interpreted in terms of the concentrations of micellar bound substrate and hydrogen ion, but in these systems there is a complication due to the formation of an unreactive conjugate acid by unproductive protonation.[14]

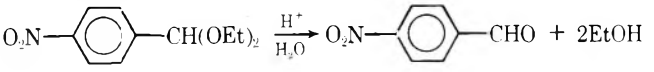
The acid benzidine rearrangement is a very convenient reaction for testing quantitative treatments of micellar catalysis because the reaction of 1,2-diphenylhydrazine (**1**) is second order in hydrogen ions in dilute acid.[15,16]

$$\underset{\mathbf{1}}{\mathrm{PhNH{-}NHPh}} \rightleftarrows \underset{\mathbf{2}}{\mathrm{PhN^{+}H_2NHPh}} \xrightarrow{H^+} \mathrm{H_2NC_6H_4{\cdot}C_6H_4NH_2}$$

The mechanism of this intramolecular rearrangement has been extensively studied, and N–N scission has been shown to be part of the rate limiting step.[17]

The catalysis of anionic micelles of sodium lauryl sulfate (NaLS) is large for two-proton rearrangements, with a maximum rate enhancement of ca. 2000 for the rearrangement of **1** and of ca. 4300 for the two-proton rearrangement of 1,2-ditolylhydrazine (**3**), whereas for one-proton rearrangements it is ca. 50.[18] These results are understandable if micellar catalysis depends strongly upon concentrations of reactants in the Stern layer at the water–micelle interface. There are sharp maxima in the rate–surfactant profiles, and at high surfactant concentrations there is dilution of hydrogen ions in the micellar pseudophase and the rate constants for reactions of **3** become smaller than in water. The aim of the present work was to interpret these profiles in terms of the concentrations of substrate and hydrogen ion in the micellar pseudophase. The distribution of **1** between water and the anionic micelles was estimated spectrophotometrically, and that of hydrogen ions had already been determined.[12,13]

In addition, we examined the rate–surfactant profiles of the hydrolysis of *p*-nitrobenzaldehyde diethyl acetal (**4**) in a similar way.[13]



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Because the rearrangement of 1,2-diphenylhydrazine (**1**) is second order with respect to hydrogen ions, its micellar catalysis provides a more sensitive test of the pseudophase distribution model than does the acetal hydrolysis.

Experimental Section

Surfactants. There are reports of the difficulties in obtaining samples of NaLS of purity such that they do not show surface tension minima.[19] In our present experience the only commercial material which did not exhibit such minima after purification was supplied by Atomergic. We also prepared material by treating lauryl alcohol (0.5 mol) with freshly distilled $ClSO_3H$ (1 mol) in Et_2O under reflux for several days under N_2. The mixture was then neutralized (NaOH), and volatiles and Na_2SO_4 were removed. Both samples were purified by several recrystallizations (EtOH), and we found no surface tension minima. The cmc of the Atomergic sample was 0.007 M, and that of our sample was 0.0076 M at 23 °C, in reasonable agreement with literature values of ca. 0.008 M.[20]

Although both of our samples of NaLS had no minima in plots of surface tension against log [NaLS], we found small (1–2 dyn) minima with mixtures of HCl and NaLS. The surface tensions of NaLS solutions are sensitive to small amounts of surface active impurities, e.g., dodecanol.[19] Micellization speeds the acid-catalyzed hydrolysis,[21] but there should have been very little hydrolysis in the time required for measurement of the surface tension. It is difficult to explain these minima, unless a monolayer of undissociated lauryl sulfuric acid forms at the air–water interface.

These minima make it difficult to estimate the cmc by the surface tension method, but the approximate values of the cmc in the presence of HCl are 0.0055, 0.0045, and 0.0035 M in 0.001, 0.003, and 0.01 M HCl, respectively. These values are similar to those in solutions of NaCl, and therefore in treating the kinetics we estimated the cmc by interpolation of literature values for mixtures of NaCl and NaLS[20,22] and used the following values for the benzidine rearrangement: 0.006, 0.006, 0.005, 0.0045, and 0.004 M for 0.00099, 0.00165, 0.00198, 0.0052, and 0.0098 M HCl, respectively. For the acetal hydrolyses we used cmc values of 0.006, 0.0045, 0.004, and 0.0028 M for 0.001, 0.00316, 0.01, and 0.03 M HCl, respectively.

Incorporation of 1,2-Diphenylhydrazine (1). The binding of **1** to NaLS was determined spectrometrically.[14,23] Freshly prepared deoxygenated solutions were used, and 0.1 mL of a stock solution of 1.3×10^{-3} M **1** in 40:60 EtOH–H_2O was added to 2 mL of the surfactant solution through a septum cap under N_2. The absorbance at 250 nm was immediately measured.

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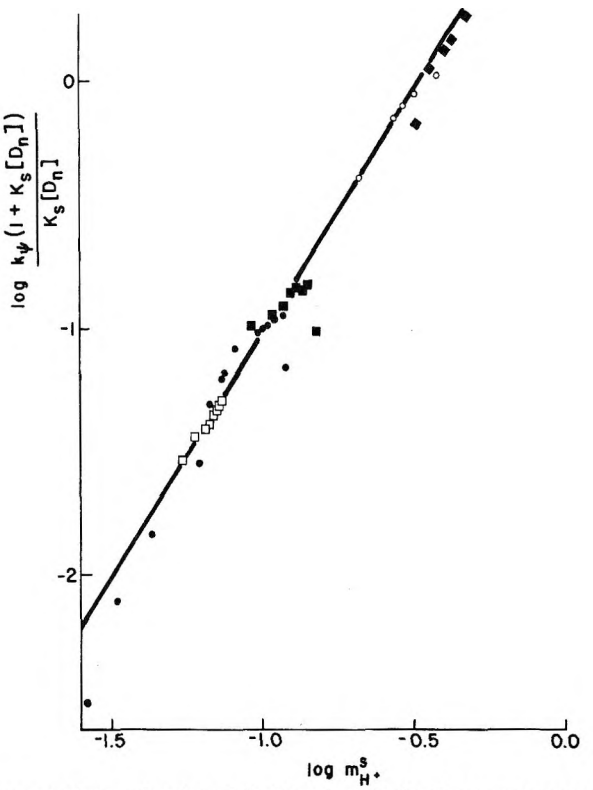


Figure 1. Determination of the kinetic order for the rearrangement of 1,2-diphenylhydrazine in solutions of NaLS at 25.0 °C: (□) 0.000992, (●) 0.00165, (■) 0.00198, (○) 0.0052, and (♦) 0.0098 M HCl.

The fraction, f, of micellar bound substrate at various surfactant concentrations was estimated from the absorbances, A:[14] $f = (A - A_o)/(A_\infty - A_o)$. The subscripts o and ∞ denote absorbances in water and with fully bound 1.

A plot of $f/(1 - f)$ against [NaLS] is linear up to 0.02 M NaLS with a slope $K_s = 220\ M^{-1}$ for both samples of NaLS. The intercept gives a cmc of 0.0075 M, in reasonable agreement with that in the absence of solute.

Results

Quantitative Treatment of Micellar Catalysis. The first-order rate constant, k_ψ, for reaction in the presence of micelles is given by eq 1,[24] where k_W' and k_M' are first-order

$$k_\psi = (k_W' + k_M'K_s[D_n])/(1 + K_s[D_n]) \quad (1)$$

rate constants in the aqueous and micellar pseudophases, respectively, [D] is the concentration of surfactant (detergent), and K_s is the binding constant of the substrate to the micelles written in terms of micellized surfactant. The concentration of micellized surfactant $[D_n]$ is that of the surfactant less that of the monomeric surfactant, which is assumed to be constant and given by the cmc.

Equation 1 is derived on the assumption that the relation between the concentration of the micellar bound substrate, $[S_M]$, and the total concentration, $[S_T]$, is given by eq 2.

$$[S_M]/[S_T] = K_s[D_n]/(1 + K_s[D_n]) \quad (2)$$

Equation 2 is valid only if there is negligible perturbation of the micelles by reactants, which requires that their concentrations must be much smaller than that of the surfactants.

The concentration of hydrogen ions in micelles of NaLS containing HCl and in the absence of added salt is written in terms of the mole ratio of hydrogen ions to micellized surfactant, $m_{H^+}{}^s$, which is given by eq 3.[12]

$$m_{H^+}{}^s = 0.82([H^+{}_T]/[H^+{}_T] + [Na^+{}_T]) \quad (3)$$

In this empirical relation, total concentrations of $H^+{}_T$ and $Na^+{}_T$ are used, and in applying it to our kinetics we assumed that it is unaffected by micellar incorporation of the substrate. The dimensionless concentration $m_{H^+}{}^s$ can be converted into molarity in the micellar pseudophase using an appropriate volume element.[11,14]

Benzidine Rearrangement. The micellar catalysis of the two-proton benzidine rearrangement is so large that we can neglect reaction in the aqueous pseudophase, except in very dilute surfactant solutions.[18] Provided that there is no build up of monoprotonated substrate, the first-order rate constant, k_M', is given by eq 4, where k_M is a third-order rate constant, s^{-1}.

$$k_M' = k_M(m_{H^+}{}^s)^2 \quad (4)$$

Equation 1 reduces to eq 5. If eq 5 is obeyed, a plot of log

$$k_\psi = \frac{k_M K_s (m_{H^+}{}^s)^2[D_n]}{1 + K_s[D_n]} \quad (5)$$

$k_\psi(1 + K_s[D_n])/K_s[D_n]$ against log $m_{H^+}{}^s$ should be linear with a slope of 2.

Several assumptions are made in this treatment. (i) The binding constant, K_s, to NaLS is assumed to be unaffected by dilute HCl. (ii) The value of monomeric surfactants is assumed to be given by the cmc in the presence of dilute HCl. (iii) The bindings of hydrogen ions and substrate to the micelle are assumed to be independent parameters. (iv) It is assumed that there is no buildup of monoprotonated substrate under the experimental conditions, which is reasonable because 1 is weakly basic.[18]

Assumptions i–iii are reasonable provided that the surfactant concentration is considerably above the cmc and [HCl], because then the counterions in the Stern layer are primarily sodium rather than hydrogen, and uncertainties in the value of the cmc become unimportant. However, there are serious problems in assigning values of the cmc under reaction conditions because there is extensive catalysis below the cmc of NaLS in water.[18]

In treating the data, we took $K_s = 220\ M^{-1}$, measured in NaLS in the absence of acid (Experimental Section), but nonetheless the results fit eq 5 reasonably well (Figure 1) over a tenfold range of $[HCl_T]$ considering the approximations in the treatment and in the estimation of $m_{H^+}{}^s$ and k_ψ.[25] The values of k_ψ are from ref 18, and from the intercept in Figure 1 we estimated k_M as $10\ s^{-1}$.

Equation 5 can be rearranged to give eq 6. The major

$$(m_{H^+}{}^s)^2/k_\psi = 1/(k_M K_s[D_n]) + 1/k_M \quad (6)$$

problem in using an equation of this form is the sensitivity to the value of the cmc, especially at low surfactant concentrations. However, for the runs at the higher concentrations of acid, where the cmc is low, the data fit reasonably well, even for surfactant concentrations as low as 0.007 M (Figure 2). The scatter is not unreasonable, especially considering the uncertainties in the cmc under the reaction conditions and the dependence of rate on $(m_{H^+}{}^+)^2$.

From the slope and intercept, we estimate $k_M = 10\ s^{-1}$ and $K_s = 160\ M^{-1}$, which are in reasonable agreement with $K_s = 220\ M^{-1}$ in the absence of acid (Experimental Section). The agreement between the values of k_M determined using equations 5 and 6 is fortuitous because of the scatter in the data; but the differences in K_s may be significant because of the different conditions of the measurements, and there may be systematic deviations due to differences in [HCl] in the various reaction solutions.

Hydrolysis of *p*-Nitrobenzaldehyde Diethyl Acetal. In aqeous dilute acid this reaction is first order with respect to hydrogen ion concentration,[26] and provided that this is also true for reaction in the micellar pseudophase, eq 1 gives eq 7,

$$k_\psi = \frac{k_W[H^+{}_W] + k_M K_s m_{H^+}{}^s[D_n]}{1 + K_s[D_n]} \quad (7)$$

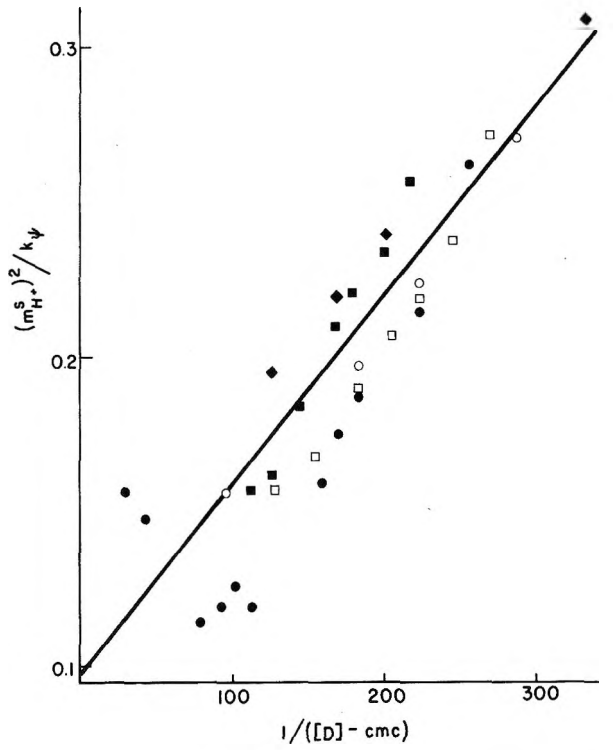


Figure 2. Determination of k_M and K_s for the rearrangement of 1,2-diphenylhydrazine in solutions of NaLS. The symbols are the same as in Figure 1.

where k_W, the second-order rate constant in water,[13] is 0.29 M^{-1} s^{-1} and k_M, s^{-1}, is the second-order rate constant in the micellar pseudophase.

The concentration of hydrogen ions in the aqueous pseudophase, $[H^+_W]$, can be written in terms of the total hydrogen ion concentration, $[H^+_T]$, by eq 8 so that eq 7 gives eq 9.

$$[H^+_W] = [H^+_T] - m_{H^+}{}^s[D_n] \quad (8)$$

$$(k_\psi - k_W[H^+_T])/m_{H^+}{}^s[D_n] = K_s k_M - k_W - k_\psi K_s/m_{H^+}{}^s \quad (9)$$

Equation 9 can be treated graphically (Figure 3). (The values of k_ψ are from ref 13.) We did not use the results for experiments in which $m_{H^+}{}^s$ is much greater than 0.5 because eq 3 fails under these conditions.[12]

The results fit eq 7 reasonably well, and from the slope and intercept we obtain K_s = 100 M^{-1} and k_M = 0.11 s^{-1}. (This value of k_M is, as expected, close to that estimated earlier from rate constants obtained under conditions in which the substrate is fully bound to the micelle.[13]) The value of K_s is in the expected range, for example, for the binding of methyl orthobenzoate to micelles of NaLS it is 73 M^{-1},[27] and we have estimated kinetically a value of K_s = 73 M^{-1} for the binding of the acetal 4 to micelles of tetradecanesulfonic acid.

Discussion

Reactivity in the Micellar Pseudophase. The rearrangement of 1,2-diphenylhydrazine is first order in substrate and second order in hydrogen ion concentration in the micellar pseudophase, and as in other systems[13,14] the rates do not depend directly on the overall hydrogen ion concentration or activity.

The value of k_M, s^{-1}, calculated using equations 5 and 6 cannot be compared directly with the usual form of the third-order rate constants, M^{-2} s^{-1}, in dilute strong acid, but comparison can be made by choosing a volume element for reaction in the micelles and so calculating the acid molarity in the micellar pseudophase. Following Stigter's model of micelles of NaLS,[28] we estimate the volume of the Stern layer in 1 mol of micellized surfactant as 140 mL.[29]

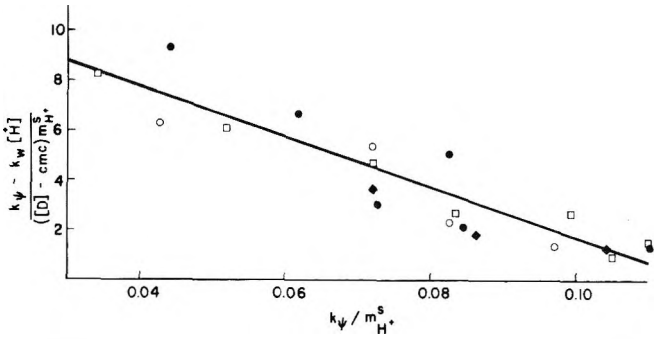


Figure 3. Determination of k_M and K_s for the acid hydrolysis of *p*-nitrobenzaldehyde diethyl acetal in solutions of NaLS at 25.0 °C: (○) 0.001, (□) 0.00316, (●) 0.01, and (♦) 0.03 M HCl.

On this basis the molarity of hydrogen ions in the Stern layer of micelles of NaLS is given by $m_{H^+}{}^s/0.14$, so that the third-order rate constant $k_3{}^m$, M^{-2} s^{-1}, is $0.14^2 k_M$. The value of $k_3{}^m$ for rearrangement of 1 is 0.2 M^{-2} s^{-1}, which is considerably smaller than the third-order rate constant of 16 M^{-2} s^{-1} for rearrangement in dilute HCl.[18]

The value of k_M, s^{-1}, for the hydrolysis of *p*-nitrobenzaldehyde diethyl acetal can be converted into the usual form of the second-order rate constant $k_2{}^m$ = 0.015 M^{-1} s^{-1}. This rate constant is smaller than that of 0.29 M^{-1} s^{-1} for reaction in dilute aqueous HCl.[13]

It appears therefore that both of these hydrogen ion catalyzed reactions are slower in the Stern layer of the micelle than in water if we estimate rate constants in terms of concentrations measured in moles per liter. This behavior is not unusual; for example, second-order rate constants for molecule–molecule reactions are generally smaller in the micellar pseudophase than in water,[8,9] as are those for the reaction of Malachite Green with 1-benzyldihydronicotinamide[11] and for the acid hydration of dihydropyridines.[14] The only reported exceptions appear to be deacylations by some imidazole anions in cationic micelles where the conclusions depend upon indirect estimates of the extent of micellar binding of the anionic nucleophiles.[8]

The effects of micelles on these second- and third-order rate constants are qualitatively akin to solvent effects because the reactions are slowed by the addition of organic solvents to water[13,15,18,26] and the Stern layers of micelles appear to be less polar than water.[4] The organic substrates have lower free energies in both micelles and organic solvents than in water, and this rate-retarding effect is apparently not offset by effects on the free energies of the hydrogen ion and the cationic transition state. In addition, micellized laurylsulfuric acid may not be strong (cf. ref 21), which would in effect reduce the acidity of micellar bound hydrogen ions. Therefore, as in so many other micellar catalyzed reactions, the rate enhancement is derived largely from concentration of reactants into a small volume.

The dependency of reaction rates upon the concentration of micellar bound hydrogen ion rather than on the total concentration or activity suggests that reaction rates and equilibria in other macromolecular systems, such as polyelectrolytes (cf. ref 30) and enzymes, should also be considered in terms of bound rather than total hydrogen ions.

Validity of the Pseudophase Model. For surfactant concentrations well above the cmc, the pseudophase distribution model (equations 1, 2, and 5) is reasonably satisfactory and the observed and predicted values of log k_ψ for the benzidine rearrangement of 1 (Figure 4) are in reasonable agreement, especially considering the sensitivity of log k_ψ to changes in $m_{H^+}{}^s$. But for the rearrangement of 1, values of k_ψ calculated from k_M and K_s using eq 5 do not agree with experiment values at low surfactant concentration. For example, in 1.65

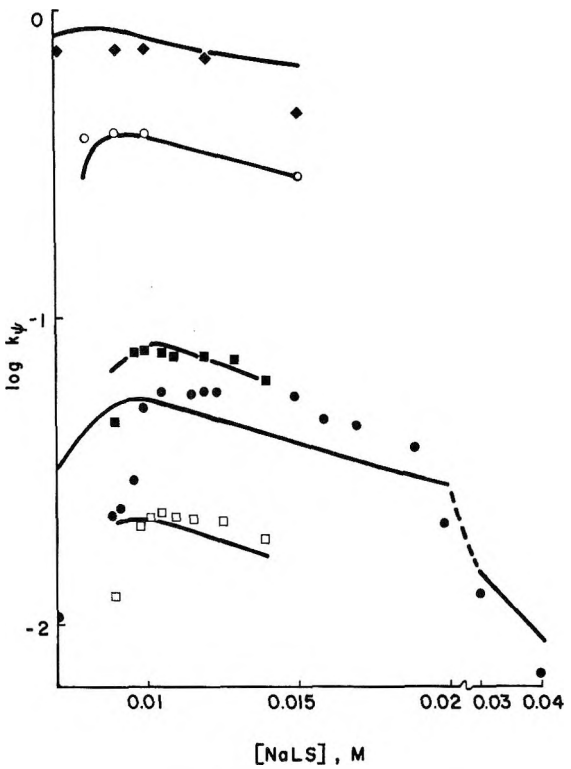


Figure 4. Comparison of observed and calculated values of the first-order rate constant, k_ψ, for rearrangement of 1,2-diphenylhydrazine. The lines are calculated using eq 5. The symbols are the same as in Figure 1.

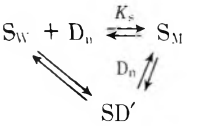
$\times 10^{-3}$ M HCl the predicted maximum value of k_ψ agrees reasonably well with the experiment value, but eq 5 does not predict the very rapid decrease of k_ψ at [NaLS] $< 10^{-2}$ M for reaction in 1.65×10^{-3} M HCl (Figure 4).

Equations 1–3 are derived on the assumption that the properties of the micelles are essentially unaffected by the reactants and that all of the surfactant is present either as monomers or as micelles. These conditions appear to be met at higher NaLS concentrations but not at low concentrations. Part of the problem lies in our method of estimating the concentration of monomeric surfactants, and even if we take the cmc as an adjustable parameter it is not possible to choose a value which fits a complete rate–surfactant profile for rearrangement of **1**.[18] (Problems of measurement of the cmc are noted in the Experimental Section.)

There are several problems with the assumption that the monomer concentration over a range of surfactant concentration is given by the cmc. Increase of ionic concentration decreases the cmc,[31] and presumably the monomer concentration. But only 70–80% of the head groups in ionic micelles are neutralized by counterions so that their concentrations in the aqueous pseudophase increase with increasing surfactant concentration,[10] and therefore the concentration of monomers should decrease, regardless of the presence of added solutes.[32] Added solutes complicate the situation because the relative concentration of surfactant to solute, e.g., substrate or hydrogen ions, changes with surfactant concentration. In addition, the micelles in our kinetic solvents can have both sodium and hydrogen ions as counterions in the Stern layer.

Failure of the assumption that the cmc gives the concentration of monomers under all conditions causes no (numerical) problem when the surfactant concentration is much larger than the cmc, but NaLS in relatively low concentration effectively catalyzes the rearrangement of **1**,[18] so it is understandable that the model fails under these conditions.

Scheme I



Many workers have noted failures of equations akin to eq 1 at low surfactant concentration and have ascribed them to induced micellization or the formation of submicellar aggregates rather than to an inherent failure of the assumptions made in deriving eq 1.[4–7,34,35]

Induced micellization does not appear to be of great importance here; for example, **1** only slightly reduces the cmc of NaLS (Experimental Section). However, submicellar aggregates must be considered (cf. ref 34–36). Such aggregates may well bind organic solutes, e.g., **1**, although not as well as a fully formed micelle. They would probably be ineffective at binding counterions, e.g., hydrogen ions, and thus would be poorer catalysts than a fully formed micelle. However, little appears to be known about the detailed structures of such aggregates, so that approaches invoking premicellar aggregates to explain these results are highly speculative.

Equation 2 describes the relation between free and bound substrate (S_W and S_M, respectively) in terms of a binding constant, K_s (Scheme I). In Scheme I, SD′ represents a submicellar–substrate complex, and if such complexes exist at low surfactant concentrations, the concentrations of S_M will be less than predicted by the usual treatment (eq 2). The relative importance of SD′ will decrease as the surfactant concentrations are increased.

It might be possible to describe the rate–surfactant profiles for reactions in very dilute NaLS in terms of equilibrium and rate constants involving SD′, but we see no way of doing this except by introducing adjustable parameters whose values could not be estimated by independent methods. The pseudophase distribution model, based on the concentration of micellar bound hydrogen ions, appears to be generally satisfactory, although we see no simple way of applying it quantitatively at low surfactant concentrations or under conditions in which reactants materially perturb micellar structures.

Registry No.—**1**, 122-66-7; **4**, 2403-62-5; NaLS, 151-21-3.

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(2) Participant in the URP program supported by the National Science Foundation.
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Role of the Furan Ring in the Formation of Meisenheimer-Type Adducts

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Received May 23, 1978

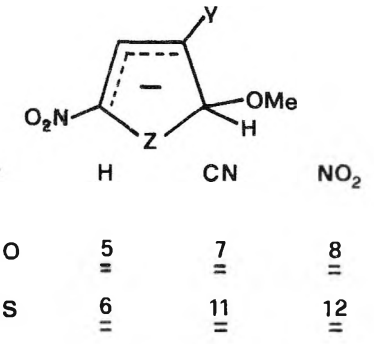
The rate and equilibrium constants for the formation of Meisenheimer adducts from 2-nitrofuran and 4-cyano-2-nitrofuran have been measured in methanol at 25 °C. Kinetic measurements have also been made for the formation of a related adduct from 2,4-dinitrofuran. The comparison of these data with those previously observed for the formation of adducts from the corresponding thiophene derivatives shows an accelerating and stabilizing effect of the furan ring in the formation of adducts. On the other hand, an increased lability of the adducts is also observed in the furan series.

The quantitative aspects of the reactivity of the furan ring in nucleophilic aromatic substitution have been recently compared with those of the thiophene ring.[1-3] The activating effect of the former is stronger than that of the thiophene ring. As to the reaction mechanism, an addition–elimination mechanism via the formation of an anionic intermediate σ complex is well established in the case of thiophene derivatives.[4]

A main piece of evidence in favor of the addition–elimination mechanism is the actual detection or isolation of Meisenheimer-type adducts from several electron-deficient thiophene compounds and nucleophilic reagents.[5-9] Rate and equilibrium constants for the formation of some of these adducts have also been reported, particularly in view of a comparison between adducts formed from benzene and thiophene derivatives.[6,7]

Similar information was lacking as to the formation of Meisenheimer adducts from furan derivatives. Therefore, we have become interested in investigating the following points: (i) whether adducts could be detected or isolated in the interaction between electron-deficient furans and methoxide ion or other nucleophiles; and (ii) to what extent the furan ring, in comparison with the thiophene ring, would affect the equilibrium and rate constants in the formation of adducts.

Following a preliminary communication,[10] where we showed that 2-nitrofuran (**1**) and 2-nitrothiophene (**2**) undergo addition of methoxide ion at the hydrogen-bearing α positions, yielding Meisenheimer adducts **5** and **6**, respectively, we report here kinetic and equilibrium data for these reactions in methanol. Moreover, we describe the formation of adducts upon interaction of methoxide ion with 4-cyano-2-nitrofuran (**3**) and 2,4-dinitrofuran (**4**). It was expected that the presence of two electron-withdrawing groups should provide a greater stabilization of the resulting adducts and give more general information on the role of the furan ring.



Y =	H	CN	NO_2
Z = O	5	7	8
Z = S	6	11	12

Experimental Section

Melting points are uncorrected. UV–vis, NMR, and mass spectral characterizations of the products were made as described in ref 5b.

Materials. 2-Nitrofuran was obtained according to an optimized procedure.[11] **2-Nitrothiophene,** free from 3-nitrothiophene, was obtained by decarboxylation of 5-nitrothienoic acid.[12]

3-Cyanofuran. The amide of 3-furoic acid was converted to the title compound by a standard procedure. After the usual workup, a solid (mp 24–26 °C) was obtained upon reduced pressure distillation (3-cyanofuran had been previously reported[13] as a liquid); IR (ν_{CN} 2250 cm^{-1}) and NMR data [(in $CDCl_3$) δ 6.60 (m, 1 H), 7.46 (m, 1 H), 7.91 (m, 1 H)] were in accordance with the structure of the compound (yield 73%).

4-Cyano-2-nitrofuran (3). A solution of 3.0 g of 3-cyanofuran in 7 g of acetic anhydride was slowly added to a well-stirred nitrating mixture made up from 20.1 g of 99% HNO_3 and 32 g of acetic anhydride at a temperature lower than 10 °C. At the end of the addition, the reaction mixture was poured onto ice and extracted repeatedly with ethyl ether. The residue on evaporation of ether was an oil containing **3** and at least another product. Upon chromatography on silica

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Table I. NMR and UV–vis Data for Substrates 3 and 4 and the Corresponding Adducts 7 and 8 in CH_3OH (CH_3OD)

compd	δ (H_α, H_β)	J, Hz	λ_{max_1}, nm	ε, L mol^{-1} cm^{-1}	λ_{max_2}, nm	ε, L mol^{-1} cm^{-1}
3	8.45, 7.72	1			286	8.7×10^3
7 (3 + CH_3O^-)	6.13, 7.35	0	242	7.7×10^3	388	1.9×10^4
4	8.84, 7.98	1.5	218	1.06×10^4	286	7.4×10^3
8 (4 + CH_3O^-)[a]	6.35, 7.32	<0.5	270	4.4×10^3	500	1.37×10^4

[a] NMR data observed at −50 °C; UV–vis data obtained from single wavelength measurements (see text).

gel, only 3 was recovered: yield 5%; mp (pentane) 55–55.5 °C; MS *m/e* 138 (M^+); NMR ($CDCl_3$) δ 7.40 (d, 1 H), 7.93 (d, 1 H, *J* = 1 Hz). It is likely that the side products of this nitration are derived from an addition of nitronium acetate to the substrate. In accordance with this hypothesis, the NMR spectrum of the crude reaction mixture showed, besides the signals of 3, intense signals at δ 2.1, 6.5, and 7.1.

Nitration of 2-Nitrofuran. 2-Nitrofuran (1.0 g, 8 mmol) was heated on a water bath with 10 g of 70% HNO_3 until complete solution, as described for the synthesis of 2,5-dinitrofuran.[14] The reaction mixture was kept another 12 h at 0 °C, neutralized with sodium bicarbonate, and extracted with ethyl ether. The residue, after evaporation of the solvent, was a yellow solid containing (TLC analysis) two compounds, which were separated by chromatography on a Lobar silica gel 60 column (Merck) with a mixture of toluene and ethyl acetate, 7:1. The first fractions yielded a small amount of 2,4-dinitrofuran (4): yield 5%; mp 87–89 °C; MS *m/e* 158 (M^+); NMR (CD_3OD) δ 7.98 (d, 1 H), 8.84 (d, 1 H, *J* = 1.5 Hz). The subsequent fractions yielded a much larger amount of 2,5-dinitrofuran (yield 67%).

Characterization of the Adducts. NMR spectra for adducts 5 and 6 were previously reported.[10] In methanol, the addition of sodium methoxide to methanolic solutions of 1 and 2, respectively, lead to a decrease of the maximum at 304 nm of 1 and at 312 nm of 2 and to the development of a new absorption band at 318 nm [adduct 5 from 2-nitrofuran (ε 1.24×10^4 L mol^{-1} cm^{-1})] and at 330 nm [adduct 6 from 2-nitrothiophene (ε 1.23×10^4 L mol^{-1} cm^{-1})].

NMR data for adducts 7 and 8 were recorded upon the addition of an equivalent amount of sodium methoxide in methanol (4 M) to a CH_3OD solution of 3 and 4. With the latter reaction, characterization of the adduct was possible only at low temperature (−50 °C). The UV–vis spectrum of adduct 7 was determined by standard procedures. The UV–vis spectrum of adduct 8 was obtained from single wavelength measurements. A 3.68×10^{-5} M solution of substrate 4 was mixed with a 1.93×10^{-2} M solution of sodium methoxide. The reaction was followed by the stopped-flow technique in the range 240–530 nm at 5-nm intervals. Complete spectra of the reaction mixture at different times were subsequently drawn up by plotting the absorbance at a definite time vs. wavelength. Since the formation rate of the adduct is first order in methoxide ion, whereas its decomposition is independent of methoxide ion concentration, the time required to obtain the absorbance maximum is methoxide concentration dependent.

Kinetic determinations for the slow reactions of 1–3 were obtained according to the usual spectrophotometric procedure, by following the absorbance increase at a wavelength corresponding to an absorbance maximum of the adduct, as described in ref 5b, in the presence of an excess of the nucleophile. A thermostatted stopped-flow Durrum 110 apparatus was used for the kinetic measurements with the very reactive dinitro derivative 4. The lability of the adduct formed from 2,4-dinitrofuran precludes any determination of the equilibrium constant for the formation of the adduct (K_f). However, extrapolation to time 0 of the absorbance values corresponding to the decomposition of adduct 8, as obtained by stopped-flow measurements, shows that the addition of a 10^{-4} M methoxide solution to a 5×10^{-5} M solution of 4 causes the practically quantitative conversion of the substrate to the adduct, in accordance with an equilibrium constant larger than 5×10^5 M^{-1}.

In the case of cyanonitrofuran 3, the equilibrium is largely shifted toward the adduct, even at a methoxide ion concentration as low as 10^{-4} M. Therefore, we allowed comparable and known amounts of 3 and 2,4,6-trinitroanisole (9), which yields a Meisenheimer adduct (10) whose K_f is known ($K_{f,10} = 1.7 \times 10^4$ M^{-1} at 25 °C),[5b] to compete for a deficiency in methoxide ion. We measured the absorbance of this mixture in the range 370–500 nm, where only the two adducts show appreciable absorption. From the molar absorption coefficients of the adducts, determined separately, we were thus able to evaluate the concentrations of adducts 7 and 10. The concentrations of 3 and 9 at equilibrium were given by the difference between the initial concentrations of the substrates and those of the corresponding adducts. The ratio between the equilibrium constants was finally given by

$$K_{f,7}/K_{f,10} = \frac{[7][9]}{[3][10]} \quad (1)$$

From several determinations, we obtained 10.5 ± 1.5 as a mean value for this ratio, corresponding to the equilibrium constant reported in Table II.

Equilibrium constants ($K_f = k_1/k_{-1}$) for the reactions of 1 and 2 were obtained from $k_{obsd} = k_1[MeO^-] + k_{-1}$ by plotting the observed rate constants vs. the methoxide ion concentration.

Results and Discussion

Synthesis of 2,4-Dinitrofuran. Owing to the tedious procedures involved in the synthesis of 3-nitrofuran,[15,16] the possibility of obtaining the title compound upon nitration of 3-nitrofuran was discarded. 2,4-Dinitrofuran was in fact obtained upon nitration of 2-nitrofuran, together with a massive amount of 2,5-dinitrofuran. The isomers were separated by chromatography. This synthesis provides a rare example of the formation of a 2,4-disubstituted furan upon electrophilic substitution of a 2-substituted furan. In this ring, the α-directing power of the heteroatom is indeed so strong as to usually overwhelm the directing power of any α substituent.[17]

Formation of Meisenheimer Adducts. The NMR and UV–vis spectrophotometric study of the reactions of 3 and 4 in methanol shows that in both cases the substrate disappears rapidly upon addition of methoxide ion, even at a low concentration of the nucleophile. In the reaction of the cyanonitrofuran, a new species, displaying new UV absorption maxima and a new NMR spectrum, is easily detected (see Table I). The spectrum changes are in accordance with the formation of an anionic adduct; the strong bathochromic shift in the UV region observed in going from 3 to the new species is comparable to that observed in the formation of a Meisenheimer adduct from 4-cyano-2-nitrothiophene.[5b] The upfield shift of the NMR spectrum and the decrease in the coupling constant again follow the same pattern as observed in the formation of an adduct from the corresponding thiophene substrate. A correlation between the NMR data for the product of this reaction and those of the adduct formed from 4-cyano-2-nitrothiophene (δ 6.20 and 7.46) suggests that also in this case methoxide ion attacks at the α position, thus yielding adduct 7.

On the other hand, the pattern of the reaction of the dinitrofuran 4 cannot be deduced immediately from the experimental data. Thus, when the UV–vis spectrum is recorded after the addition of a slight excess of sodium methoxide to a 1.8×10^{-4} M solution of 4, only a strong decrease of absorbance in the UV region, and no trace of absorbance in the visible region is observed, even if the rapid and transient appearance of a red color is seen. Similarly, the addition of 1 equiv of sodium methoxide to a 2.5×10^{-1} M solution of 4 in methanol brings about the complete disappearance of the NMR signals of the substrate without the formation of any detectable signal downfield from δ 5. The spectral data corresponding to the formation of adduct 8, reported in Table I, have been obtained with techniques allowing the very fast recording of the features of the first reaction product before its rapid decomposition. Thus, the NMR spectrum of the adduct has been detected only at low temperature. Under

Table II. Rate and Equilibrium Constants for the Formation of Meisenheimer Adducts in Methanol at 25 °C

compd	Z	k, M^{-1} s^{-1}	K, M^{-1}	k_{-1}, s^{-1}
5	O[a]	1.37×10^{-2}	1.4×10^{2}	10^{-4}
6	S[a]	1.8×10^{-3}	5.6	3.2×10^{-4}
7	O	5.7×10	1.8×10^{5}	3.2×10^{-4}
11[b]	S	7.8×10^{-1}	1.5×10^{2} [a]	5.2×10^{-3}
8	O	4.5×10^{3}	$\geq 5 \times 10^{5}$ [c]	$\leq 9 \times 10^{-3}$ [c]
12[b]	S	1.5×10	8×10^{2}	1.9×10^{-2}

[a] Measurements made at total salt concentration = 0.2 M (balanced with $NaClO_4$). [b] Reference 5b. [c] Estimated.

these conditions, the addition of methoxide ion leads to the disappearance of the signals of the substrate and to the appearance of those reported in the Table I; at the same time, a very intense red color develops. The red color and the NMR spectrum of the adduct disappear upon an increase of temperature.

The UV–vis spectrophotometric course of the reaction has been followed by the stopped-flow technique (see Experimental Section).

Lability is not a peculiarity of the Meisenheimer adduct formed from 2,4-dinitrofuran; the adducts formed from 2-nitrofuran and 4-cyano-2-nitrofuran also undergo decomposition reactions, even if these reactions are much slower than that of the dinitro adduct. This fact explains why Meisenheimer adducts from furan substrates cannot be isolated, so that evidence for their formation has so far been obtained in solution only. It is likely that the decomposition reactions of the adducts formed from **3** and **4** are ring-opening reactions of the same kind observed in the reaction of 2-nitrofuran[18] and 2-nitrothiophene[19] with nucleophiles. However, a study of the decomposition reaction has not yet been carried out. In going from 2-nitrofuran to **3** and **4**, rate and equilibrium constants increase markedly because of the presence of two electron-attracting groups. The rate increase is particularly evident in the formation of adduct **8** from dinitrofuran. Also, because of the exceptional lability of this adduct, which precludes the use of the competitive method or of buffer solutions, the equilibrium constant cannot be determined, and only a lower limit for it has been estimated. The data in Table II substantiate the previous qualitative indication that equilibria from furan derivatives are more shifted toward the adducts than those from the corresponding thiophene derivatives. The equilibrium constant increase is mainly to ascribe to the increase of reactivity of the furan substrates in the addition reaction (k_1). This increase corresponds to the finding that nucleophilic aromatic substitution of furan derivatives is generally faster than in similarly substituted thiophene derivatives.[1,3] However, an inspection of the k_{-1} values of Table II shows that also the decreased rate of return of the adducts to the reagents may affect the equilibrium constants in the same way.

Two main factors seem to be involved in determining the higher tendency of furan derivatives to yield adducts. One of them should be the higher electronegativity of the oxygen atom, which is expected to give a more effective contribution than the sulfur atom to the formation of an anionic adduct. Another major factor favoring the addition reaction is the low aromaticity of the furan ring. It is well known that the furan ring is indeed more apt than the thiophene ring to undergo addition reactions, both with polar reagents and in cycloaddition reactions.

A final remark can be made about the different responses of furan and thiophene rings to the nature of the substituent in **3**. Our starting point has been the observation that linear

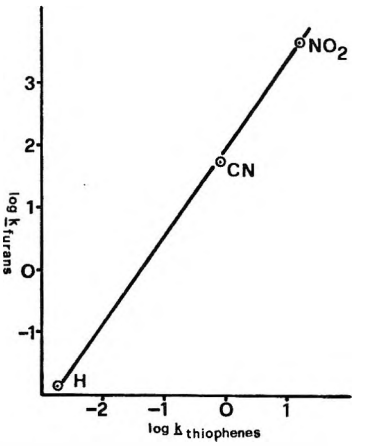

Figure 1. Free energy plot for rates of addition of methoxide ion to 2-nitro-4-X compounds in methanol at 25 °C.

free-energy ortho correlations are satisfactory in thiophene[20] and presumably other five-membered rings where steric interactions between vicinal substituents are lower than in the benzene ring. A plot (Figure 1) of log k of furan derivatives against log k of the corresponding thiophene derivatives is linear (slope = 1.4).

In view of the higher reactivity of the furan ring, the higher selectivity of the same ring could seem surprising. However, a similar reactivity–selectivity pattern has been observed in electrophilic aromatic substitutions and other electronically related reactions. Thus, the selectivity ratio of furan and thiophene ring in the trifluoroacetylation reaction is nearly 1.3,[17] which is surprisingly similar to that observed in our nucleophilic addition. Even if the coincidence of the numerical value is probably fortuitous, it is likely that the same structural factor, low aromaticity of the furan ring, has a role in determining a similar situation in two reactions having different electronic requirements.

Registry No.—**1**, 609-39-2; **2**, 609-40-5; **3**, 67382-56-3; **4**, 67382-57-4; **5**, 67382-54-1; **6**, 67382-55-2; **7**, 67382-26-7; **8**, 67382-27-8; 3-furoic acid amide, 609-35-8; 3-cyanofuran, 30078-65-0.

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Synthesis and Solvolysis of 4-Substituted Nortricyclenes

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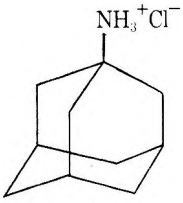
Received March 28, 1978

A number of 4-substituted nortricyclenes (**2**) have been synthesized, including 4-aminonortricyclene hydrochloride (**2a**), nortricyclyl-4-carbinol (**2f**), and its tosylate (**2e**). The synthesis of these compounds is discussed. Amine hydrochloride **2a** was synthesized because of its similarity in structure to 1-aminoadamantane hydrochloride (**1**), which has antiviral properties against certain influenzas. Tosylate **2e** was solvolyzed in acetic acid; the pK_a of nortricyclene-4-carboxylic acid (**2c**) was determined in 50% ethanol. These results measure a substantial inductive withdrawal by the cyclopropane ring when compared to the 1-norbornylcarbinyl system. This inductive effect for a cyclopropane ring has not previously been measured completely free of other effects such as ring strain or π participation. These studies require a reinterpretation of the extreme slowness of 4-nortricyclyl bridgehead solvolyses compared to the 1-norbornyl bridgehead system, which in the past was explained solely on the basis of an increase in ring strain, but now must include an inductive effect.

In 1964 it was announced that 1-aminoadamantane hydrochloride (**1**) would be marketed as an antiviral agent



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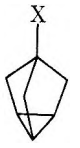
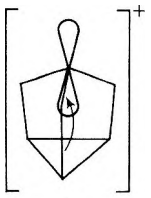
against certain influenza viruses.[1,2] It appears to act by interfering with the penetration of the host cell by the virus. Its chief limitations are that protection stops shortly after daily dosage is terminated and it does not extend to all viral types. Early in 1966 one of us began working in another laboratory[3] on the synthesis of 4-substituted nortricyclenes (**2**), especially



2a, X = $NH_3^+Cl^-$
b, X = Cl
c, X = COOH
d, X = OTf
e, X = CH_2OTs
f, X = CH_2OH
h, X = OTs

4-aminonortricyclene hydrochloride (**2a**), which is very similar in structure to **1**. Both have a bulky but symmetrical ring structure linked to a polar functional group. The hydrochloride salt is used because of its desirable solubility. The only difference in the two is that in **2a** the bridgehead amino group is joined to a cyclopropane ring by three bridging methylene groups, while in **1** the bridgehead amino group is joined to a cyclohexane ring by three bridging methylene groups.

A second purpose of the research was to measure the effect of the face of a cyclopropane ring on stabilization of a positive charge at the bridgehead position above its middle, as in ion **3**.



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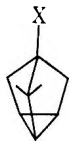
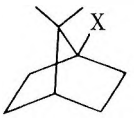
4-Chloronortricyclene (**2b**)[3] and 4-chlorotricyclene (**4b**)[4] were synthesized, and their reactivity was studied. Extensive testing with **4b** showed it to be nearly if not completely inert



4

to silver ion even under the most strenuous conditions.[3] Consequently, this research was terminated.

In 1967 the synthesis of 4-chloronortricyclene (**2b**) and nortricyclene-4-carboxylic acid (**2c**) was published.[5] Three years later the solvolyses of 4-nortricyclyl and 4-tricyclyl triflates (**2d** and **4d**) were reported.[6] These studies showed, as we had found earlier, that there was no stabilization of the bridgehead carbonium ion **3** by the cyclopropane ring. In fact, 1-apocamphyl triflate (**5d**) reacts 28 400 times faster than **4d**



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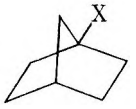

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in 60% ethanol at 25 °C, and 1-norbornyl triflate (**6d**) is some 174 000 times faster than **2d** in 50% ethanol at 100 °C. There is thus a very dramatic *de*stabilization of the bridgehead carbonium ions in cyclopropyl systems **2** and **4**. Of the two possible reasons for this inertness, i.e., the electron-withdrawing inductive effect of the cyclopropane ring and the increased ring strain of the nortricyclyl and tricyclyl systems, the latter viewpoint has been favored.[6] The basis for this preference lies in results of strain energy calculations,[6,7] but not on experimental data. We are of the opinion that the former effect is also operating.

There are two alternative ways of determining if the inductive effect of the cyclopropane ring is operating in 4-substituted nortricyclenes. One method involves a study of the solvolysis of the bridgehead carbinyl tosylates **2e** vs. **6e**. If **2e** is slower than **6e** in solvolysis, it would be due to the electron-withdrawing inductive effect of the cyclopropane ring. Although increased ring strain is a possible factor in bridgehead ion stability, it cannot be an important factor in bridgehead carbinyl ion stability. Furthermore, if **2e** is slower than **6e** by this inductive withdrawal, then most certainly at least part of the solvolytic deceleration of **2d** vs. **6d** is due to this same effect since the developing positive charge is one carbon closer to the cyclopropane ring and inductive effects increase dramatically with decreasing distance between interacting centers.

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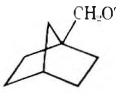
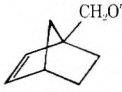
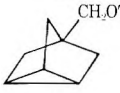
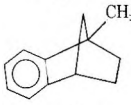
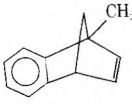
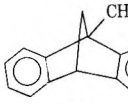
Table I. Acetolysis Rates at 130.4 °C

tosylate	ref	10^5k, s^{-1}	k_{rel}
 6e	*a,b*	21.5	1400
 14e	*b,c*	5.9	390
 2e	*d*	0.82	55
 15e	*a,b*	0.65	43
 16e	*b,e*	0.050	3.3
 17e	*b,e*	0.015	1.0

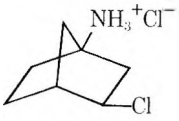
[a] Reference 10. [b] Extrapolation from data at other temperatures. [c] Reference 14. The rate constant for the brosylate was assumed to be 2.9 times the rate of the corresponding tosylate. [d] This work. Our results give a rate constant of (0.820 ± 0.030) × 10^{-5} s^{-1} at the 95% confidence level. [e] Reference 16. The rate constant for the triflate was assumed to be 1.34 × 10^4 times the rate of the corresponding tosylate.

A second accepted method of determining inductive effects of molecules is measurement of acidity constants. If acid **2c** was found to be stronger than **6c**, it would be due to an inductive effect of the cyclopropane ring, withdrawing electron density and stabilizing the anion of **2c** relative to **6c**.

Results

For these reasons we reopened our earlier investigation of the 4-nortricyclyl system and set out to synthesize amine hydrochloride **2a** for its possible antiviral activity and tosylate **2e** and acid **2c** for their theoretical significance. Acid **2c** was synthesized by the published method,[5] and the acid chloride was obtained by standard procedures. The Curtius reaction,[8] with sodium azide in aqueous acetone followed by heating in benzene, gave the rearranged isocyanate, which was hydrolyzed with dilute hydrochloric acid at room temperature to give the desired amine salt **2a** in 54% yield overall from the acid. Its structure was proven by spectral and elemental analyses. Detailed antiviral studies are now being conducted in other laboratories and are not reported here.

The use of higher temperatures or more concentrated acid to hydrolyze the isocyanate gave none of the desired amine hydrochloride. A complete analysis of the side product was not undertaken, but it appears to be **7**, formed by opening of the cyclopropane ring with hydrochloric acid.



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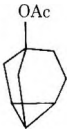
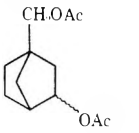
Acid **2c** was reduced to the alcohol **2f** with lithium aluminum hydride and tosylate **2e** was made in normal fashion. The acetolysis of **2e** was run at 130.4 °C and contrasted with previous kinetic data available, especially for tosylate **6e**.[9,10] Table I gives the rate constants for appropriate tosylates in acetolysis at 130.4 °C.

Table II. Percentages of Acetolysis Products

temp, time	products, %			
	 8	 9	 10	11, 12, or 13
120 °C, 6 days[a]	9.2	25.1	48.4	17.2
	34.3		65.6	
137 °C, 13 days[b]	4.4	5.7	49.5	40.4
	10.1		89.9	

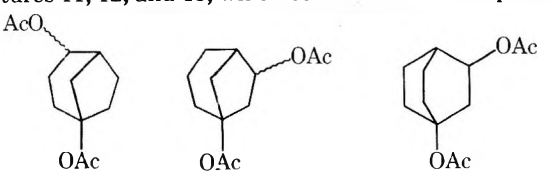
[a] Total ring expansion under these conditions (**9** + **11**) is 42.3%. [b] Total ring expansion is 46.1%.

Table III. pK_a Values

carboxylic acid	ref	pK_a
benzoic	*a*	5.35
	b	5.50
	c	5.55
	d	5.58
norbornane-1 (**6c**)	*b*	6.37
norbornene-1 (**14c**)	*b*	5.98
nortricyclene-4 (**2c**)	*a*	5.89
benzonorbornene-1 (**15c**)	*b*	5.88
benzonorbornadiene-1 (**16c**)	*c,d*	5.45
dibenzonorbornadiene-1 (**17c**)	*c*	5.50

[a] This work. [b] Reference 10. [c] Reference 16. [d] Reference 15.

A product study on a sample heated in acetic acid for a long period of time (120 °C, 6 days) showed the presence of two isomers of very short retention times and two isomers with long retention times. When the solvolysis was allowed to proceed at a higher temperature and a much longer time (137 °C, 13 days), the percentages of the products of short retention times became very low while the longer retained compounds increased in percentage. Unrearranged acetate **8** and ring-expanded acetate **9** were identified as the two isomers with short times. Unrearranged but cyclopropane ring-opened diacetate **10** was identified as a product with long retention time. The second diacetate is a ring-expanded and ring-opened product, but our data does not differentiate between structures **11**, **12**, and **13**, which could be formed depending



11 12 13

on which bond is broken in the ring opening of acetate **9** and the orientation of addition of acetic acid.

Table II gives the products and percentages under different conditions. Note that the total percentage of acetates formed (34.4%) under less stringent conditions is much larger than that produced (10.1%) when the reaction is forced with higher temperature and longer time. The solvolysis of the tosylate therefore is occurring first followed by subsequent ring opening with acetic acid.

The pK_a of acid **2c** was determined in 50% aqueous ethanol. A summary of these results and data from other appropriate acids are given in Table III for 23–25 °C.

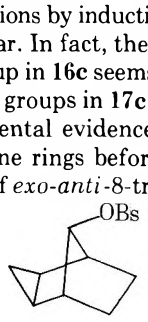
Discussion

The electron-withdrawing inductive effect of a double bond or aromatic ring is well established. The most common range of values is 5- to 10-fold for a homoallylically (γ) positioned double bond. Although usually accompanied by a rate acceleration caused by π participation of the double bond or aromatic ring in solvolysis, in one study not complicated by this participation Wilcox and Chibber[11] found that δ-unsaturated substrates solvolyze 2.5–4 times slower than their saturated counterparts. A movement of the double bond from the δ to the γ (homoallylic) position should increase the inductive effect by a factor of 2.8.[12] This same homology factor is also obtained for other series, i.e., $ClCH_2-$ vs. $ClCH_2CH_2-$ and CH_3CO- vs. CH_3COCH_2-, where an extra methylene group is interposed. An inductive similarity between vinyl and phenyl groups has been reported.[13]

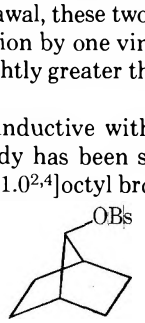
The best measure of the isolated inductive effect of the vinyl and phenyl groups is exemplified by the data summarized in Tables I and III. Norbornenyl-1-carbinyl tosylate (**14e**) has been found to be about 3.6 times slower than its saturated analogue norbornyl-1-carbinyl tosylate (**6e**),[14] and benzonorbornenyl-1-carbinyl tosylate (**15e**) is 33 times slower.[10] Our group[15] and others[16] have found that the concurrent presence of both a homoallylic vinyl and phenyl group as in benzonorbornadienyl-1-carbinyl tosylate (**16e**) retards the rate by a factor of 430 compared to the saturated system **6e** and a factor of 13–120 compared to the monounsaturated effects seen in **15e** and **14e.** Likewise, a recent study of dibenzonorbornadienyl-1-carbinyl tosylate (**17e**)[16] showed a rate deceleration of 1400 compared to **6e** and 43–390 compared to unsaturated systems **15e** and **14e.** These solvolytic studies prove the inductive withdrawal of the vinyl group, the somewhat larger but similar effect of a phenyl group, and the additivity of the effects.

The data in Table III indicate a similar conclusion by measurement of a different phenomenon entirely, that of the acidity of the corresponding acids. The only substantial difference in the two studies is the relative degrees of inductive withdrawal for vinyl and phenyl groups. In stabilizing carboxylate anions by inductive withdrawal, these two groups are quite similar. In fact, the stabilization by one vinyl and one phenyl group in **16c** seems to be slightly greater than that for two phenyl groups in **17c.**

Experimental evidence for the inductive withdrawal by cyclopropane rings before this study has been scarce. The acetolysis of *exo-anti*-8-tricyclo[3.2.1.$0^{2,4}$]octyl brosylate (**18**)

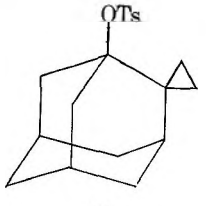


18

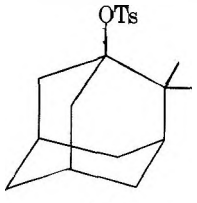


19

is slower by a factor of 3 than the acetolysis of 7-norbornyl brosylate (**19**).[17] This has been explained as either steric interference or electron withdrawal by the cyclopropane ring. The exo cyclopropane ring cannot participate in the solvolysis. Similarly, the adamantyl derivative **20** undergoes acetolysis



20



21

at 45 °C 350 times slower than its dimethyl analogue **21.**[18] The chloride corresponding to tosylate **20** is 625 times slower than 1-adamantyl chloride in 50% ethanol at 25 °C.[19] Since there is no appreciable steric difference between **20** and **21** and a good Hammett–Taft correlation exists for these systems, the results were originally interpreted in terms of an inductive withdrawal by the cyclopropane ring,[18–20] although some of this effect may be due to increased ring strain in **20.** These results have recently been reinterpreted solely in terms of a ring strain argument to the exclusion of any inductive effect.[6b]

Mentioned earlier was the work on 4-nortricyclyl (**2d**) and 4-tricyclyl triflate (**4d**)[6] and the very dramatic decelerating effect of the cyclopropane ring compared to 1-norbornyl (**6d**) and 1-apocamphyl (**5d**) triflate, interpreted by Schleyer[6a] and Bergman[6b] to be caused by ring strain, with the inductive effect of the cyclopropane ring playing little or no role in retarding ionization in these systems. No experimental evidence for one theory over the other was presented.

We believe that we have for the first time isolated the inductive withdrawal of the cyclopropane ring from any possible ring strain effect or π participation and have provided experimental evidence for its magnitude. The nature of the nortricyclyl-4-carbinyl system makes these two other phenomena impossible. Yet our results of the acetolysis of tosylate **2e** and of the acidity of **2c,** when compared with other bridgehead carbinyl systems, show that the cyclopropane ring of system **2** is nearly equal to the phenyl group of **15** in its well-documented inductive withdrawal. In acetolysis, **2e** solvolyzes 26 times slower than norbornyl-1-carbinyl tosylate (**6e**), compared to a decelerating effect of 33 for the phenyl group. The cyclopropyl ring in **2e** has a much stronger decelerating effect than the vinyl group of norbornenyl-1-carbinyl tosylate (**14e**), which is only 3.6 times slower than its saturated analogue **6e.**

Similarly, the acidity of nortricyclene-4-carboxylic acid (**2c**) is close to the two unsaturated acids **14c** and **15c** and, because of inductive withdrawal, is much more acidic than the saturated acid **6c.**

The only reasonable explanation of these results lies in assuming a strong inductive withdrawal of the cyclopropane ring. It should be noted that the cyclopropane ring in **2e** is actually one carbon further removed from the reaction site than the vinyl and phenyl groups of **14e** and **15e.** If we apply the factor of 2.8 mentioned by Taft[12] as the value of the inductive effect of many groups when placed one carbon closer to the reaction site, then the cyclopropyl inductive effect would be 2.8 times greater if it were present at the homocyclopropylcarbinyl (γ) position instead of the δ position. Based on the acetolysis data in Table I and the Taft homology factor, Table IV compares the pure inductive effect of the three groups under discussion at equal distances from the reaction site. The decelerating effect of the cyclopropane ring at the δ position, 26 as calculated from Table I for k_{6e}/k_{2e}, multiplied by the homology factor (2.8), gives 73 for the isolated inductive effect of a homocyclopropylcarbinyl (γ) system as in tosylate **2h.** In view of the fact that each carbon of the cyclopropane ring is connected to the reacting site by one of three carbon bridges, this type of system might be more accurately described as a tris(homocyclopropylcarbinyl) system. Although the homocyclopropylcarbinyl deceleration effect in **2h** is 73, it may be considerably less in a normal mono(homocyclopropylcarbinyl) system, perhaps one-third of this value if the entire effect is being transmitted through bonds and not through space. The present study in no way attempts to differentiate between through-bond and through-space effects.

If we correct the reported rate of 4-nortricyclyl triflate **2d**[6a] for temperature differences, a leaving group change (assum-

Table IV. Isolated Inductive-Withdrawing Effects in Acetolysis

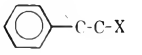
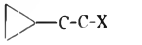
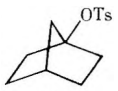
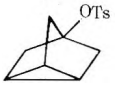
name	structure	deceleration effect
saturated	C-C-C-C-X	1.0
homoallyl	C=CCC—X	3.6
homobenzyl		33
homocyclopropylcarbinyl		73

Table V. Acetolysis Rates at 130.4 °C

tosylate	k, s^{-1}	k_{rel}
 6h	2.97×10^{-9}	1.5×10^5
 2h	2.01×10^{-14}	1.0

ing[16] k_{OTf}/k_{OTs} is 1.34×10^4), and a solvent change (assuming[6a] k in 50% ethanol/k in acetic acid is 185 at 130.4 °C), then the relative rates of 4-nortricyclyl tosylate (**2h**) and 1-norbornyl tosylate (**6h**) can be calculated for acetolysis at 130.4 °C. These values are given in Table V.

It appears that of the 10^5 factor which separates these two bridgehead systems in solvolytic rate, a factor of 73 or about 10^2 of this can be explained by inductive withdrawal of the homocyclopropylcarbinyl (γ) group present in tosylate **2h** and triflate **2d.** Therefore, on the basis of studies of the nortricyclyl-4-carbinyl system, we cannot agree with those who say that for the tricyclyl and nortricyclyl bridgehead solvolysis ". . . the inductive effect of the cyclopropane ring plays little or no role in retarding ionization in this system," [6b] or that "The slow rates of solvolysis are accounted for completely by the 'stiff' potential function which describes the deviation of C-4 from planarity, and the distortion of the C–C–C angle at the methylene carbons caused by the partial flattening of C-4 which does occur." [6b] We believe that a substantial portion of the bridgehead reactivity difference between **2** and **6** is due to the inductive withdrawal of the cyclopropane ring situated at a position that is γ to the reaction site.

Experimental Section

Melting and boiling points are uncorrected. The melting points were taken by capillary in a Thomas-Hoover apparatus. The following instruments were used: a Varian T-60 NMR spectrometer, Perkin-Elmer 727 and 283 infrared spectrophotometers, and Varian Aerograph A-90-P and 700 Autoprep gas chromatographs. NMR data are given in parts per million (δ) relative to internal Me_4Si. Only significant IR absorptions are listed in cm^{-1}. Gas chromatography was performed on SE-30 and QF-1 columns with helium carrier gas. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill. High-resolution mass spectral analyses and ^{13}C NMR spectra were done at the Department of Chemistry, University of Minnesota, Minneapolis, Minn.

Nortricyclene-4-carboxylic Acid (2c). This acid was prepared by the published procedure[5] starting from 4-chlorononorcamphor, which is synthesized from norcamphor[21] or norbornene.[22]

4-Aminonortricyclene Hydrochloride (2a). A mixture of 4.47 g (0.0324 mol) of acid **2c,** 6 mL (0.08 mol) of thionyl chloride, and 6 mL of benzene (dried by calcium chloride) was refluxed for 2 h. The excess benzene and thionyl chloride were rotary evaporated in vacuo, and the residue was distilled to give 4.18 g (0.0267 mol, 82%) of the acid chloride: bp 80–83 °C (10 mm); IR (neat) 3068 (cyclopropyl C–H), 2940 and 2868 (C–H), 1789 (C=O), 1275, 1270, 1143, 941, 797, 751 cm^{-1}.

The acid chloride in 9 mL of reagent acetone was added dropwise to a stirred solution of 2.43 g (0.0374 mol) of sodium azide in 9 mL of distilled water below 10 °C. The addition required 0.5 h, and the mixture was stirred an additional 1.5 h. The sweet odor of the azo ketone was readily detectable. The layers were separated, and the top layer was added dropwise to 27 mL of warm dry benzene while being stirred magnetically. The addition took 0.5 h with a slow evolution of nitrogen. The mixture was refluxed for 2 h. The lachrymatory isocyanate was apparent.

The cooled benzene solution was added to 111 mL (0.0267 mol) of 2% hydrochloric acid (98:2 water–concentrated acid), and the two layers were stirred at room temperature for 4 days. The layers were separated, and the bottom aqueous layer was filtered and evaporated at <1 mm from a warm water bath while being stirred. The solid was dried in vacuo overnight to give 2.55 g (0.0175 mol, 54%) of hydrochloride **2a** as a white powder: IR (KBr) 3440 (N–H), 3082 (cyclopropyl C–H), 2400–2600 (NH^+Cl^-), 2005 (NH^+Cl^-), 1498 (N–H), 1353, 1297, 1248, 801, 732 cm^{-1}; NMR (D_2O, external Me_4Si) δ 4.70 (s, H_2O and NH), 1.65 (s, 6, CH_2), 1.37 (s, 3, CH); ^{13}C NMR (D_2O, TSP-d_4) 54.78 (CN^+), 35.55 (CH_2), 11.61 (CH) ppm. Mass spectral analysis showed a molecular ion with loss of HCl at m/e 109. Exact mass calcd for $C_7H_{11}N$, 109.0891; found, 109.0892. Exact mass calcd for $C_7H_{10}N$, 108.0813; found, 108.0820.

A pure sample was obtained by three recrystallizations from methanol–ether: white plates; mp >275 °C. Anal. Calcd for $C_7H_{12}NCl$: C, 57.73; H, 8.31. Found: C, 57.50; H, 8.22.

When refluxing concentrated hydrochloric acid was used to hydrolyze the isocyanate, a different product was obtained, mp 227–229 °C. It was partially characterized as being an amine hydrochloride [IR (KBr) 2000 cm^{-1} (NH^+Cl^-)], but its NMR spectrum (D_2O) showed a small multiplet at δ 4.0–4.4 (CHCl) and a large complex pattern at δ 1.4–2.8. This compound is believed to be *exo*-3-chloro-1-aminonorbornane hydrochloride (7).

Nortricyclyl-4-carbinyl Tosylate (2e). Alcohol **2f** was formed by treating 2.5 g (0.018 mol) of acid **2c** with 1.5 g (0.040 mol) of lithium aluminum hydride in 80 mL of dry ether under reflux for 2 h in normal fashion.[23] The product had bp 82–84 °C (6.0 mm) and was obtained in a good yield of 2.0 g (0.016 mol, 89%): IR (neat) 3340 (O–H), 3070 (cyclopropyl C–H), 2940 and 2870 (C–H), 1250, 1160, 1040 (C–O), 1000, 810 cm^{-1}; NMR (CCl_4) δ 4.40 (s, 1, OH), 3.68 (s, 2, CH_2O), 1.20 (s, 6 CH_2), 1.08 (s, 3, CH).

Alcohol **2f** was converted into the tosylate **2e** without further purification. In the usual manner,[24] 1.80 g (0.0145 mol) of **2f** was treated with 6.15 g (0.0323 mol) of tosyl chloride in pyridine at 0 °C for 72 h to give 2.20 g (0.00791 mol, 54%) of **2e:** IR (melt) 3070 (cyclopropyl C–H), 3050 (Ar–H), 2940 and 2860 (C–H), 1600 (C=C), 1355 and 1165 (S=O), 1245, 1100, 975, 960, 855, 845, 820, 800, 660 cm^{-1}; NMR (CCl_4) δ 7.1–7.8 (AA'XX', 4, ArH), 4.07 (s, 2, CH_2O), 2.37 (s, 3, CH_3Ar), 1.17 (s, 6, CH_2), 1.03 (s, 3, CH).

Tosylate **2e** was purified for analysis by seven recrystallizations from 30–60 °C petroleum ether, mp 74.5–76.0 °C. Anal. Calcd for $C_{15}H_{18}SO_3$: C, 64.72; H, 6.52. Found: C, 64.89; H, 6.57.

Kinetic Studies. Standard procedures were followed for the acetolysis studies. Standardized 0.04 M sodium acetate in redistilled glacial acetic acid containing 0.3% acetic anhydride was the solvent, with a tosylate concentration of 0.025 M. Aliquots (2 mL) were sealed in ampules and heated to the reaction temperature. The excess sodium acetate was back-titrated in the ampule with standard 0.014 *p*-toluenesulfonic acid in acetic acid using bromophenol blue indicator (yellow to colorless end point). The first-order plot of **2e** was linear to 79% completion. The infinity titre was calculated to be 96%. Results are given in Table I.

Acetolysis Products. To 10 mL of acetic acid containing 0.3% acetic anhydride was added 0.287 g (1.03 mmol) of tosylate **2e** and 0.17 g (2.07 mmol) of anhydrous sodium acetate. The mixture was refluxed at 120 °C for 138 h. The solution was cooled, diluted with 125 mL of water, and extracted with four portions of 30 mL of ether. The ether layers were combined and washed twice with 50 mL of 10% sodium bicarbonate, once with 35 mL of water, and once with 25 mL of brine. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the solvent was distilled at atmospheric pressure from a water bath.

Gas chromatographic analysis (14 ft, 10% SE-30, 166 °C) showed the presence of four products at 9, 11, 26, and 28 min. The two products of short retention times were collected separately at 141 °C with retention times of 19 and 23 min and were determined by NMR analysis to be **8** and **9,** respectively. NMR of **8**: (CCl_4) δ 4.17 (s, 2, CH_2O), 1.93 (s, 3, CH_3CO), 1.22 (near s, 6, CH_2), 1.07 (near s, 3, CH). NMR of **9**: (CCl_4) δ 1.6–2.2 (m, 8, CH_2), 1.87 (s, 3, CH_3CO), 1.1–1.4 (d of m, J = 7 Hz, 2, CH), 0.5–0.8 (m, 1, CH).

Acetates **8** and **9** were recollected together for analysis. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.94; H, 8.34.

The two products of longer retention times were collected separately at 155 °C with retention times of 52 and 55 min and were determined by NMR analysis to be **10** and **11, 12,** or **13,** respectively. The NMR data is given below.

In a second product study, 1.00 g (3.60 mmol) of tosylate **2e** and 0.59 g (7.20 mmol) of anhydrous sodium acetate in 30 mL of acetic acid containing 0.3% acetic anhydride were heated in a pressure bottle at 133–141 °C for 13 days. A workup analogous to the first product study gave 0.70 g of crude product mixture: IR (neat) 2950 and 2870 (C–H), 1732 (C=O), 1250 (asymmetric C–O), 1030 (symmetric C–O) cm^{-1}.

Gas chromatographic analysis (20 ft, 15% SE-30, 201 °C) showed the presence of four products at 10, 12, 26, and 28 min. With another column (QF-1, 198 °C), the order of the two diacetate products was reversed with 15- and 17-min retention times. The two diacetates were separated and collected (QF-1, 165 °C) with retention times of 17 and 23 min and were determined to be **11, 12,** or **13** and **10,** respectively.

NMR of **10:** (CCl_4) δ 4.5–4.7 (m, 1, CHO), 4.13 (s, 2, CH_2O), 2.2–2.4 (m, 1, bridgehead), 2.00 (s, 3, CH_3CO), 1.93 (s, 3, CH_3CO), 1.1–2.0 (m, 8, CH_2). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.40; H, 8.07.

NMR of the ring-expanded, ring-opened diacetate **11, 12,** or **13:** (CCl_4) δ 4.4–4.8 (m, 1, CHO), 2.00 (s, 3, CH_3CO), 1.92 (s, 3, CH_3CO), 1.3–2.4 (m, 11, CH_2 and CH). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.58; H, 8.08.

The percentages of products for both studies are given in Table II.

pK_a of Nortricyclene-4-carboxylic Acid (2c). The pK_a of acid **2c** was taken by dissolving 41.4 mg (0.300 mmol) in 50% ethanol (50 mL, 1:1 absolute ethanol–distilled water by volume) and titrating with 0.0529 N aqueous sodium hydroxide at ambient temperature while the pH was measured with a Corning Model 7 pH meter. The pK_a was obtained from the pH at the half-neutralization point. Benzoic acid was run as a control.

Acknowledgment. The authors wish to express their sincere thanks to the Wolcott Gibbs Fund of the National Academy of Sciences and the University of Wisconsin-Eau Claire Faculty Research Fund for grants in partial support of this investigation. We also thank Professor James W. Wilt, Loyola University of Chicago, for helpful discussions in the early stages of the research and Ms. Irene Gennick, University of Minnesota, for running the ^{13}C NMR spectrum of amine hydrochloride **2a.**

Registry No.—**2a,** 67393-42-4; **2a** free base, 67393-43-5; **2c,** 17294-83-6; **2c** acid chloride, 67393-44-6; **2e,** 67393-45-7; **2f,** 67393-46-8; **2h,** 67393-47-9; **6h,** 33175-47-2; **7,** 15023-54-8; **8,** 67393-48-0; **9,** 67393-49-1; **10,** 67393-50-4.

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Thermolysis and Transannular Reactions of 8,8-Dichloro-2,3:5,6-dibenzobicyclo[5.1.0]octane Derivatives

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Received April 13, 1978

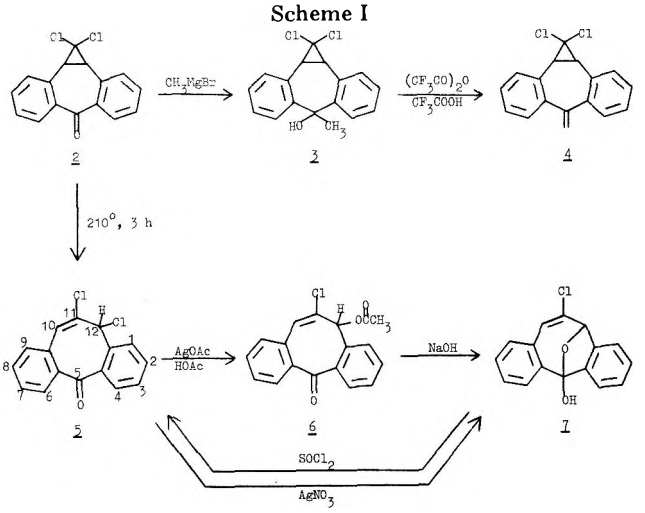
Several 8,8-dichloro-2,3:5,6-dibenzobicyclo[5.1.0]octane derivatives have been prepared and their propensity to thermolyze to functionally substituted, ring-expanded, dibenzo[*a,d*]cyclooctene derivatives has been investigated. 8,8-Dichloro-2,3:5,6-dibenzobicyclo[5.1.0]octan-4-one (**2**) undergoes a facile dichlorocyclopropane ring opening to give **5** in 93% yield, but the corresponding 4-methylene (**4**), 4-hydro (**13**), cis-4 alcohol (**8**), *cis*-4-methyl ether (**14**), and *cis*-4-methylamine (**16**) derivatives fail to undergo similar dichlorocyclopropane ring-opening reactions on heating. Thermolysis of trans alcohol **9** and *trans*-methyl ether **15**, however, leads to the ring-expanded, bridged ring ether **12**, and thermolysis of *trans*-methylamine **17** affords the bridged ring imine **18**. A possible explanation of these transformations in terms of anchimerically assisted dichlorocyclopropane ring-opening reactions is proposed.

Many molecules containing the dibenzo[*a,d*]cycloheptene ring system as a principle structural entity are richly endowed with a spectrum of biological activities.[1a-e] Consequently, the chemistry of derivatives of this type has been studied extensively, including the synthesis of carbon,[2,3] nitrogen,[4a-e] and oxygen[1c,5] bridged analogues. Surprisingly, the use of 5*H*-dibenzo[*a,d*]cycloheptenes as templates for the construction of derivatives of the next higher homologue, dibenzo[*a,d*]-cyclooctene, has not been reported. The availability of 8,8-dichloro-2,3:5,6-dibenzobicyclo[5.1.0]octan-4-one (**2**),[6,7] derived from dichlorocarbene addition to 5*H*-dibenzo[*a,d*]cyclohepten-5-one, suggested that entry into the homologous ring system via the well-documeted thermal-ring expansion of bicyclic 1,1-dihalocyclopropane compounds[8-10] would be feasible. Furthermore, the possibility that analogues of **2** containing appropriate oxygen and nitrogen substituents at C-4 (see Figure 1) might be converted directly to heteroatom bridged structures through transannular participation in the ring-opening process was attractive. Reported here is the experimental verification that both the ring expansion and heteroatom bridging processes occur and that they are related and dependent on the nature of the functionality at C-4 in 8,8-dichloro-2,3:5,6-dibenzobicyclo[5.1.0]octane derivatives.

Reactants, Synthesis, and Stereochemistry

Although 8,8-dichloro-2,3:5,6-dibenzobicyclo[5.1.0]-octan-4-one (**2**) was recovered unchanged after prolonged heating with an aqueous ethanolic solution of silver nitrate,[9] it undergoes a facile ring opening reaction when heated for 3 h in refluxing nitrobenzene to afford a 93% yield of the dichlorocyclopropyl ring-opened ketone **5**. Reaction of **5** with silver acetate in glacial acetic acid at reflux gave acetoxy ketone **6** in 98% yield. Saponification of the ester moiety of **6** led to the transannular hemiketal **7** (99% yield). The same product was obtained by treatment of **5** with aqueous ethanolic silver nitrate solution. Treatment of the hemiketal **7** with refluxing thionyl chloride proceeded smoothly to give crystalline **5** as the sole product.

Scheme I



The addition of methylmagnesium bromide to **2** gave alcohol **3** which was dehydrated to the olefin, **4**, by trifluoroacetic anhydride in trifluoroacetic acid. Attempts to effect thermolysis of the dichlorocyclopropane ring moiety of **4** in refluxing nitrobenzene (bp 210 °C), *o*-bromochlorobenzene (bp 204 °C), or in a neat melt at 200–210 °C were not successful. Starting material was substantially recovered after heating for 2 h. Prolonged heating at this temperature resulted in extensive decomposition.

Potassium borohydride reduction of **2** gave alcohol **8** that was obtained as a single stereoisomer as determined by GLC and ^{1}H NMR analysis. This alcohol has been assigned a *cis* configuration by analogy with Winstein's observation[11,12] that sodium borohydride reduction of 8,8-dibromo-2,3:5,6-dibenzobicyclo[5.1.0]octan-4-one gave the single stereoisomer **1** (X = Br, R_{ax} = H, R_{eq} = OH) that has the hydroxyl group cis with respect to the cyclopropyl ring. In this study of 2,3:5,6-dibenzobicyclo[5.1.0]octane derivatives, Winstein[12] also showed that not only do the cyclopropane rings in these compounds occupy a pseudoequatorial position, but that in C-4 epimeric alcohols, acetates, and methoxy ethers, the resonance of the pseudoaxial C-4 proton (R_{ax}) occurs further downfield in the NMR spectrum than that of the pseudoequatorial C-4 proton (R_{eq}). Equilibration of **8** in acidified aqueous dioxane for 48 h gave a mixture of the epimeric alcohols **8** and **9**. Analysis of this mixture by GLC showed an equilibrium composition in an 85/15 ratio with the more abundant isomer being the starting alcohol **8**. The trans alcohol **9** was separated from this mixture of epimers by chromatography. The ^{1}H NMR spectrum of *trans*-**9** is similar to the NMR spectrum of *cis*-**8** except for the chemical shift of the carbinyl proton (C-4). The pseudoaxial C-4 proton of the cis alcohol **8** has a chemical shift at δ 6.35 while the pseudoequatorial C-4 proton of the trans alcohol **9** has a chemical shift at δ 5.31.

The cis alcohol **8** (mp 170.5–172 °C) when heated at 190 °C melted and then crystallized cleanly to a new product that was identified as the bisether **10**. The same product was formed on heating **8** for 1 h in refluxing nitrobenzene. In this case, however, there appeared to be some decomposition as evi-

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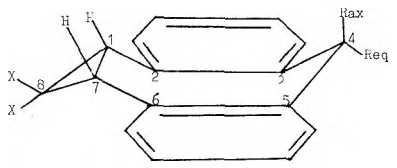


Figure 1.

denced by a slight evolution of HCl gas and rapid darkening of the solution.

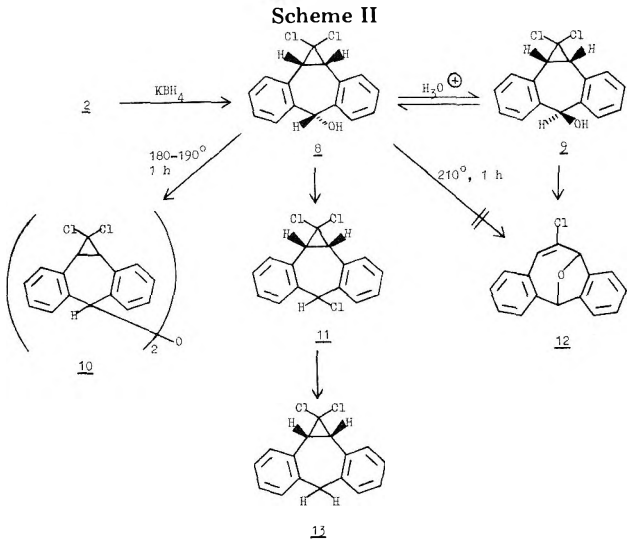
The trans alcohol **9**, when heated for 2 h in refluxing nitrobenzene, gave a new, bridged ring ether **12**. This ether, isolated in crystalline form by chromatography, results from a dichlorocyclopropane ring opening with an intramolecular, transannular participation of the C-4 pseudoaxial hydroxyl group.

Reaction of **8** with thionyl chloride gave a trichloro compound **11** that was solvolyzed in aqueous dimethoxyethane in the presence of sodium borohydride according to the procedure of Bell and Brown.[13] The crystalline chlorohydrocarbon **13** was stable at 150–160 °C for 1 h in a neat melt but underwent rapid decomposition in refluxing nitrobenzene.

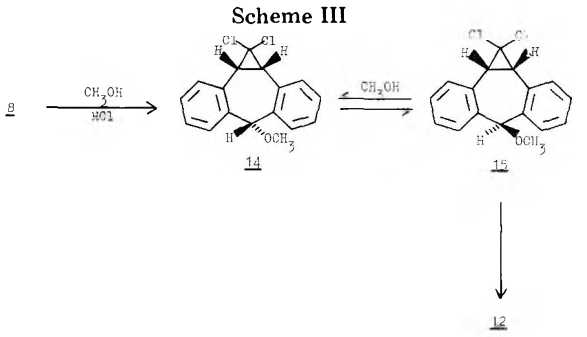
Treatment of the cis alcohol **8** with acidic methanol under reflux for 144 h gave a mixture of the methoxy ethers **14** and **15**. Analysis of this mixture by GLC showed an equilibrium composition in a 21 to 79 ratio. The more abundant isomer was isolated by direct crystallization while the less abundant isomer was isolated by chromatography. As with the epimeric alcohols **8** and **9**, the ^{1}H NMR spectra of methoxy ethers **14** and **15** were similar except for the resonances attributed to the protons α to the methoxy groups. The less abundant epimer was assigned the cis configuration **14** based on the low-field position of its pseudoaxial proton (δ 5.87) relative to the position of the pseudoequatorial proton (δ 4.82) in the more abundant trans isomer **15**. Thermolysis of trans ether **15** at 190–195 °C for 30 min in a neat melt gave the same bridged ring ether **12** as was obtained by thermolysis of trans alcohol **9**. Under the same conditions, cis ether **14** was recovered unchanged.

Titanium tetrachloride promoted addition of methylamine to ketone **2** followed by in situ reduction of the resulting imine with sodium cyanoborohydride gave a mixture of the methylamines **16** and **17**.[14] These amines were readily separated by fractional crystallization of their hydrochloride salts. The ^{1}H NMR spectra of these amines, as bases or as salts, were quite similar except for the chemical shifts of the C-4 protons. By analogy with the alcohols **8** and **9** and the ethers **14** and **15**, the epimeric amine having the low-field C-4 singlet proton resonance (δ 5.36) was assigned the cis configuration **16** while

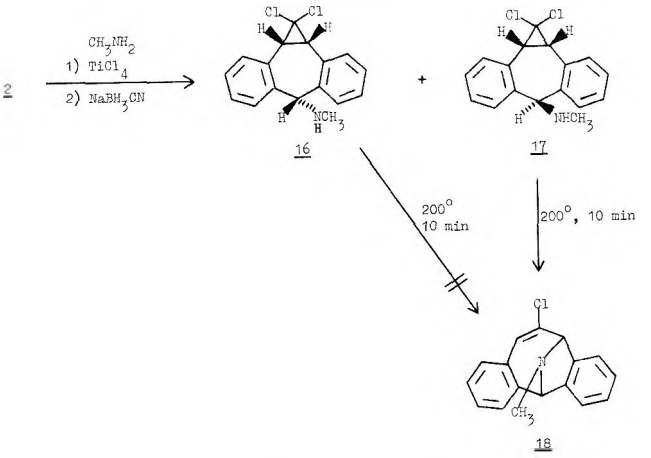
Scheme II



Scheme III



Scheme IV



the amine having the upfield resonance (δ 4.33) was assigned the trans configuration **17**. Additional confirmation of the stereochemical assignments of **16** and **17** was obtained by a comparison of the ^{1}H NMR spectra of the hydrochloride salts *vs.* the free amines. Examination of a Dreiding model of the trans isomer **17** indicates that the nitrogen atom is in close proximity to the bridgehead protons of the cyclopropane ring (see Figure 1, C_1C_7–H). For *trans*-**17**, these bridgehead protons have a signal at δ 3.49 ($CDCl_3$) in the base and at δ 3.74 (Me_2SO-d_6) in the hydrochloride salt. In cis isomer **16**, the bridgehead protons have a resonance at δ 3.55 ($CDCl_3$) in the base and at δ 3.62 (Me_2SO-d_6) in the hydrochloride salt. Thus, in *trans*-**17** the resonance of these protons is displaced 0.18 ppm further downfield on salt formation than for *cis*-**16**. The selective deshielding of the bridgehead protons of **17** that occurs by salt formation thus agrees with the assigned trans configuration.

When **17** was thermolyzed without solvent at 200 °C (10 min), heated for 10 min at 200 °C in hexamethylphosphoramide, or heated in refluxing tetramethylurea (bp 177 °C) for 2 h, it was smoothly converted to the nitrogen bridged compound **18**. Under the same conditions, *cis*-**16** was recovered unchanged.

Discussion

The observation that the dichlorocyclopropyl ketone **2** undergoes a facile thermolysis to give **5** appears to be another example of the well-known thermal rearrangement of a dichlorocyclopropane ring to an allyl cation resulting in a ring-expanded product.[8–10] It was surprising, therefore, that when thermolysis reactions were carried out on the closely related methylene compound **4** or on the dichlorohydrocarbon **13** no apparent ring-opening reactions occurred. The failure of these compounds to undergo the thermolysis reaction suggests a role for the carbonyl oxygen atom of **2** in the ring-opening process leading to **5**. Participation of an oxygen atom in transannular reactions in dibenzo[*a*,*d*]cycloheptene nuclei is well known.[5] Indeed, if neighboring group participation is required during thermolysis for the dichlorocyclopropane ring of 8,8-di-

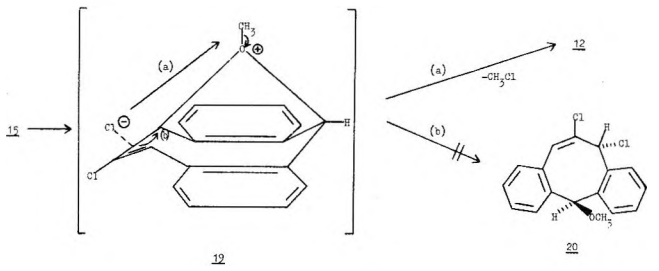


Figure 2.

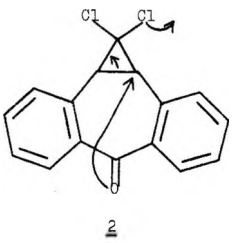


Figure 3.

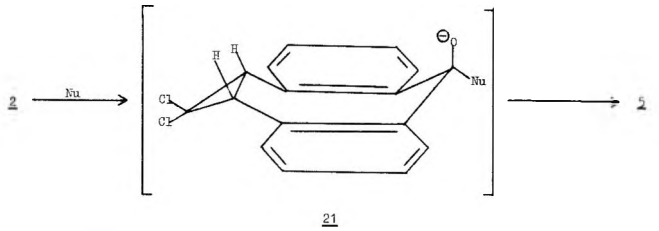


Figure 4.

chloro-2,3:5,6-dibenzobicyclo[5.1.0]octane derivatives to open to product at a temperature lower than that which induces decomposition, then the trans alcohol 9, having an oxygen atom in the pseudoaxial position and hence in close proximity to the C_1C_7 bond, should undergo thermolysis with a concomitant transannular ring formation while cis alcohol 8, with its hydroxyl group positioned in an unfavorable pseudoequatorial orientation, should not undergo a facile thermolysis of the dichlorocyclopropane ring. In fact, this conclusion was borne out by the experimental results described above. The thermolysis experiments of the epimeric amines **16** and **17** and ethers **14** and **15** provide further support for the idea that nucleophilic assistance from a heteroatom is needed to lower the activation energy for ring opening below that required for general decomposition. Thus, with the chlorohydrocarbons **4** and **13**, prolonged heating led to gross decomposition whereas compounds **2**, **9**, **15**, and **17** gave clean thermolysis products. In one of the latter cases, the smooth conversion of **15** to **12**, rather than to **20**, with methyl chloride evolution, suggested that the reaction passes through an intermediate such as **19** in which the oxygen bears a positive charge.

The degree and nature of oxygen participation in the conversion of ketone **2** to **5**, of course, remains open to question. The limiting intermediate oxonium ion structure arising from **2** would appear to be of high energy. The conversion of **7** to **5** on treatment with thionyl chloride, however, suggests that bridged oxygen structures of this type may also tolerate a significant degree of positive charge on C-4. One possibility might involve reversible attack of adventitious nucleophiles (Nu), either in solution or on the surfaces of the reaction vessel, to produce the intermediate **21** in which the participating nucleophile is the negatively charged oxygen atom. However, with the available data, a precise formulation is not possible.[15]

In general, we conclude that the formation of a resonance-stabilized allylic, benzylic carbonium ion and the attendant relief of the strain energy of the cyclopropane ring does not appear to be sufficient to account for any of these ring openings. Rather, the above observations suggest a requirement of participation by a group in the C-4 position capable of efficiently stabilizing or accepting the developing positive charge arising from cleavage of the C_1C_7 bond. For compounds **9**, **15**, and **17**, such participation is clearly evident from the configurational dependence of the process, though for ketone **2** such participation is a matter of surmise.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were determined on Varian A-60A, T-60, EM-90, and HA-100 spectrometers. Except for the hydrochloride salts of **16** and **17**, which were recorded in deuterated dimethyl sulfoxide, all NMR spectra were recorded using deuteriochloroform as solvent and all chemical shifts are relative to tetramethylsilane as an internal standard. Gas-liquid chromatographic analyses were carried out on a Hewlett-Packard Model 5700A/3370B gas chromatograph using a column (6 ft × 2 mm) packed with 1% OV-17 on 100/120 Gas-Chromosorb Q. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer. Analytical TLC was carried out on 250 μm, 5 × 20 cm, Silica Gel GF plates (Analtech, Inc.) using ultraviolet light and iodine vapor for visualization.

5,6-Dichloro-5,12-dihydrodibenzo[*a,d*]cycloocten-12-one (5). A solution of 12.0 g (0.0415 mol) of ketone **2** dissolved in 125 mL of nitrobenzene was stirred and heated at reflux for 3 h. The nitrobenzene was steam distilled from the reaction mixture as rapidly as possible. The dark reaction mixture was extracted with benzene which was washed with water, dried, and evaporated. The residue was chromatographed on a silica gel column using benzene as an eluant to give 9.25 g (93%) of ketone **5**. An analytical sample was prepared by recrystallization from methanol: mp 120–122 °C; NMR δ 6.43 (s, 1 H, allylic C**H**), 6.92 (s, 1 H, vinyl C**H**), 7.2–8.3 (m, 8 H, ArH). The material gave an immediate positive test with alcoholic silver nitrate.

Anal. Calcd for $C_{16}H_{10}Cl_2O$: C, 66.45; H, 3.49; C, 24.52. Found: C, 66.67; H, 3.35; Cl, 24.44.

5-Acetoxy-6-chloro-5,12-chloro-5,12-dihydrodibenzo[*a,d*]-cycloocten-12-one (6). A mixture of 7.06 g (0.0245 mol) of ketone **5**, 4.18 g (0.025 mol) of silver acetate, and 140 mL of glacial acetic acid was heated at reflux for 3 h. The cooled mixture was filtered and the solvent was removed. The residue was recrystallized from benzene to give 7.53 g (98%) of the acetoxy ketone **6**: mp 117–118 °C; NMR δ 2.14 (s, 3 H, CH_3CO), 6.72 (s, 1 H, C_5H), 6.94 (s, 1 H, C_7H), 7.3–7.7 (m, 7 H, ArH), and 8.1–8.3 (m, 1 H, ArH).

Anal. Calcd for $C_{18}H_{13}ClO_3$: C, 69.13; H, 4.19; Cl, 11.34. Found: C, 69.20; H, 4.07; Cl, 11.45.

6-Chloro-5,12-dihydro-5,12-epoxydibenzo[*a,d*]cycloocten-12-ol (7). A solution of 1.0 g (0.0031 mol) of the acetoxy ketone **6**, 10 mL of 5 N sodium hydroxide, and 10 mL of ethanol was heated on the steam bath for 5 min. The cooled solution was filtered and concentrated. The oil that precipitated was extracted into benzene, washed with water, and dried over magnesium sulfate. After evaporation of the benzene, 0.83 g (99%) of hemiketal **7** was obtained. The product was recrystallized from benzene: mp 167–168 °C; NMR δ 4.1 (s, 1 H, OH), 5.40 (s, 1 H, C_5H), 6.32 (s, 1 H, C_7H), 7.0–7.5 and 7.8–8.0 (m, 8 H, ArH); IR (Nujol) 3450 cm^{-1} (OH), no C=O.

Anal. Calcd for $C_{16}H_{11}ClO_2$: C, 70.99; H, 4.10; Cl, 13.09. Found: C, 70.94; H, 4.20; Cl, 12.89.

A solution of 5.37 g (0.0186 mol) of ketone **5** in 100 mL of aqueous acetone (1:3) was treated with a solution of 3.46 g (0.0204 mol) of silver nitrate dissolved in 6.5 mL of water. The mixture was stirred and refluxed for 3 h. The silver chloride was removed by filtration, and the solution was concentrated. The oil that precipitated was extracted into ether and the ether layer was washed with water, dried ($MgSO_4$), and then concentrated. The solid obtained (2.62 g) was recrystallized from benzene to give the hemiketal **7**, mp 167–169 °C; an infrared spectrum of this material was identical to the spectrum of material obtained by saponification of the acetoxy ketone **6**.

Reaction of 6-Chloro-5,12-dihydro-5,12-epoxydibenzo[*a,d*]-cycloocten-12-ol (7) with Thionyl Chloride. A solution of 3.43 g (0.0127 mol) of the hemiketal **7** in 75 mL of thionyl chloride was stirred and refluxed for 4 h. The solvent was removed under reduced pressure and the residue was coevaporated with two 100-mL portions of toluene. Examination of the crystalline residue by TLC (fluorescent silica

gel/toluene) showed essentially a single spot. Recrystallization of the material from methanol gave 2.30 g (63%) of **5** as white needles, mp 117–120 °C, mixture melting point with authentic **5** 116–120 °C; TLC homogeneous both alone and when admixed with authentic **5**. An infrared spectrum of the material was identical to an infrared spectrum of authentic ketone 5.

4-Methylene-8,8-dichloro-2,3:5,6-dibenzobicyclo[5.1.0]octane (4). To an ice-cooled solution of 15.0 g (0.0519 mol) of ketone **2** dissolved in 200 mL of dry THF was added dropwise over 30 min 28.6 mL of a 1.92 M solution of methylmagnesium bromide in THF–benzene. After the addition was complete, the solvent was removed on a rotary evaporator. The remaining red oily residue was dissolved in ether and water was added dropwise until a clear ether supernatant and a semisolid aqueous residue were obtained. The ether phase was decanted and the residue was extracted twice more with ether. The combined ether phases were dried ($MgSO_4$) and filtered and the filtrate was concentrated to afford 14.1 g (89%) of the crystalline alcohol **3**, mp 141–148 °C.

A solution of 6.0 g (0.020 mol) of the above alcohol dissolved in 50 mL of trifluoroacetic anhydride and 50 mL of trifluoroacetic acid was stirred and refluxed for 3 h. The solid that precipitated on cooling was removed by filtration. Recrystallization from acetonitrile gave 4.9 g (87%) of **4**: mp 187–189 °C; NMR δ 3.30 (s, 2 H, bridge H), 5.36 (s, 2 H, vinyl C**H**), 7.1–7.4 (m, 8 H, ArH).

Anal. Calcd for $C_{17}H_{12}Cl_2$: C, 71.09; H, 4.21; Cl, 24.70. Found: C, 70.72; H, 4.39; Cl, 24.63.

The olefin **4** was held as a neat melt in an oil bath at 200–210 °C for 2.5 h. On cooling, the material crystallized, mp 184–187 °C. An NMR spectrum was identical to that of the starting material, **4**. Olefin **4** was heated in refluxing nitrobenzene and also in refluxing 2-bromochlorobenzene (bp 204 °C). Employing the same procedure used in the isolation of **5**, olefin **4** was recovered after 1 h of heating, but then decomposition began to occur.

8,8-Dichloro-*cis*-4-hydroxy-2,3:5,6-dibenzobicyclo[5.1.0]octane (8). To a solution of 2.0 g (0.0069 mol) of ketone **2** dissolved in 40 mL of refluxing methanol was added dropwise over 15 min a solution of 0.941 g (0.0175 mol) of potassium borohydride dissolved in 10 mL of water. After the addition had been completed, the solution was refluxed for 1.5 h. Evaporation of the methanol gave a crystalline product that was collected by filtration, washed with water, and then collected and dried. The colorless material was recrystallized from aqueous methanol to give 1.51 g (75%) of cis-alcohol **8**: mp 170.5–172.5 °C; NMR δ 2.38 (d, 1 H, J = 2 Hz, D_2O exchangeable, HCO**H**), 3.26 (s, 2 H, bridge C**H**), 6.35 (d, 1 H, J = 2 Hz, H-COH), 7.1–7.6 (m, 8 H, Ar**H**).

Anal. Calcd for $C_{16}H_{12}Cl_2O$: C, 66.00; H, 4.14; Cl, 24.36. Found: C, 65.85; H, 4.22; Cl, 24.44.

Bis(8,8-dichloro-2,3:5,6-dibenzobicyclo[5.1.0]oct-4-yl) Ether (10) from the Attempted Thermolysis of cis-Alcohol 8. A sample of the cis-alcohol **8** (2.0 g, mp 170.5–172.5 °C) in a round-bottom flask was placed in an oil bath at 190 °C for 30 min. The compound quickly melted and then crystallized. Examination of this solid by TLC (fluorescent silica gel/toluene) showed none of the cis-alcohol **8** (R_f 0.39), but only a new product at R_f 0.92. Recrystallization from toluene gave 1.0 g of the bisether **10**: mp 250–252 °C; NMR δ 3.10 (s, 2 H, bridge H), 3.42 (s, 2 H, bridge H), 5.10 (s, 1 H, C_4**H**), 6.02 (s, 1 H, C_4**H**), 7.0–7.6 (m, 16 H, Ar**H**).

Anal. Calcd for $C_{32}H_{22}Cl_4O$: C, 68.10; H, 3.93; Cl, 25.13. Found: C, 67.94; H, 3.87; Cl, 24.79.

A solution of 0.75 g of the cis-alcohol **8** in 2 mL of nitrobenzene was heated under reflux for 1 h. The nitrobenzene was removed by coevaporation with water on a rotary evaporator. Examination of the black residue by TLC (fluorescent silica gel/toluene) showed no alcohol **8**, but rather a spot at R_f 0.93 indicative of the ether **10**. There was black decomposition material at the origin.

Equilibration of 8,8-Dichloro-*cis*-4-hydroxy-2,3:5,6-dibenzobicyclo[5.1.0]octane (8) to a Mixture of *cis*-8 and *trans*-9 Alcohols. A solution of 4.54 g of cis-alcohol **8** in 200 mL of peroxide free dioxane and 50 mL of water containing 0.5 mL of 72% perchloric acid was stirred and heated at 80–85 °C under a nitrogen atmosphere for 48 h. The bulk of the dioxane was removed under reduced pressure and 500 mL of water and 100 mL of a saturated sodium bicarbonate solution were added. The oil that precipitated was extracted into two 200-mL portions of ether. The ether phase was washed with water and dried over $MgSO_4$. Evaporation of the ether under reduced pressure gave 4.4 g of a mixture of the alcohols **8** and **9**. Analysis of this mixture by GLC showed 85% cis-alcohol **8** and 15% trans-alcohol **9** at equilibrium. The epimeric alcohols are readily distinguished by TLC (fluorescent silica gel/toluene): cis-alcohol **8**, R_f 0.39; trans-alcohol **9**, R_f 0.16.

8,8-Dichloro-*trans*-4-hydroxy-2,3:5,6-dibenzobicyclo[5.1.0]octane (9). The mixture of epimeric alcohols **8** and **9**, obtained from the previous equilibration experiment, (4.4 g), was separated into its constituent epimers by chromatography on 12 preparative, fluorescent, silica gel plates (2000 μm, 8 in. × 8 in.) using toluene as a developing solvent. The band centered at R_f 0.16 was removed from each plate and the product was eluted by washing the silica gel with warm methanol. The methanol extracts were filtered and the methanol was removed on a rotary evaporator. The residue was recrystallized from acetonitrile to give 0.41 g of TLC homogeneous trans-alcohol **9**: mp 115.5–117.5 °C; NMR δ 2.81 (d, 1 H, $J \sim 1$ Hz, D_2O exchangeable, H–C–O**H**), 3.40 (s, 2 H, bridge CH), 5.31 (d, 1 H, $J \sim 1$ Hz, **H**–C–OH), 7.1–7.8 (m, 8 H, ArH).

Anal. Calcd for $C_{16}H_{12}Cl_2O$: C, 66.00; H, 4.14; Cl, 24.36. Found: C, 66.14; H, 4.05; Cl, 24.28.

6-Chloro-5,12-epoxy-5,12-dihydrodibenzo[*a,d*]cyclooctene (12). A solution of 0.25 g of trans-alcohol **9** in 2.5 mL of nitrobenzene was stirred at reflux for 2 h. The nitrobenzene was removed by coevaporation with water on a rotary evaporator. The remaining dark residue was chromatographed on two preparative silica gel plates (2000 μm, 8 in. × 8 in.) using toluene as a developing solvent. Apart from some black decomposition byproduct at the origin, the only UV absorbing material was located in bands centered at R_f 0.79. These bands were removed from each plate and the product was eluted by washing the silica gel with warm methanol. The extracts were filtered and the methanol was removed on a rotary evaporator to give 0.077 g (35%) of an oil that crystallized on standing. The product was purified by sublimation at 100 °C (0.1 mm) followed by recrystallization from methanol to give **12** as colorless prisms: mp 112.5–114 °C; NMR δ 5.6 (s, 1 H, C_5H), 6.0 (s, 1 H, C_{12}H), 6.25 (s, 1 H, C_7H), 6.8–8.0 (m, 8 H, Ar**H**).

Anal. Calcd for $C_{16}H_{11}ClO$: C, 75.44; H, 4.35; Cl, 13.92. Found: C, 75.48; H, 4.47; Cl, 13.79.

8,8-Dichloro-2,3:5,6-dibenzobicyclo[5.1.0]octane (13). A solution of 10.0 g of the alcohol **8** dissolved in 100 mL of thionyl chloride was stirred and refluxed for 18 h. Removal of the thionyl chloride on a rotary evaporator afforded a crystalline solid **11**. A solution of 7.0 g (0.023 mol) of this solid and 6.0 g of sodium borohydride in 87.5 mL of 80% aqueous dimethoxyethane containing 10 mL of 10% aqueous sodium hydroxide was stirred at 45 °C for 4 h and then was allowed to stand overnight at room temperature. The solution was diluted with 200 mL of water and the oil that precipitated was extracted into ether. The ether layer was washed with three 100-mL portions of water and dried ($MgSO_4$), and the ether was removed to give crude **13**. This material was chromatographed on Alumina using petroleum ether as an eluant to give **13** as TLC homogeneous, colorless crystals. An analytical sample was prepared by recrystallization from ethanol: mp 109–110 °C; NMR δ 3.22 (s, 2 H, bridge **H**), 3.22 and 4.48 (d of d, 2 H, J = 6.5 Hz, ArCH_2Ar), 7.0–7.4 (m, 8 H, ArH).

Anal. Calcd for $C_{16}H_{12}Cl_2$: C, 69.83; H, 4.40; Cl, 25.77. Found: C, 69.81; H, 4.58; Cl, 25.58.

The chlorohydrocarbon **13** was recovered unchanged after being held in a neat melt at 150–160 °C for 1 h. When **13** was heated for 2 h in refluxing nitrobenzene, extensive decomposition occurred.

8,8-Dichloro-*trans*-4-methoxy-2,3:5,6-dibenzobicyclo[5.1.0]octane (15). A solution of 6.0 g of **8** in 250 mL of methanol containing 0.5 mL of concentrated hydrochloric acid was stirred and refluxed for 65 h. The bulk of the methanol was removed on a rotary evaporator. The residue was dissolved in ether and this ethereal solution was washed with a saturated sodium carbonate solution and water and then dried ($MgSO_4$). After filtration, the ether was removed under reduced pressure. The white crystalline residue was recrystallized from methanol to afford 3.27 g of trans-ether **15** that was TLC homogeneous (fluorescent silica gel, toluene, R_f 0.53): mp 118–120 °C; NMR δ 3.30 (s, 3 H, OCH_3), 3.40 (s, 2 H, bridge CH), 4.82 (s, 1 H, C_4H), 7.1–7.4 (m, 8 H, ArH).

Anal. Calcd for $C_{17}H_{14}Cl_2O$: C, 66.90; H, 4.62; Cl, 23.24. Found: C, 67.13; H, 4.52; Cl, 23.18.

6-Chloro-5,12-epoxy-5,12-dihydrodibenzo[*a,d*]cyclooctane (12) from Thermolysis of *trans*-Methyl Ether 15. A 1.0-g sample of *trans*-methyl ether **15** in a round-bottom flask was placed in an oil bath at 190–195 °C for 30 min. The compound quickly melted and gas evolution was observed. The clear, light tan residue was chromatographed on two preparative silica gel plates (2000 μm, 8 in. × 8 in.) using toluene as a developing solvent. The only fluorescent band, at R_f 0.65 to 0.80, was removed from each plate and the product was eluted by washing the silica gel with warm methanol. The extracts were filtered and the methanol was removed on a rotary evaporator. The residue was dissolved in chloroform and filtered, and the chloroform was removed under reduced pressure. The residue was rec-

rystallized from methanol to afford 0.50 g (60%) of colorless prisms, **12**, mp 112–114 °C (mmp with **12**, 112–114 °C). The material was homogeneous by TLC (fluorescent silica gel/toluene), R_f 0.75, when assayed alone or when admixed with authentic **12**.

8,8-Dichloro-*cis*-4-methoxy-2,3:5,6-dibenzobicyclo[5.1.0]octane (14). A solution of 6.32 g of cis-alcohol **8** in 250 mL of methanol containing 2 mL of concentrated hydrochloric acid was refluxed for 144 h. The cooled solution was poured into an excess of sodium carbonate solution and was extracted with ether. The ether phase was washed with water and dried ($MgSO_4$), and the ether was removed on a rotary evaporator to give a mixture of the methyl ethers **14** and **15**. Analysis of this mixture by GLC showed 21% cis-ether **14** and 79% trans-ether **15**. The bulk of the trans-ether **15** was removed by crystallization and the mother liquor, containing the desired cis-ether **14**, was concentrated on a rotary evaporator. The residue, 2.04 g, was chromatographed on four preparative silica gel plates (2000 μm, 8 in. × 8 in.) using toluene as a developing solvent. The band at R_f 0.70 to 0.80 was removed from each plate and the product was eluted by washing the silica gel with warm methanol. After filtration, the methanol was removed under reduced pressure. The residue was recrystallized from methanol to give 0.51 g of TLC homogeneous (silica gel/toluene, R_f 0.74) cis-ether **14**: mp 136–138 °C; NMR δ 3.25 (s, 2 H, bridge CH), 3.50 (s, 3 H, OCH_3), 5.87 (s, 1 H, C_4H), 7.1–7.5 (m, 8 H, ArH).

Anal. Calcd for $C_{17}H_{14}Cl_2O$: C, 66.90; H, 4.62; Cl, 23.24. Found: C, 66.69; H, 4.67; Cl, 23.37.

Cis-ether **14** was recovered unchanged after heating in a neat melt at 190–195 °C for 30 min.

***N*-Methyl-8,8-dichloro-*trans*-2,3:5,6-dibenzobicyclo[5.1.0]-octan-4-amine (17).** To a solution of 3.1 g (0.10 mol) of anhydrous methylamine in 150 mL of benzene was added 7.5 g (0.026 mol) of ketone **2**. A solution of 2.47 g (0.013 mol) of titanium tetrachloride in 20 mL of benzene was added and the mixture was stirred overnight at room temperature. The mixture was filtered. Evaporation of the solvent under reduced pressure gave an oil that was dissolved in 75 mL of acetonitrile and then 2.36 g (0.037 mol) of sodium cyanoborohydride was added. The solution was stirred overnight at room temperature. The solution was diluted with 150 mL of water and 100 mL of 1 N sodium hydroxide. The mixture was extracted with three 100-mL portions of ether and the combined ethereal layers were washed with water and dried over anhydrous sodium sulfate. Removal of the solvent gave 8.9 g of a pale orange oil that was dissolved in 50 mL of methanol and was acidified with 8 N ethanolic HCl. On standing, a white crystalline solid separated. Recrystallization of this solid from methanol (250 mL)–ethanol (150 mL) afforded 2.53 g (29%) of the hydrochloride salt of the trans-amine **17**, mp 280–285 °C. An NMR spectrum was taken on the free base **17**: NMR ($CDCl_3$) δ 1.80 (s, 1 H, NH), 2.23 (s, 3 H, CH_3), 3.49 (s, 2 H, bridge CH), 4.33 (s, 1 H, C_4H), 7.0–7.4 (m, 8 H, ArH).

Anal. Calcd for $C_{17}H_{15}Cl_2N$·HCl: C, 59.93; H, 4.73; Cl, 31.22; N, 4.11. Found: C, 59.92; H, 4.88; Cl, 31.14; N, 4.23.

***N*-Methyl-8,8-dichloro-*cis*-2,3:5,6-dibenzobicyclo[5.1.0]octan-4-amine (16).** All of the mother liquors from the preceding experiment were combined and concentrated by boiling to a volume of 150 mL. On standing, 2.2 g (25%) of the hydrochloride salt of the cis-amine **16** crystallized, mp >340 °C. An NMR spectrum was taken on the free base **16** that was generated from the crystalline hydrochloride salt: NMR ($CDCl_3$) δ 1.70 (s, 1 H, NH), 2.52 (s, 3 H, CH_3), 3.55 (s, 2 H, bridge H), 5.36 (s, 1 H, C_4H), 7.0–7.5 (m, 8 H, ArH).

Anal. Calcd for $C_{17}H_{15}Cl_2N$·HCl: C, 59.93; H, 4.73; Cl, 31.22; N, 4.11. Found: C, 59.60; H, 4.87; Cl, 31.23; N, 4.29.

The amine **16** was recovered unchanged after being held in a neat melt at 200 °C for 10 min, being heated in HMPA at 200 °C for 10 min, or being heated in refluxing tetramethylurea for 2 h.

***N*-Methyl-6-chloro-5,12-dihydrodibenzo[*a,d*]cyclooctene-5,12-imine (18).** A solution of 2.0 g (0.0059 mol) of the free base **17** in 25 mL of HMPA was heated at 200 °C for 10 min. The solvent was removed under reduced pressure, and the residue was slurried with 100 mL of 1 N sodium hydroxide solution. The mixture was extracted with three 100-mL portions of chloroform, and the combined chloroform extracts were dried (Na_2SO_4) and filtered. Removal of the chloroform gave an oil that was dissolved in 100 mL of 1 N methanolic HCl. Evaporation of the solvent gave 1.5 g of a crystalline solid that was recrystallized from acetonitrile–acetone (1:1) to afford 1.3 g (73%) of the hydrochloride salt of **18**, mp 225–228 °C. An NMR spectrum was taken on the free base **18** that was generated from the hydrochloride salt: NMR ($CDCl_3$) δ 2.32 (s, 3 H, NCH_3), 4.7 (s, 1 H, allylic CH), 5.03 (s, 1 H, benzhydryl CH), 6.42 (s, 1 H, vinyl CH), 7.0–7.4 (m, 8 H, ArH).

Anal. Calcd for $C_{17}H_{14}ClN$·HCl: C, 67.11; H, 4.97; N, 4.60. Found: C, 66.81; H, 5.06; N, 4.50.

The same product, **18**, was obtained when **17** was held in a neat melt at 200 °C for 10 min, and also when **17** was heated in refluxing tetramethylurea (bp 177 °C) for 2 h.

Acknowledgment. It is a pleasure to thank Drs. S. Danishefsky and R. V. Stevens for many stimulating discussions held during the course of this work. The authors are indebted to Dr. W. Randall and his staff for the microanalyses, Mr. A. Augenblick for the GLC analysis, and Mr. W. R. McGaughran and Mrs. J. Murphy for the ^1H NMR spectra. Dr. B. Arison kindly provided the 100-MHz ^1H NMR comparison of the free base vs. salt for **16** and **17**.

Registry No.—**2**, 31594-02-2; **3**, 67464-58-8; **4**, 67464-59-9; **5**, 67464-60-2; **6**, 67464-61-3; **7**, 67464-62-4; **8**, 67504-75-0; **9**, 67504-76-1; **10**, 67464-63-5; **11**, 67464-64-6; **12**, 67464-65-7; **13**, 67464-66-8; **14**, 67464-67-9; **15**, 67504; 77-2; **16**, 67464-68-0; **16**·HCl, 67504; 78-3; **17**, 67504-79-4; **17**·HCl, 67528-18-1; **18**, 67464-69-1; **18**·HCL, 67464-70-4.

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(14) This reaction may be viewed as a modification of the Borsch reaction in which methylamine hydrochloride, a byproduct of imine formation, acts as an in situ proton source thus allowing reduction of the protonated imine by sodium cyanoborohydride. This method avoids isolation of potentially unstable imines.

(15) That **2** undergoes dichlorocyclopropane ring opening via a diradical mechanism remains an alternate possibility. If such a mechanism were operative for C-4 trigonally substituted compounds, however, then olefin **4** might be expected to undergo thermolytic ring expansion.

Perhydroindan Derivatives. 19. Opening of a Cyclopropyl Ketone That Is Part of an Indanone System[1]

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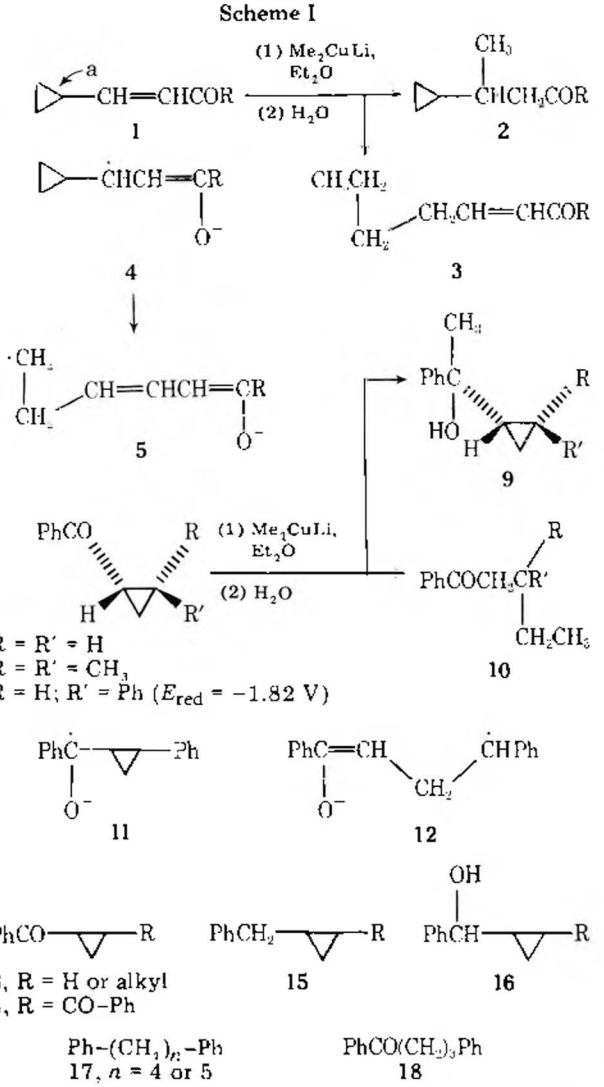
Received May 15, 1978

Reaction of the relatively rigid cyclopropyl ketone **19** with Me_2CuLi gives significantly more ring-opened product **30** than is found in an analogous reaction with the less rigid cyclopropyl ketone **8**. However, both the direction of ring opening and the effect of added donor solvents on the reaction **19** → **30** indicate that this reaction does not involve an initial electron transfer step. Reduction of the ketone with Li and *t*-BuOH in liquid NH_3 (a process that does involve initial electron transfer) results in the formation of products **41–43**. These products are thought to result from rearrangement of the initial anion radical **20** to the anion radical **21b** followed by further transformations to yield the products.

A number of β-cyclopropyl enones **1** (Scheme I) react normally with Me_2CuLi and other cuprate reagents to form the conjugate adducts **2**. However, when special structural features hold the cyclopropyl bond a (structure **1**) approximately perpendicular to the plane of the enone system, then an alternative reaction path involving formation of a ring-opened product **3** becomes either a significant competing reaction or the dominant reaction.[2] This ring-opening reaction **1** → **3** appears to predominate only in those cases where rearrangement of the intermediate enone anion radical **4** to the ring-opened radical **5** is relatively fast (half-life of **4** is 10^{-3} s or less); a geometry with bond a (structure **1**) perpendicular to the enone system is of course favorable to this anion radical rearrangement **4** → **5**.

Scheme I



6, R = R′ = H
7, R = R′ = CH_3
8, R = H; R′ = Ph (E_{red} = −1.82 V)

13, R = H or alkyl
14, R = CO–Ph
15
16

Ph–$(CH_2)_n$–Ph
17, *n* = 4 or 5

$PhCO(CH_2)_3Ph$
18

In a related study of the reaction of Me_2CuLi with the aryl cyclopropyl ketones **6–8** (all of which have reduction potentials in the range −1.8 to −2.1 V vs. SCE),[3] the major product was invariably the 1,2-adduct **9** with only minor amounts (0.6–3.5%) of ring-opened products **10**. Electrochemical reduction[3] of the ketones **6** and **7** in an aprotic medium formed relatively stable anion radicals (half-lives 4–5 s). A much less stable anion radical **11** (half-life 0.005 s) was formed from the ketone **8** with a phenyl substituent that could stabilize the rearranged anion radical **12**. In keeping with these relative anion radical stabilities, both reduction of various cyclopropyl ketones **13** with Li or Na in NH_3[4] and electrochemical reduction of ketone **6** in aqueous EtOH[5] formed products (**15**, **16**, and the corresponding pinacol) with the cyclopropyl ring intact. In contrast, the cyclopropyl ring was opened in the electrochemical reduction of ketone **8** to form ketone **18**[5] and in the reduction of ketones **8** and **14** with Na in NH_3 to form hydrocarbons **17**.[4a] However, the structures of the ring-opened products **10** (attack at the less substituted cyclopropane carbon atom) formed in the cuprate reactions all corresponded to the result expected from an S_N2 attack by the cuprate reagent rather than rebonding to a rearranged radical anion (eg., **12**) derived from the cyclopropyl ketone (eg., **8**). To explore further the question of whether any cuprate–aryl cyclopropyl ketone reaction might involve, at least in part, an initial electron transfer step to form an anion radical (eg., **11**), we wished to examine the cuprate reaction with a cyclopropyl ketone whose anion radical underwent rearrangement faster than the ketyl **11**.

For this purpose we elected to study the fused cyclopropyl ketone **19** (Scheme II) since this molecule is held in a rigid conformation with one cyclopropyl bond (bond a in structure **19**) approximately perpendicular to the plane of the carbonyl group. Our selection of this substrate was also influenced by the possibility of an efficient conversion of ketone **19** via the intermediates **20** and **21a** to indanone derivatives of interest in other synthetic work.[6] Known procedures[7] were used to convert the styrenes **22** and **23** to the esters **24** and **25** (mixtures of stereoisomers) and the acids **26** and **27** (mixtures of stereoisomers). Reaction of the acid **26** (a mixture of stereoisomers) with polyphosphoric acid[7d] or, preferably, with $SOCl_2$ to form **28** followed by reaction with $AlCl_3$[8] produced the desired ketone **19**. In at least the latter procedure, where the ketone **19** was obtained in 61% yield, trans → cis epimerization is believed[8b] to occur during the cyclization of the acid chloride **28**. Our efforts to effect the same cyclization with the methoxy acid **27** led to complex mixtures even when we employed reaction conditions that are satisfactory[6a] for the formation of the methoxyindanone **49** from the corresponding acid chlo-

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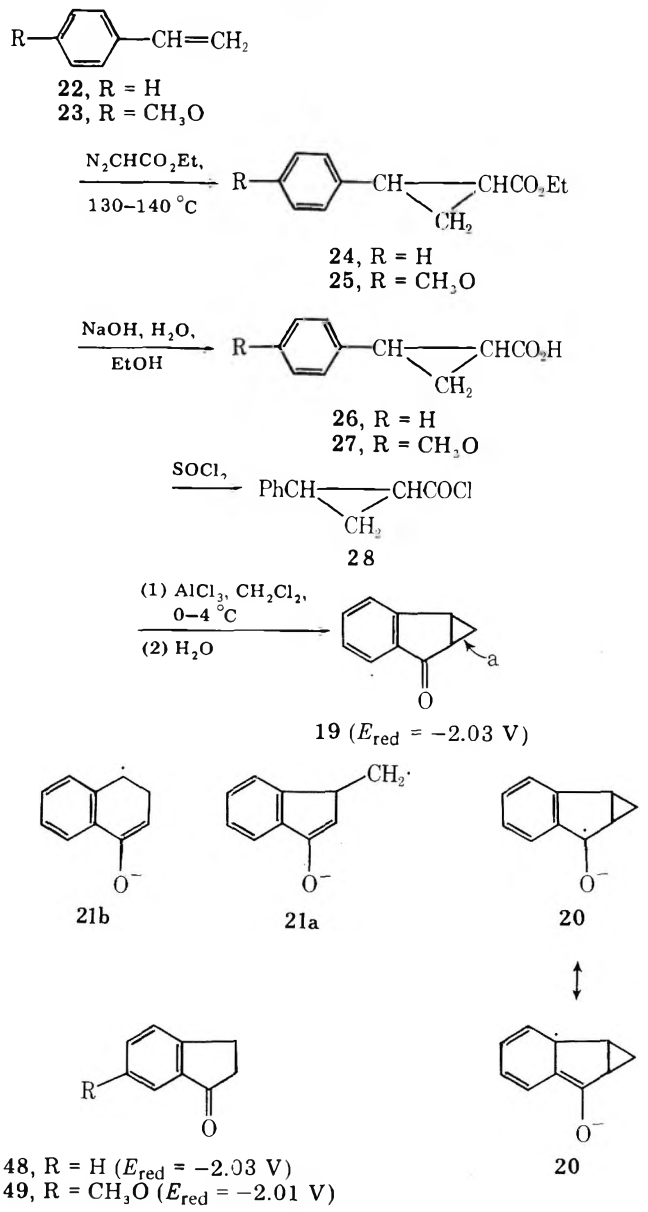
Scheme II

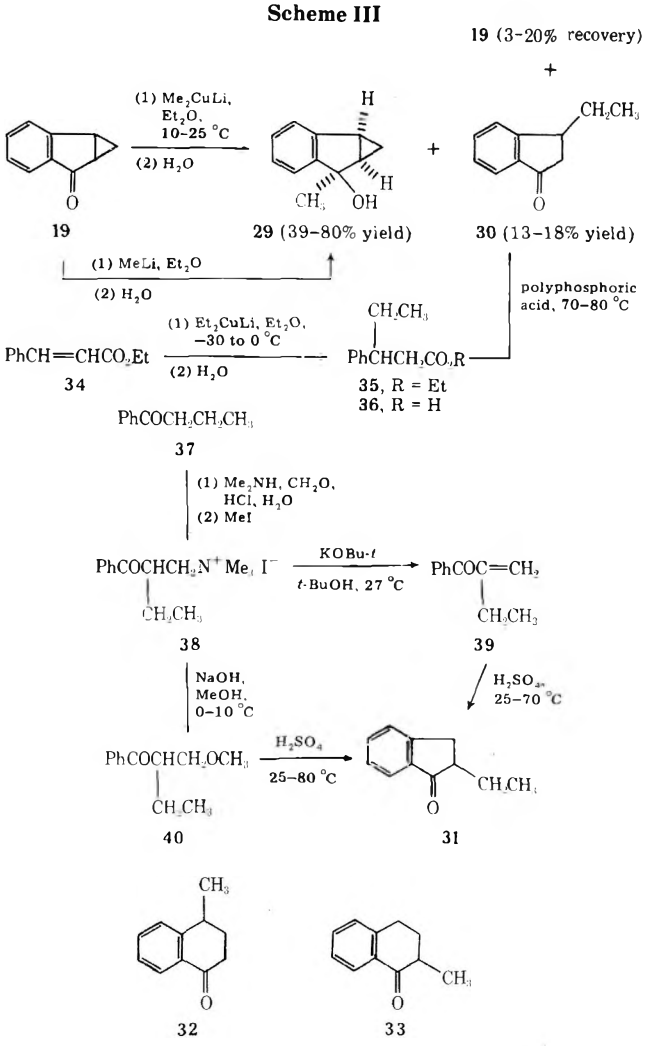


ride. In view of our subsequently described results obtained with the indanone **19**, other possible synthetic routes to the 6-methoxy derivative of indanone **19** were not investigated.

The reduction potentials of the cyclopropyl ketone **19** (E_{red} = −2.03 V vs. SCE) and the analogous indanone **48** (E_{red} = −2.03 V vs. SCE) were the same and were in a range where one-electron reduction by Me_2CuLi to form the ketyl **20** was reasonable.[9] As we had hoped, the anion radical **20** was less stable than its open chain analogue **11** and had a half-life (0.001 s) sufficiently short enough that a significant amount of rearrangement could occur during a cuprate reaction. In fact, reaction of the ketone **19** (Scheme III) with ethereal Me_2CuLi produced a mixture of the 1,2-adduct **29** (75–82% of the product) and a substantial amount of the ring-opened product **30** (18–25% of the product). Only the 1,2-adduct **29** was isolated from the reaction of the cyclopropyl ketone **19** with MeLi. Consequently, in the cuprate reaction the proportion of ring-opened product **30** (or **10**; R = H, R′ = Ph) was enhanced at least 20-fold by changing the substrate from the flexible ketone **8** to the rigid system **19**.

One could imagine that any one of the three cyclopropane C–C bonds in ketone **19** might be cleaved during the cuprate reaction so that any or all of the ketone products **30–33** might be formed. To insure that our ring-opened product was in fact the ketone **30**, we obtained authentic samples of the ketones

Scheme III

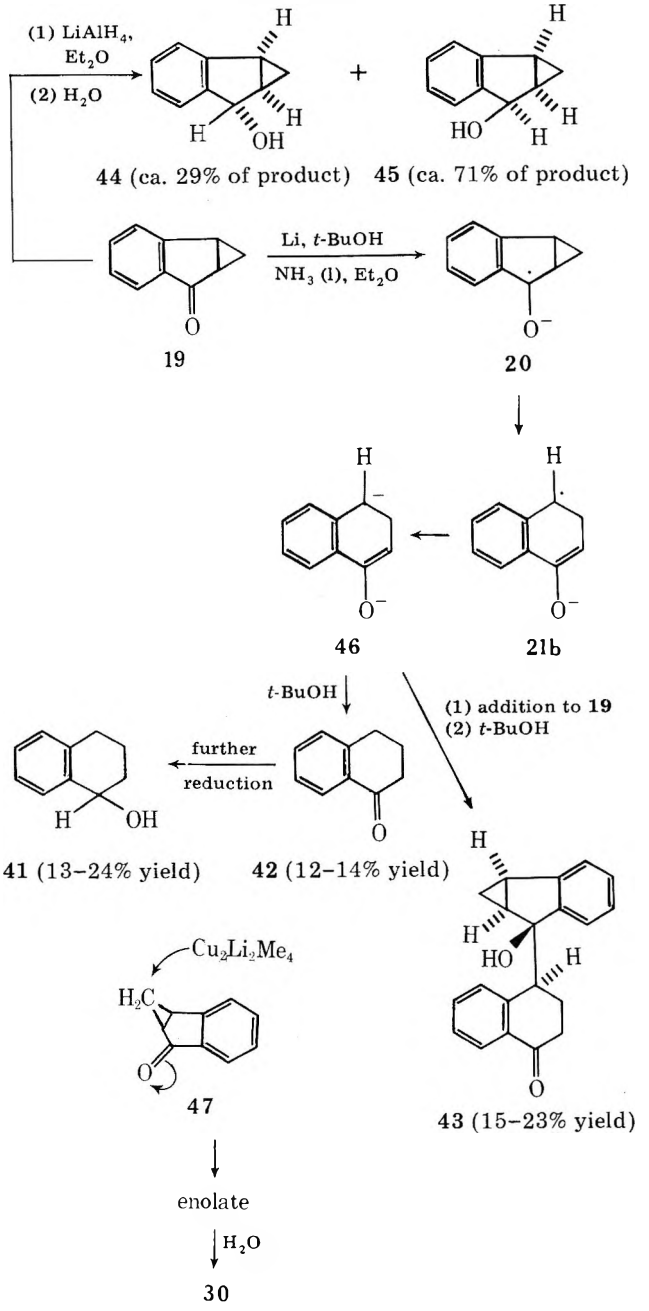


30–33 and demonstrated that our product **30** contained less than 5% (if any) of the isomeric ketones **31–33**. Authentic samples of ketones **30** and **31** were prepared by the routes indicated in Scheme III.

The foregoing results might be interpreted as reaction of the ketone **19** with Me_2CuLi to form the ketyl **20** followed by partial rearrangement to **21a** and rebonding to form **29** and **30**. However, such a conclusion would be warranted only if the ketyl **20** actually rearranges to the anion radical **21a** (favored by the geometry of the system) rather than some other anion radical such as **21b** (which allows stabilization of the radical by the adjacent phenyl ring). A clear indication that this second possibility might be correct was provided by an earlier study[10] of the reduction of ketone **19** with Li in an NH_3–Et_2O mixture. The reported products were an unidentified solid (mp 160–185 °C), tetralin, and tetralone.

We have repeated this reduction of ketone **19** (Scheme IV) employing a solution containing 2 equiv of Li and 1 equiv of *t*-BuOH in an NH_3–Et_2O mixture. The products were tetralol (**41**), tetralone (**42**), and the dihydro dimer **43** (mp 188–189.9 °C). Authentic samples of the alternative reduction products, the known[11] alcohols **44** and **45**, were prepared to demonstrate their absence among the reduction products. Consideration of the products (**41–43**) formed in this metal–NH_3 reduction leaves little doubt that the initially formed ketyl **20** rearranges to form anion radical **21b** and not **21a**. Further reduction of anion radical **21b** to the dianion **46** readily accounts for all of the isolated products **41–43**. In view of this, we conclude that reaction of the ketone **19** with Me_2CuLi to form ketone **30** does not involve the intermediate ketyl **20** since this latter intermediate should have rearranged to **21b** and then formed ketone **32**. Instead, the reaction with the cuprate to form ketone

Scheme IV



30 must again be an example of an S_N2 ring opening (see structure 47) in which the geometry of the substrate is especially favorable for attack at the cyclopropyl CH_2 group to displace an enolate anion. In agreement with this conclusion, the yield of ketone 30 from reaction of Me_2CuLi with ketone 19 was increased (see Table III) by the addition of good donor solvents (DME or THF). In reactions of cuprates with ketones where an initial electron transfer step is involved, the presence of good donor solvents normally retards or inhibits the reaction.[12]

The structure of the dihydro dimer 43, determined by a single crystal X-ray diffraction study, is shown in Figure 1. The bond lengths and bond angles obtained from this structural determination are listed in Table I.

Experimental Section[13]

Preparation of the Acid Derivatives 24, 26, and 28. A cold (0 °C) solution of 28.53 g (0.25 mol) of N_2CHCO_2Et[14] in 26.04 g (0.25 mol) of styrene (22) was added dropwise with stirring during 15 min to 13.02 g (0.125 mol) of styrene (22) that was maintained at 130–140 °C under

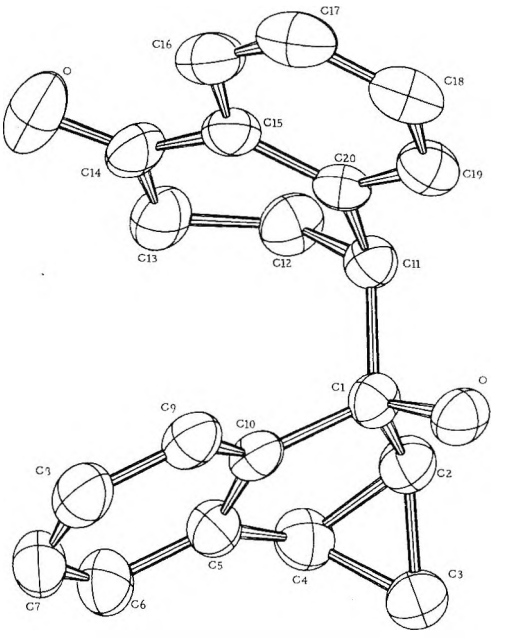


Figure 1. A perspective view of the molecular structure of the dihydro dimer 43.

an N_2 atmosphere. The resulting mixture was stirred at 130–135 °C for 24 h and then distilled to separate 4.89 g of forerun (mainly $PhCH{=}CH_2$) followed by 36.93 g of the crude ester 24 as a pale yellow liquid: bp 80–90 °C (0.15 mm); $n^{25}D$ 1.5182. Redistillation afforded 34.28 g (72%) of the ester 24 (a mixture of stereoisomers) as a colorless liquid: bp 80.5–82 °C (0.14 mm); $n^{25}D$ 1.5182 [lit. bp 103–105 °C (0.5–0.7 mm),[7a] $n^{20}D$ 1.518[7d]]; IR (CCl_4) 1725 cm^{-1} (ester C=O); UV (95% EtOH) intense end absorption with a series of weak maxima (ϵ 251–472) in the region 253–273 nm; NMR (CCl_4) δ 6.8–7.4 (5 H, m, aryl CH), 4.10 and 3.81 (2 H, overlapping quartets, J = 7 Hz, CH_2O), and 0.7–2.7 (7 H, m, ethoxyl CH_3 and cyclopropyl CH and CH_2); mass spectrum, m/e (relative intensity) 190 (M^+, 29), 145 (21), 144 (18), 117 (100), 116 (23), 115 (50), and 91 (22).

Saponification of 32.64 g (172 mmol) of the ester 24 with a refluxing solution of 10.35 g (259 mmol) of NaOH and 15 mL of H_2O in 100 mL of EtOH for 24 h followed by the usual isolation procedure yielded the crude acid 26 (a mixture of stereoisomers) as a cream-colored solid, mp 68–73 °C (lit.[7c] mp 55–63 °C). Recrystallization from H_2O afforded a mixture of stereoisomeric acids 26 in 57% yield as colorless crystals, mp 62.5–101 °C [lit.[7a] mp 93 (trans isomer) and 106–107 °C (cis isomer)].

This crude acid (8.11 g, 50 mmol) was dissolved in 17.85 g (150 mmol) of warm $SOCl_2$ and then stirred at 25 °C for 24 h, concentrated, and distilled. The acid chloride 28 (a mixture of stereoisomers) was collected as 8.69 g (96%) of pale yellow liquid: bp 126–128 °C (24 mm) [lit. bp 108–110 (2.1 mm)[7a] and 130 °C (10 mm)[7c]; $n^{25}D$ 1.5548–1.5551; IR (CCl_4) 1780 cm^{-1} (C=O); NMR (CCl_4) δ 6.7–7.6 (5 H, m, aryl CH) and 1.2–3.0 (4 H, m, CH and CH_2); mass spectrum, m/e (relative intensity) 182 (M^+, <1), 180 (M^+, 3), 145 (79), 127 (48), 125 (48), 117 (89), 116 (70), 115 (99), 91 (58), 55 (100), and 39 (37).

Preparation of the Ketone 19. A solution of 24.33 g (150 mmol) of the acid chloride 28 in 40 mL of CH_2Cl_2 was added dropwise and with stirring during 1 h to a cold (0–3 °C) mixture of 26.0 g (195 mmol) of anhydrous $AlCl_3$ and 40 mL of CH_2Cl_2. After the resulting mixture had been stirred at 0–4 °C for 24 h, it was poured into ice water, acidified with HCl, and extracted with CH_2Cl_2. The organic layer was stirred for 24 h with aqueous Na_2CO_3 and then separated, dried, and concentrated. Distillation of the residual brown liquid (23.5 g) afforded 13.28 g (61%) of the ketone 19 as a colorless liquid: bp 77–85 °C (0.15–0.20 mm) [lit.[15] bp 80 °C (0.4 mm)]; $n^{25}D$ 1.5850–1.5855; IR (CCl_4) 1720 cm^{-1} (C=O); UV max (95% EtOH) 255 nm (ϵ 6450) and 298 (1530), with a shoulder at 305 nm (ϵ 1360); NMR (CCl_4) δ 6.8–7.5 (4 H, m, aryl CH), 2.1–3.0 (2 H, m, cyclopropyl CH), and 1.0–1.7 (2 H, m, cyclopropyl CH_2); mass spectrum, m/e (relative intensity) 144 (M^+, 68), 117 (13), 116 (72), 115 (100), 89 (14), and 63 (15).

In an alternative preparation, a mixture of 27.83 g (146 mmol) of the acid 26 (a mixture of stereoisomers) and 300 g of polyphosphoric acid was stirred at 40–65 °C for 1.5 h and then poured into ice water and extracted with Et_2O. After the ethereal extract had been dried and concentrated, distillation of the residual amber liquid (13.7 g)

Table I. Molecular Geometry of the Dihydro Dimer 43 [a]

A. Bond Lengths

atoms	distance, Å	atoms	distance, Å
C1–O1	1.437 (3)	C11–C1	1.557 (4)
C1–C2	1.520 (3)	C11–C12	1.538 (4)
C2–C3	1.497 (4)	C11–C20	1.514 (4)
C2–C4	1.506 (4)	C12–C13	1.525 (4)
C3–C4	1.511 (4)	C13–C14	1.492 (4)
C4–C5	1.493 (4)	C14–O2	1.232 (3)
C5–C6	1.381 (4)	C14–C15	1.478 (4)
C5–C10	1.394 (3)	C15–C16	1.401 (4)
C6–C7	1.391 (4)	C16–C17	1.374 (4)
C7–C8	1.382 (4)	C17–C18	1.392 (4)
C8–C9	1.388 (4)	C18–C19	1.380 (4)
C9–C10	1.387 (3)	C19–C20	1.391 (3)
C10–C1	1.516 (3)	C20–C15	1.405 (4)

B. Bond Angles

atoms	angle, deg	atoms	angle, deg
O1–C1–C2	113.1 (2)	C9–C10–C1	128.2 (2)
O1–C1–C10	111.7 (2)	C10–C1–C2	103.4 (2)
O1–C1–C11	105.1 (2)	C11–C1–C10	114.7 (2)
C1–C2–C3	119.0 (2)	C11–C12–C13	113.9 (2)
C1–C2–C4	108.8 (2)	C11–C20–C19	120.1 (2)
C2–C3–C4	60.1 (2)	C12–C11–C1	114.2 (2)
C2–C4–C3	59.5 (2)	C12–C13–C14	113.8 (2)
C2–C4–C5	105.6 (2)	C13–C14–C15	118.4 (2)
C2–C1–C11	109.1 (2)	C13–C14–O2	120.9 (3)
C3–C2–C4	60.4 (2)	C14–C15–C16	118.4 (2)
C3–C4–C5	113.4 (2)	C15–C14–O2	120.8 (3)
C4–C5–C6	129.3 (2)	C15–C16–C17	120.8 (3)
C4–C5–C10	110.1 (2)	C15–C20–C11	121.6 (2)
C5–C6–C7	118.6 (3)	C15–C20–C19	118.2 (2)
C5–C10–C1	111.2 (2)	C16–C17–C18	119.5 (2)
C5–C10–C9	120.5 (2)	C19–C18–C17	120.2 (3)
C6–C5–C10	120.5 (2)	C20–C11–C1	114.4 (2)
C6–C7–C8	121.0 (2)	C20–C11–C12	110.3 (2)
C7–C8–C9	120.5 (2)	C20–C15–C14	121.6 (2)
C8–C9–C10	118.8 (2)	C20–C15–C16	119.9 (2)
		C20–C19–C18	121.4 (2)

[a] Numbers in parentheses indicate estimated standard deviations in the least significant digit.

afforded 4.79 g (23%) of the ketone **19**: bp 74–78 °C (0.1 mm); $n^{25}D$ 1.5841–1.5847.

Preparation of the Alcohol 29. To a cold (0 °C) solution of 1.442 g (10.0 mmol) of the ketone **19** in 50 mL of Et_2O was added dropwise and with stirring during 5 min 12 mL of an Et_2O solution containing 12 mmol of MeLi. After the resulting solution had been stirred at 25 °C for 10 min, it was partitioned between H_2O and Et_2O. The organic layer was dried and concentrated to leave 1.52 g (95%) of the crude alcohol **29** as a colorless liquid that solidified on standing, mp 47.9–52.6 °C. One recrystallization from pentane sharpened the melting point to 50–52.4 °C, and an additional recrystallization gave 384 mg of the pure alcohol **29** as colorless plates: mp 53.8–54.2 °C; IR (CCl_4) 3590 and 3460 cm^{-1} (OH); UV max (95% EtOH) 264 nm (ε 682), 270 (891), 277.5 (800), 296 (136), and 307 (109); NMR ($CDCl_3$) δ 6.9–7.4 (4 H, m, aryl CH), 1.3–2.5 (6 H, m, cyclopropyl CH, OH, and a CH_3 singlet at δ 1.52), and 0.2–1.1 (2 H, m, cyclopropyl CH_2); mass spectrum, *m/e* (relative intensity) 160 (M^+, 14), 146 (24), 145 (99), 141 (24), 128 (31), 127 (45), 118 (28), 117 (100), 116 (45), 115 (59), and 91 (24).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.49; H, 7.59.

Reaction of the Ketone 19 with Me_2CuLi. A solution of 434 mg (3.00 mmol) of the ketone **19** in 2 mL of Et_2O was added dropwise and with stirring during 2 min to a cold (0 °C) solution of Me_2CuLi from 926 mg (4.5 mmol) of Me_2SCuBr, 9.0 mmol of MeLi (halide-free), 9 mL of Me_2S, and 21 mL of Et_2O. As the resulting orange solution was slowly warmed from 0 °C, a yellow precipitate began to separate at about 10 °C. The mixture was stirred at 10 °C for 15 min and at 25 °C for 1 h and then partitioned between Et_2O and an aqueous solution of NH_4Cl and NH_3. After the organic solution had been dried and concentrated, the residual green liquid (470 mg) was subjected to a preparative TLC separation on silica gel with an Et_2O–hexane mixture (1:5 v/v) as eluent. The components separated were 61 mg (13%) of the ketone **30** (R_f 0.49), 72 mg (17%) of the starting ketone **19** (R_f 0.36), and 188 mg (39%) of the alcohol **29** (R_f 0.17). The alcohol **29** and the ketone **19** were identified with previously described samples by comparison of NMR and IR spectra and TLC R_f values. The crude ketone **30** was distilled in a short-path still (ca. 100 °C at 0.15 mm) to separate 42 mg of the pure ketone **30** as a colorless liquid, $n^{25}D$ 1.5477, that was identified with a subsequently described sample by comparison of GLC retention times and IR, NMR, and mass spectra.

Table II. GLC Retention Times for Various Possible Components in the Mixture from the Reaction of Ketone 19 with Me_2CuLi

compd	GLC retention time, min: silicone SE-52, 176 °C	silicone QF-1, 150 °C	UCON 50-HB, 217 °C
ketone **19**	8.3	21.0	
ketone **30**	9.3[a]	23.9[b]	62.7
ketone **32**	10.5[a]	23.8[b]	68.2
ketone **31**		18.0[c]	
ketone **33**	9.6[a]	18.3[c]	
alcohol **29**	5.1[d]	5.2–11.0 (broad)	
$PhCH_2CH_2Ph$	14.0	13.5	

[a] Ketones **30**, **32**, and **33** are not resolved. [b] Ketones **30** and **32** are not resolved. [c] Ketones **31** and **33** are not resolved. [d] This peak contains one or more dehydration products from the alcohol **29**.

The following experiment was performed to demonstrate the absence of ketones **31**, **32**, and **33** in the reaction product. To a cold (−5–0 °C) solution of Me_2CuLi, from 1.26 g (6.13 mmol) of Me_2SCuBr, 12.0 mmol of MeLi, 6 mL of Et_2O, and 15 mL of THF, was added a solution of 428 mg (2.97 mmol) of the ketone **19** in 2.0 mL of THF. After the mixture had been stirred for 1 h at −5–0 °C and for 5 h at 25 °C, the previously described isolation procedure separated 431 mg of crude liquid product. One-half of this product was mixed with 147 mg of $PhCH_2CH_2Ph$ (an internal standard) and subjected to GLC analysis (silicone SE-52 on Chromosorb P; apparatus was calibrated with known mixtures). The calculated yields were 24% of ketone **19**, 31% of alcohol **29**, and 19% of ketone **30**. The GLC retention times for the various possible components on three different GLC columns are summarized in Table II. Under these GLC conditions, samples of the alcohol **29** gave a single broad GLC peak as indicated in Table II. However, samples of this peak collected from the GLC apparatus had IR [1645 cm^{-1} (C=C)] and mass spectra (M^+ at *m/e* 142) corresponding to one or more dehydration products from the alcohol **29**. Since the GLC response factor for this peak was relatively constant, this peak was used to estimate the yield of the alcohol **29** formed with the realization that some uncertainty in the yield of alcohol **29** may result from this analytical procedure. The second half of the crude reaction product was subjected to GLC analysis (silicone QF-1 on Chromosorb P) to demonstrate the absence of ketones **31** and **33**. When authentic samples of these ketones **31** and **33** were added to aliquots of the crude product in amounts corresponding to 5% of the amount of ketone **30** present, each ketone **31** or **33** was easily detected. The GLC peak (silicone QF-1 on Chromosorb P) corresponding in retention time to either ketone **30** or ketone **32** was collected; after short-path distillation, one portion of this collected sample was identified with an authentic sample of ketone **30** by comparison of IR spectra. A second portion of the collected sample was analyzed on a third GLC column (UCON 50-HB on Chromosorb P) to demonstrate the absence of ketone **32**. When a synthetic mixture of 5% of ketone **32** and 95% of ketone **30** was subjected to this same analytical procedure, the minor constituent, ketone **32**, was readily detected. Thus, we have found no evidence indicating the presence of any of the ketones **31**, **32**, or **33** in the crude product and can conclude that more than 95% of the ketonic product formed in this reaction is 3-ethylindanone (**30**).

In an additional series of experiments, colorless solutions of Me_2CuLi [containing a very small amount of yellow $(MeCu)_n$ precipitate to ensure the absence of excess MeLi], prepared from 6.0 mmol of Me_2SCuBr, 12 mmol of MeLi (halide-free), and 6 mL of Et_2O, were diluted with the solvents indicated in Table III, and then 3.0 mmol of the ketone **19** was added dropwise and with stirring during 1–5 min at the initial reaction temperature indicated in Table III. After the reaction mixtures had been stirred and allowed to warm to

Table III. Reaction of Ketone 19 with Me_2CuLi in Various Solvents

solvents (mL)	initial reaction temp, °C	reaction time, h	yields, % ketone 19	ketone 30	alcohol 29
Et_2O (14) + Me_2S (9)	5–15	1	3–20	17–18	62–80
Et_2O (5–7) + pentane (17–22)	5–15	1.5–17	1–6	6–7	87–92
Et_2O (6) + THF (17)	5	18	13	27	60
Et_2O (6) + DME (17–27)	5–15	17–18	28–36	18–21	40–47

25 °C during the times indicated in Table III, they were siphoned into an aqueous solution of NH_4Cl and NH_3 and then extracted with Et_2O. The ethereal extracts were mixed with a known weight of $PhCH_2CH_2Ph$, dried, and subjected to GLC analysis (silicone SE-52 on Chromosorb P at 176 °C; apparatus was calibrated with known mixtures). The yields of the various products **19**, **29**, and **30** are summarized in Table III.

Sources of Ketones 48, 49, 31–33, 39, and 40. The preparation and properties of indanones **48** and **49** are described elsewhere,[6c] and authentic samples of tetralones **32** and **33** were obtained from Aldrich Chemical Co., Inc. A sample of the tetralone **32**, purified by short-path distillation, was obtained as a colorless liquid: n^{25}_D 1.5597 [lit.[16] bp 133–134 °C (12 mm), n^{19}_D 1.5620]; IR (CCl_4) 1691 cm^{-1} (C=O); UV max (95% EtOH) 212 nm (ε 9840), 249 (10 200), and 293 (1700); NMR (CCl_4) δ 6.6–7.9 (4 H, m, aryl CH) and 0.9–3.3 (8 H, m, aliphatic CH including a CH_3 doublet, J = 6.5 Hz, at δ 1.28); mass spectrum, *m/e* (relative intensity) 160 (M^+, 100), 145 (67), 132 (66), 118 (64), 117 (32), 115 (23), 104 (58), 77 (21), and 51 (22).

Purification by short-path distillation afforded a sample of the tetralone **33** as a colorless liquid: n^{25}_D 1.5523 [lit.[17] bp 136–138 °C (16 mm), n^{25}_D 1.5538]; IR (CCl_4) 1692 cm^{-1} (C=O); UV max (95% EtOH) 210 nm (ε 14 200), 247.5 (11 400), and 292 (1540); NMR (CCl_4) δ 7.0–8.2 (4 H, m, aryl CH), 1.4–3.2 (5 H, m, aliphatic CH), and 1.17 (3 H, d, J = 6 Hz, CH_3); mass spectrum, *m/e* (relative intensity) 161 (39), 160 (M^+, 92), 145 (76), 142 (39), 141 (33), 132 (42), 131 (65), 119 (49), 118 (100), 117 (36), 115 (37), 91 (37), 90 (68), 89 (42), and 77 (34).

A previously described procedure[18] was used to convert $PhCOCH_2CH_2CH_3$ to the methiodide **38** of its Mannich base. A solution of KOBu-*t*, from 0.49 g (12.5 mg-atom) of K and 25 mL of *t*-BuOH, was added dropwise and with stirring during 5 min to a suspension of 4.34 g (12.5 mmol) of the ammonium salt **38** in 25 mL of *t*-BuOH. The resulting solution was stirred at 25–27 °C for 10 min and then partitioned between H_2O and Et_2O. After the ethereal layer had dried and concentrated, distillation of the residual liquid separated 1.13 g (56%) of the pure (GLC analyses) unsaturated ketone **39** (bp 58–60 °C (0.15 mm); n^{25}_D 1.5294–1.5299) accompanied by 267 mg of less pure ketone **39** (bp 64–67 °C (0.15 mm); n^{25}_D 1.5275 [lit.[18] bp 49–50 °C (0.15 mm), n^{25}_D 1.5300]): IR (CCl_4) 1660 (C=O), 1625 (C=C), and 930 (C=CH_2) cm^{-1}; UV max (95% EtOH) 246 nm (ε 9510) and 335.5 (93); NMR (CCl_4) δ 6.9–7.6 (5 H, m, aryl CH), 5.5–5.6 (1 H, m, vinyl CH), 5.2–5.4 (1 H, m, vinyl CH), 2.38 (2 H, q, J = 7 Hz, CH_2), and 1.06 (3 H, t, J = 7 Hz, CH_3); mass spectrum, *m/e* (relative intensity) 160 (M^+, 20), 145 (15), 105 (100), 77 (52), and 51 (17).

A previously described[19] cyclization was effected by adding 974 mg (6.1 mmol) of the unsaturated ketone **39** dropwise and with stirring during 1 min to 4.0 mL of concentrated H_2SO_4. The resulting solution, whose temperature initially rose to 70 °C, was stirred, allowed to cool for 90 min, and then poured onto ice and partitioned between H_2O and Et_2O. The Et_2O solution was washed with aqueous $NaHCO_3$, dried, and concentrated to leave a crude yellow liquid product containing (GLC, silicone SE-30 on Chromosorb P) the indanone **31** (retention time 24.6 min) but lacking peaks corresponding to the enone **39** (15.9 min) or the subsequently described methoxy ketone **40** (29.1 min). Distillation afforded 866 mg (89%) of the indanone **31** as a colorless liquid: bp 65–66 °C (0.05 mm); n^{25}_D 1.5452–1.5456 [lit.[19] bp 143 °C (18 mm), n^{31}_D 1.5420]; IR (CCl_4) 1718 cm^{-1} (C=O); UV max (95% EtOH) 245 nm (ε 12 100) and 291.5 (2170); NMR (CCl_4) δ 6.7–7.5 (4 H, m, aryl CH), 1.1–3.5 (5 H, m, CH and CH_2), and 0.91 (3, H, t, J = 7 Hz, CH_3); mass spectrum, *m/e* (relative intensity) 160 (M^+, 4), 133 (19), 132 (100), 131 (50), and 103 (15).

In an alternative procedure, 94 mL of aqueous 6 M NaOH (564 mmol) was added dropwise with stirring and cooling during 30 min to a cold (−1 to −4 °C) suspension of 50.3 g (171 mmol) of the methiodide **38** in 500 mL of MeOH. After the resulting mixture had been stirred at 0 °C for 1 h and at 10 °C for 2 h, it was partitioned between H_2O and Et_2O. After the Et_2O solution had been dried and concentrated, distillation of the residual liquid (20.92 g) afforded 19.9 g of fractions (bp 90–95 °C (0.14 mm); n^{25}_D 1.5111–1.5145) containing (GLC) various mixtures of the enone **39** and the methoxy ketone **40**. Fractions rich in the methoxy ketone **40** were redistilled to separate 3.86 g of the higher boiling pure (GLC) methoxy ketone **40**: bp 114–116 °C (6 mm); n^{25}_D 1.5114; IR (CCl_4) 1685 cm^{-1} (C=O); UV max (95% EtOH) 244 nm (ε 12 500), 279 (1060). and 320 (80); NMR (CCl_4) δ 7.2–8.1 (5 H, m, aryl CH), 3.3–3.8 (3 H, m, CH and CH_2O), 3.17 (3 H, s, OCH_3), 1.3–1.9 (2 H, m, CH_2), and 0.83 (3 H, t, J = 7 Hz, CH_3); mass spectrum, *m/e* (relative intensity) 192 (M^+, 2), 163 (64), 160 (50), 137 (55), 136 (34), 106 (28), 105 (100), 77 (66), 51 (28), and 45 (45).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.00; H, 8.42.

The methoxy ketone **40** (1.92 g, 10 mmol) was added dropwise and with stirring during 1 min to 4.0 mL of concentrated H_2SO_4. The resulting solution was warmed to 80 °C for 2 h and then cooled, poured onto ice, and partitioned between H_2O and Et_2O. After the Et_2O solution had been washed with aqueous $NaHCO_3$, dried, and concentrated, the residual liquid was distilled to separate 1.34 g (84%) of the indanone **31**: bp 73–74 °C (0.13 mm); n^{25}_D 1.5456.

Preparation of an Authentic Sample of the Indanone 30. A solution of 11.5 mmol of EtLi in 14 mL of PhH and 15 mL of Et_2O was added dropwise with stirring and cooling to a cold (−50 °C) mixture of 1.88 g (5.78 mmol) of Me_2SCuBr and 5 mL of Et_2O. As the resulting mixture (unchanged Me_2SCuBr still present) was warmed to −38 to −40 °C, the Me_2SCuBr dissolved and a black colloidal solid (presumably Cu^0) began to separate. While this cuprate reagent was kept at −25 to −30 °C, a solution of 782 mg (4.44 mmol) of the ester **34** in 5 mL of Et_2O was added dropwise and with stirring during 5 min. The resulting mixture was allowed to warm to 0 °C with stirring during 30 min and then was added to an aqueous solution of NH_3 and NH_4Cl and extracted with Et_2O. After the ethereal extract had been dried and concentrated, the residual liquid (1.029 g) was distilled to separate 542 mg (59%) of the ester **35** as a colorless liquid: bp 71.5–73 °C (0.07 mm); n^{25}_D 1.4878–1.4887; IR (CCl_4) 1735 cm^{-1} (ester C=O); NMR (CCl_4) δ 6.8–7.2 (5 H, m, aryl CH), 3.86 (2 H, q, J = 7 Hz, ethoxyl CH_2), 1.3–3.2 (5 H, m, CH and CH_2), 1.03 (3 H, t, J = 7 Hz, ethoxyl CH_3), and 0.75 (3 H, t, J = 7 Hz, CH_3); mass spectrum, *m/e* (relative intensity) 206 (M^+, 17), 135 (47), 132 (55), 131 (21), 119 (56), 118 (54), 117 (21), 105 (30), 91 (100), and 88 (33). The product exhibited a single GLC peak (silicone SE-52 on Chromosorb P) corresponding to the ester **35** (retention time 17.2 min) and lacked a peak corresponding to the starting ester **34** (18.6 min).

A solution of 1.218 g (5.9 mmol) of the ester **35**, 523 mg (13.1 mmol) of NaOH, and 2 mL of H_2O in 25 mL of EtOH was refluxed for 4 h and then partitioned between H_2O and Et_2O. This ethereal extract contained 35 mg (3%) of the unchanged ester. After the aqueous solution had been acidified (HCl) and extracted with Et_2O, the ethereal extract was dried, concentrated, and distilled in a short-path still (100 °C and 0.5 mm) to separate 913 mg (87%) of the acid **36** as a pale yellow liquid, n^{25}_D 1.5173, that solidified on standing, mp 50–54.2 °C. Successive recrystallization from Et_2O–pentane and pentane separated the pure acid **36** as a colorless powder: mp 59–60 °C [lit.[20] mp 62–64 °C]; IR (CCl_4) 2950 (broad, associated OH) and 1713 (carboxyl C=O) cm^{-1}; UV (95% EtOH) end absorption (ε 6580 at 210 nm) with a series of weak maxima (ε 73–244) in the region 237–268 nm; NMR (CCl_4) δ 11.88 (1 H, s, OH), 6.8–7.5 (5 H, m, aryl CH), 1.4–3.3 (5 H, m, CH and CH_2), and 0.75 (3 H, t, J = 7 Hz, CH_3); mass spectrum, *m/e* (relative intensity) 178 (M^+, 86), 150 (29), 149 (50), 132 (25), 119 (75), 118 (69), 107 (100), 105 (39), 104 (36), 103 (42), 91 (81), 79 (32), 77 (35), and 43 (24).

The solid acid **36** (824 mg or 4.62 mmol) was dissolved in 50 g of warm (50 °C) polyphosphoric acid, and the resulting solution was heated to 70–80 °C for 2 h and then poured into cold H_2O and extracted with Et_2O. The Et_2O solution was washed with aqueous $NaHCO_3$, dried, and concentrated to leave 780 mg of crude liquid product. Distillation in a short-path still (110–130 °C and 0.06 mm) separated 530 mg (72%) of the indanone **30** as a colorless liquid [lit.[21] bp 116 ° (10 mm)]: n^{25}_D 1.5482; IR (CCl_4) 1720 cm^{-1} (C=O); UV max (95% EtOH) 244.5 nm (ε 11 500), 288 (2450), and 293 (2480); NMR

(CCl_4) δ 7.0–8.0 (4 H, m, aryl CH), 1.1–3.5 (5 H, m, CH and CH_2), and 0.90 (3 H, t, J = 7 Hz, CH_3); mass spectrum, *m/e* (relative intensity) 160 (M^+, 63), 145 (37), 133 (46), 132 (100), 131 (86), 117 (29), 115 (39), 104 (29), 103 (61), 102 (29), and 77 (39).

Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.35; H, 7.56.

Electrochemical Measurements. Polarographic and cyclic voltammetry measurements employed a custom-made polarographic module, utilizing solid-state amplifiers, that followed the typical three-electrode design. Descriptions of the cell, working electrodes, reference electrode, reagent purification, and measurement procedures have been published previously.[22] For cyclic voltammetry measurements that involved anion radicals with short half-lives (0.01 s or less), we found it advantageous to use a previously described[22e] cell design in which the tube leading to the reference electrode was placed directly above an inverted spherical Hg-coated Pt working electrode and both electrodes were surrounded by a cylindrical Pt gauze counter electrode. All measurements were performed at 25 °C in anhydrous DMF containing 0.5 M n-Bu_4NBF_4 as the supporting electrolyte. The results of these measurements are summarized in Table IV.

Preparation of *p*-Methoxystyrene (23). Following a previously described procedure,[23] a mixture of 50.0 g (0.28 mol) of *p*-methoxycinnamic acid, 5.0 g of Cu powder, and 100 mL of quinoline was heated to boiling during 40 min and then held at the boiling point for 15 min while the volatile materials were allowed to distill from the reaction flask. The yellow liquid distillate was decanted from a small amount of the solid starting acid that had codistilled, and then it was partitioned between Et_2O and aqueous 6 M HCl. The ethereal layer was dried, concentrated, and distilled to separate 20.25 g (54%) of the styrene **23** as a colorless liquid: bp 60–64 °C (1.7 mm); n^{25}_D 1.5600–1.5670 [lit.[23] bp 77–80 °C (3 mm), n^{20}_D 1.5609–1.5620]; IR (CCl_4) 1628 (C=C) and 908 (CH=CH_2) cm^{-1}; UV max (95% EtOH) 259 nm (ε 18 100), 292 (2450), and 303 (1420); NMR (CCl_4) δ 6.2–7.3 (5 H, m, aryl CH and vinyl CH), 5.45 (1 H, d of d, J = 1 and 17 Hz, vinyl CH), 4.98 (1 H, d of d, J = 1 and 11 Hz, vinyl CH), and 3.57 (3 H, s, OCH_3); mass spectrum, *m/e* (relative intensity) 134 (M^+, 100), 119 (20), and 91 (20).

Preparation of the Acid Derivatives 25 and 27. A solution of 11.41 g (100 mmol) of N_2CHCO_2Et in 13.42 g (100 mmol) of the styrene 23 was added dropwise and with stirring during 40 min to 4.80 g (35.8 mmol) of the styrene **23** while the temperature of the mixture was maintained at 130–145 °C.[7b] The resulting solution was heated to 130 °C for an additional 12 h, during which time the color of the solution turned from orange to red to amber. The resulting mixture was fractionally distilled to separate 7.74 g of low boiling fractions (bp 38–52 °C (0.11–0.13 mm); n^{25}_D 1.5595–1.5653) containing (NMR analysis) the unchanged olefin **23.** Subsequent distillation fractions contained 12.06 g (55%) of the crude ester **25** as a liquid, bp 52–145 °C (0.13 mm), that solidified on standing, mp 58–74 °C. Recrystallization from pentane separated 6.21 g of ester **25** (a mixture of cis and trans isomers) as fractions of colorless crystals melting within the range 76–83 °C. Repeated recrystallization from pentane afforded a sample of the trans ester **25** as colorless plates: mp 81.1–82.8 °C (lit.[24] mp 83–84 °C); IR (CCl_4) 1727 cm^{-1} (ester C=O); UV max (95% EtOH) 232 nm (ε 14 900), 279.5 (1690), 282 (1650), and 289 shoulder (1190); nmr ($CDCl_3$) δ 6.8–7.1 (4 H, m, aryl CH), 4.18 (2 H, q, J = 7 Hz, ethoxyl CH_2), 3.75 (3 H, s, OCH_3), and 0.9–2.8 (7 H, m, CH_3 and cyclopropyl CH and CH_2); mass spectrum, *m/e* (relative intensity) 220 (M^+, 78), 191 (46), 175 (55), 174 (32), 165 (31), 163 (30), 148 (45), 147 (100), 146 (49), 145 (49), 131 (31), 115 (37), 103 (30), and 91 (27).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.96; H, 7.32.

A solution of 3.34 g (15 mmol) of the ester **25,** 1.05 g (26 mmol) of NaOH, and 2.6 mL of H_2O in 15 mL of EtOH was refluxed for 15 h and then diluted with H_2O and distilled to remove most of the EtOH. After the resulting basic aqueous solution had been extracted with Et_2O, it was cooled, acidified (HCl), and again extracted with Et_2O. This latter ethereal extract was dried and concentrated to leave 2.72 g (93%) of the acid 27 as a white powder, mp 112.1–113.9 °C. Recrystallization from a $CHCl_3$–hexane mixture gave the trans acid **27:** mp 113–114 °C (lit. trans acid mp 113.2–114.2[25] and 114–114.5 °C,[24] cis acid mp 100.8–101 °C[25]); IR ($CHCl_3$) 2950 (broad, associated OH) and 1690 (carboxyl C=O) cm^{-1}; UV max (95% EtOH) 231 nm (ε 14 200), 278.5 (1650), and 281.5 (1630); NMR (CD_3COCD_3) δ 7.83 (1 H, broad, OH), 6.7–7.2 (4 H, m, aryl CH), 3.76 (3 H, s, OCH_3), and 1.0–2.7 (4 H, m, cyclopropyl CH and CH_2); mass spectrum, *m/e* (relative intensity) 192 (M^+, 57), 147 (100), 131 (32), 115 (31), 105 (36), 103 (36), 91 (36), and 77 (56).

Table IV. Electrochemical Reduction of Ketones

	polarography			cyclic voltammetry	
ketone (concn, M × 10^3)	$E_{1/2}$ (V) vs. SCE	n	i_d, μA	$E_{1/2}$ (V) vs. SCE	half-life, s
48 (1.1–2.8)	−2.03	1.0	32–37	−2.05	0.08
49 (0.8–1.1)	−2.01	1.4	28–46	−2.03	0.3
19 (0.6–1.8)	−2.03	0.9	12–17	−2.03	0.001
8 (0.98)	−1.82[a]	0.8[a]		−1.82	0.005

[a] These values were described previously in ref 3.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.68; H, 6.33.

Reduction of the Ketone 19. A. With $LiAlH_4$. A solution of 1.44 g (10 mmol) of the ketone **19** in 20 mL of Et_2O was added dropwise and with stirring during 5 min to a solution of 0.57 g (15 mmol) of $LiAlH_4$ in 80 mL of Et_2O. After the resulting solution had been stirred at 25 °C for 24 h, EtOAc was added to consume the excess $LiAlH_4$ and the mixture was partitioned between Et_2O and H_2O. The organic layer was washed with aqueous NaCl, dried, and concentrated to leave 1.36 g (93%) of a waxy solid, mp 40–69 °C, containing (IR, NMR, and TLC analysis; silica gel coating with an EtOAc–hexane eluent, 15:85 v/v) a mixture of the alcohol **44** (ca. 29%, R_f 0.36) and the alcohol **45** (ca. 71%, R_f 0.29) but lacking IR absorption attributable to the starting ketone **19.** This mixture was subjected to low-pressure liquid chromatography on silica gel with EtOAc–hexane eluent (1:4 v/v) to separate 595 mg of early fractions containing (NMR analysis) various mixtures of alcohols **44** and **45** and 449 mg of later fractions containing alcohol **45** as colorless needles, mp 82–82.9 °C. Repeated chromatography of these latter fractions afforded the pure (NMR analysis) alcohol **45:** mp 85.2–86 °C (lit.[11b] mp 85.5–87.5 °C); IR (CCl_4) 3574 and 3370 cm^{-1} (OH); NMR ($CDCl_3$) δ 6.8–7.5 (4 H, m, aryl CH), 5.55 (1 H, broad d, J = 6 Hz, O–CH), 1.7–2.7 (3 H, m, OH and cyclopropyl CH), 0.6–1.2 (1 H, m, cyclopropyl CH), and 0.2–0.6 (1 H, m, cyclopropyl CH); mass spectrum, *m/e* (relative intensity) 146 (M^+, 30), 145 (26), 131 (32), 129 (25), 128 (100), 127 (27), 117 (94), 116 (82), 115 (72), 63 (27), 51 (30), and 39 (21).

The early chromatographic fractions (containing mixtures of alcohols **44** and **45**) from several reactions were combined and rechromatographed to separate the alcohol **44** as a colorless oil that thus far has not crystallized (lit.[11b] mp 67–68.5 °C). However, the spectral properties of the sample correspond to those previously reported[11b] for alcohol **44:** IR (CCl_4) 3565 and 3310 cm^{-1} (OH); NMR ($CDCl_3$) δ 6.8–7.6 (4 H, m, aryl CH), 4.88 (1 H, partially resolved multiplet, O–CH), 1.8–2.9 (3 H, m, OH and cyclopropyl CH), 0.9–1.5 (1 H, m, cyclopropyl CH), and −0.1–0.2 (1 H, m, cyclopropyl CH); mass spectrum, *m/e* (relative intensity) 146 (M^+, 13), 145 (25), 131 (42), 129 (27), 128 (85), 127 (29), 117 (100), 116 (42), 115 (57), 91 (28), 77 (28), 63 (33), 51 (49), 50 (24), and 39 (38).

B. With Li in NH_3. To a cold (−33 °C) solution of 139 mg (20 mg-atom) of Li in 100 mL of NH_3 was added dropwise and with stirring during 2 min a solution of 1.44 g (10 mmol) of the ketone **19** and 740 mg (10 mmol) of *t*-BuOH in 20 mL of Et_2O. The resulting solution, from which the blue color was discharged as the last of the ketone solution was added, was stirred for 5 min and neutralized by the addition of excess solid NH_4Cl, and then the NH_3 was allowed to evaporate. The residue was partitioned between Et_2O and H_2O, and the organic layer was washed with aqueous NaCl, dried, and concentrated. The residual colorless semisolid (1.506 g) was triturated with Et_2O to separate several fractions of the crude dihydro dimer **43** (total 335 mg, 23%), melting within the range 181–187.5 °C. Concentration of the mother liquors from this separation left 1.124 g of crude liquid product. NMR and GLC analyses allowed us to conclude that neither tetralin nor either of the isomeric alcohols **44** or **45** was present in any significant quantity. An aliquot of this product mixture was mixed with a known weight of $PhCH_2CH_2Ph$ (an internal standard) for GLC analysis (silicone SE-30 on Chromosorb P; apparatus was calibrated with known mixtures). The crude product contained the tetralol **41** (24% yield; eluted as the corresponding olefin with retention time 12.1 min), a mixture of the tetralone **42** and the starting ketone **19** (25.4 min, not resolved, total yield ca. 30%), and $PhCH_2CH_2Ph$ (43.5 min). Under the same GLC conditions the retention times for tetralin and the alcohols **44** and **45** (not resolved, eluted from the GLC column as naphthalene) were 11.4 and 13.1 min and the dihydro dimer **43** was not eluted. A 977-mg aliquot of the crude liquid product was chromatographed on silica gel with

EtOAc–hexane eluent (15:85 v/v) to separate 153 mg (12%) of early fractions containing tetralone **42** (identified with an authentic sample by comparison of IR and NMR spectra) followed by 110 mg (9%) of the starting ketone **19** (identified by comparison of IR and NMR spectra). Subsequent chromatographic fractions contained 505 mg of various mixtures of the tetralol **41** and a second solid product. Further purification by preparative TLC separated 279 mg (19%) of the tetralol **41** (identified with an authentic sample by comparison of IR and NMR spectra) and 89 mg of a colorless solid, mp 148.5–149.7 °C, believed to be a second stereoisomer of the dihydro dimer **43**: IR ($CHCl_3$) 3560, 3460 (OH), and 1670 (conjugated C=O) cm^{-1}; mass spectrum, *m/e* (relative intensity) 273 (20), 272 (82), 244 (74), 243 (32), 239 (22), 230 (42), 229 (45), 228 (28), 216 (40), 215 (100), 141 (29), 129 (22), 128 (73), 116 (29), 115 (76), 91 (23), 77 (23), 63 (28), 51 (28), 40 (97), and 39 (35).

In a second comparable experiment involving reduction of 1.44 g (10 mmol) of the ketone **19** with 143 mg (21 mg-atom) of Li and 740 mg (10 mmol) of *t*-BuOH in 20 mL of Et_2O and 100 mL of NH_3, the isolated dihydro dimer **43** (mp 182.6–187.7 °C) amounted to 187 mg (13%). The semisolid (1.23 g) recovered from the mother liquor exhibited TLC spots (silica gel coating; EtOAc–hexane eluent, 15:85 v/v) corresponding to tetralone **42** (R_f 0.50), the starting ketone **19** (R_f 0.40), and two (or more) more slowly eluted components (R_f 0.32 and 0.21) but lacked a spot corresponding to tetralin (R_f 0.86). This mixture was subjected to low-pressure liquid chromatography (silica gel with EtOAc–hexane eluent) to separate early fractions containing 203 mg (14%) of tetralone (**42**) followed by 74 mg (5%) of the starting ketone **19**. Both materials **42** and **19** were identified with authentic samples by comparison of IR and NMR spectra. Subsequent chromatographic fractions (506 mg) contained (IR and NMR analyses) mixtures of mainly tetralol (**41**) and the dihydro dimer **43** (or its stereoisomer), and the final fractions contained 30 mg (total yield 217 mg or 15%) of the dihydro dimer **43**, mp 186–187.5 °C. The intermediate fractions were subjected to preparative TLC to separate 186 mg (13%) of tetralol (**41**) and 22 mg of a solid, mp 147.2–150 °C, believed to be a stereoisomer of the dihydro dimer **43**. The fractions containing the tetralol (**41**) were distilled in a short-path still (ca. 80 °C at 0.15 mm) to separate the tetralol as a colorless liquid, $n^{25}D$ 1.5628. This material was identified with an authentic sample [bp 85–87 °C (0.35 mm); $n^{25}D$ 1.5620–1.5623; prepared in 75% yield by the reduction of tetralone with $LiAlH_4$] by comparison of IR and NMR spectra.

The dihydro dimer crystallized from a $CHCl_3$–hexane mixture as colorless needles: mp 188–189.9 °C; IR ($CHCl_3$) 3562, 3390 (OH), and 1675 (conjugated C=O) cm^{-1}; UV max (95% EtOH) 251.5 nm (ε 10 600), 279.5 (1760), and 297 (1680); NMR ($CDCl_3$) δ 6.7–8.2 (7 H, m, aryl CH), 6.1–6.4 (1 H, m, aryl CH), 3.3–3.6 (1 H, m, benzylic CH), 1.4–2.9 (7 H, m, aliphatic CH and OH), 0.8–1.4 (1 H, m, cyclopropyl CH), and 0.2–0.7 (1 H, m, cyclopropyl CH); mass spectrum, *m/e* (relative intensity) 290 (M^+, 0.4), 147 (11), 146 (100), 145 (57), 117 (12), and 115 (19).

Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.73; H, 6.27.

In an experiment where 10 mmol of the ketone **19** was reduced with 20 mg-atom of Li in a mixture of 100 mL of NH_3 and 20 mL of Et_2O with no added *t*-BuOH, 386 mg (27%) of the dihydro dimer **43**, mp 182.3–185 °C, was isolated from the crude product by trituration with Et_2O. Although the residual product contained (GLC analysis) some tetralol (**41**) and tetralone (**42**), the bulk of the material separated by subsequent chromatography was 734 mg of the crude dihydro dimer **43** (and/or its stereoisomer), mp 128–182 °C.

Structure Determination of Dihydro Dimer 43. A plate-like crystal fragment with approximate dimensions 0.5 × 0.7 × 0.3 mm was mounted on a glass fiber with epoxy cement. Unit cell parameters and the orientation matrix were determined on a Syntex $P2_1$, four-circle diffractometer equipped with a graphite monochromator (Bragg 2θ angle = 12.2°) using Mo Kα radiation at a takeoff angle of 6.75°. A total of 15 reflections whose 2θ values ranged from 7.24 to 19.33° were machine-centered and used in least-squares refinement of the lattice parameters and orientation matrix. Unit cell parameters obtained were the following:[26] a = 8.619 (4) Å, b = 14.803 (6) Å, c = 11.463 (3) Å, β = 92.26 (3)°, and V = 1462 Å^3. The calculated density of 1.32 g cm^{-3} for 4 molecules per unit cell agrees with the experimental density of 1.31 (1) g cm^{-3} measured by the flotation method using aqueous zinc chloride solution at room temperature. ω scans of several low 2θ angle reflections gave peak widths at half-height of less than 0.20°, indicating a satisfactory mosaic spread for the crystal.

Axial photographs indicated that the crystal belonged to the monoclinic system. Intensity data for 0 and upper levels were collected at a rapid scan rate and the intensities examined carefully for systematic absences. The absence of $k = 2n + 1$ for $0k0$ reflections and $h + l = 2n + 1$ for $h0l$ reflections is consistent with only space group $P2_1/n$ (a nonstandard setting of $P2_1/c$, No. 14[27]).

Intensity data were collected using θ–2θ scans with X-ray source and monochromator settings identical with those used for determination of the unit cell parameters. A variable scan rate of from 2.93 to 29.3° per min was used, and a scan width of 2.0° was sufficient to collect all of the peak intensity. Stationary background counts were measured at the beginning ($bgd1$) and end ($bgd2$) of each scan with a total background to scan time ratio of 1.0. No significant fluctuations were observed in the intensities of three standard reflections (4,0,0; 0,4,0; 0,0,6) monitored every 97 reflections. Intensities (I) were calculated by subtracting the sum of the two background counts ($bgd1 + bgd2$) from the total scan count (CT). Standard deviations were assigned to the intensities according to the formula $\sigma(I) = (CT + bgd1 + bgd2)^{1/2}$. From a total of 2857 reflections collected in a complete quadrant $k \geq 0$, $l \geq 0$ of data out to 2θ = 50°, 1602 were accepted as statistically above background ($I \geq 3\sigma(I)$). Lorentz and polarization corrections were made in the usual way; no corrections were made for absorption.

The structure was solved[28] by direct methods utilizing the program MULTAN to generate phases. E values were calculated for all nonzero reflections. The 260 largest E values were used as input for MULTAN, and it automatically produced a set of phases with an absolute figure-of-merit of 1.25 and ψ_0 of 0.18 × 10^3; the resulting E map revealed the positions of all nonhydrogen atoms. Hydrogen positions were located from a combination of difference Fourier peaks and calculations based on ideal geometry after three cycles of full-matrix least-squares refinement. Further cycles of least-squares refinement, varying a scale factor, coordinates of all nonhydrogen atoms, anisotropic temperature parameters for all nonhydrogen atoms, not varying the positions of the hydrogens, and fixing the isotropic temperature parameters of all hydrogen atoms at 5.0 caused the refinement to converge[30] to R = 0.048 and R_w = 0.040 (199 variables, 1602 reflections). Final positional and thermal parameters are available as supplementary material, and a list of calculated and observed structure factors may be obtained from the authors.

Registry No.—**8**, 1145-92-2; **9**, 5771-62-0; **22**, 100-42-5; **23**, 637-69-4; *cis*-**24**, 946-38-3; *trans*-**24**, 946-39-4; *cis*-**25**, 67478-53-9; *trans*-**25**, 6142-64-9; *cis*-**26**, 939-89-9; *trans*-**26**, 939-90-2; *trans*-**27**, 34919-28-3; *cis*-**28**, 62624-90-2; *trans*-**28**, 939-87-7; **29**, 65731-99-9; **30**, 19832-99-6; **31**, 22351-56-0; **32**, 19832-98-5; **33**, 1590-08-5; **34**, 103-36-6; **35**, 67478-54-0; **36**, 5669-17-0; **37**, 495-40-9; **38**, 67478-55-1; **39**, 22731-65-3; **40**, 67478-56-2; **41**, 529-33-9; **42**, 529-34-0; **43**, 67478-57-3; **44**, 57378-74-2; **45**, 57378-75-3; **48**, 83-33-0; **49**, 13623-25-1; $PhCH_2CH_2Ph$, 103-29-7; N_2CHCO_2Et, 623-73-4; *p*-methoxycinnamic acid, 830-09-1.

Supplementary Material Available: Tables of atomic coordinates and isotropic temperature factors (Table V) and anisotropic thermal parameters (Table VI) (2 pages). Ordering information is given on any current masthead page.

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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spectra were determined with a Perkin-Elmer Model 257 infrared recording spectrophotometer fitted with a grating. The UV spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The proton NMR spectra were determined at 60 mHz with a Varian Model A-60 or T-60-A NMR spectrometer, and the ^{13}C NMR spectra were determined at 25 mHz with a JEOL Model PFT-100 Fourier transform spectrometer. The chemical shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi (Perkin-Elmer) Model RMU-7 mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

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(30) $R = \sum(|F_o| - |F_c|)/\sum|F_o|$ and $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w(|F_o|)^2]^{1/2}$.

Base-Catalyzed Isomerization of *cis*- and *trans*-2,2-Dimethyl-3-formylcyclopropanecarboxylates. Nature of the Base-Stable Cis Intermediate

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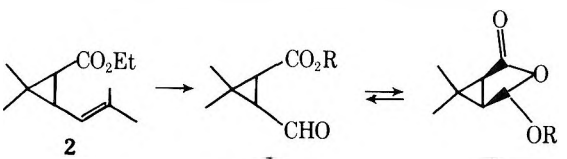
Received February 21, 1978

A mixture of isomers of ethyl 2,2-dimethyl-3-formylcyclopropanecarboxylate (**1b**), obtained by ozonolysis of commercial ethyl chrysanthemate, undergoes rapid transesterification and isomerization to the *trans* methyl ester in 15 min at 25 °C in sodium methoxide–methanol. Reaction at this temperature for 24 h rather than 15 min, or refluxing for 3 h, results in the accumulation of a relatively base-stable cis intermediate which is hydrolyzed under acid conditions to hydroxy lactone **3c**. The intermediate has been isolated and identified as the dimethyl acetal of *cis*-2,2-dimethyl-3-formylcyclopropanecarboxylic acid (**9**) instead of the previously postulated methoxy lactone **3a**, although methoxy lactone **3a** is implicated as a precursor of the accumulated dimethyl acetal. Anhydrous sodium ethoxide–ethanol can also be used for conversion of a mixture of isomers of **1b** to the pure trans isomer, but it cannot be used for the preparation of the cis isomer, since reaction of **1b** in this medium for 24 h at 25 °C results exclusively in the formation of the *hydrolysis* product *trans*-2,2-dimethyl-3-formylcyclopropanecarboxylic acid. A reaction scheme which rationalizes these observations is suggested. The isomerically pure *cis*- and *trans*-2,2-dimethyl-3-vinylcyclopropanecarboxylic acids and amides have been prepared from the corresponding formyl precursors **3c** and **1a**.

Methodology for stereospecific preparation of 2,2-dimethyl-3-formylcyclopropanecarboxylates (**1**), particularly

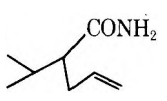


2

a, R = Me
b, R = Et
c, R = H

1

3



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the thermodynamically less stable cis isomers, is of considerable current interest because of the pivotal role these structures play in elaboration of vinyl-modified chrysanthemic acid analogues, essential components of the highly promising pyrethroid insecticides.[1,2] Among methods reported in recent years for the synthesis of isomerically pure *cis*- and *trans*-2,2-dimethyl-3-formylcyclopropanecarboxylates,[3] that disclosed by J. Martel of Roussel UCLAF is particularly ingenious.[4] It involves ozonolysis of *trans*-methyl chrysanthemate (**2a**) to give trans ester aldehyde **1a**, which is converted in refluxing sodium methoxide–methanol to a latent form of the cis isomer, essentially uncharacterized but assigned structure **3a** in the patent.[4] This unisolated precursor is directly hydrolyzed under acidic conditions to hydroxy lactone **3c**, the preferred tautomeric form of the desired *cis*-**1c**.

Our interest in this process stems from our desire, in connection with a study of the destruction of cytochrome P450 by 2-isopropyl-4-pentenamide (**4**),[5,6] to synthesize the conformationally restricted analogues, *cis*- (**5**) and *trans*-2,2-dimethyl-3-vinylcyclopropanecarboxamide (**6**). The procedure outlined by Martel was particularly attractive because of the ready commercial availability of a mixture of *cis*- and *trans*-ethyl chrysanthemates. To our surprise, only poor and erratic yields of **3c** were obtained when a mixture of isomers of ethyl chrysanthemate was subjected to the literature procedure reported for the pure *trans*-methyl ester.[4] Subsequent detailed studies, the results of which are presented here, demonstrate that the isomerization process is a complex one

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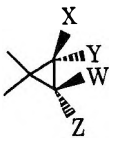


5, X = $CONH_2$; W = $CH{=}CH_2$; Y = Z = H
6, X = $CONH_2$; Z = $CH{=}CH_2$; Y = W = H
7, X = CO_2Et; Y = H; W, Z = H, $CH(OEt)_2$
8a, X = W = CH_2OH; Y = Z = H
8b, X = W = CH_2OAc; Y = Z = H
9, X = CO_2H; W = $CH(OMe)_2$; Y = Z = H
10, X = CO_2H; Z = $CH{=}CH_2$; Y = W = H
11, X = CO_2H; W = $CH{=}CH_2$; Y = Z = H

whose outcome depends on the interplay of several finely balanced competing reactions. Of particular interest is the discovery that **3** (R = alkyl) is *not* the stable form which allows accumulation of the latent cis isomer in the face of basic reaction conditions, the sine qua non of the isomerization process. These results simplify extension of the isomerization sequence to other ring systems.

Ethyl chrysanthemate obtained commercially was found by NMR analysis to be a 7:3 mixture of trans/cis isomers, even though the isomers were not resolved by gas chromatographic analysis on a 6-ft OV-225 column. The physical similarity between the isomers, exemplified by the identity of their retention times on OV-225, makes their separation by physical methods unattractive, although the free acids have been separated by tedious crystallizations.[7] Ozonolysis of the isomer mixture in ethanol at −78 °C, followed by reduction of the ozonide with dimethyl sulfide, gave, presumably, a mixture of the cis and trans isomers of diethyl acetal **7**.[4] These were hydrolyzed in aqueous acetic acid without isolation, as described by Martel for the trans isomer,[4] giving **1b** (34:66 cis/trans) in 82% overall yield. Pure *trans*-**1a** was obtained from the mixture of isomers of ethyl ester **1b** by stirring in 1.25 M sodium methoxide–methanol for 15 min at 25 °C. The transesterification and isomerization reactions are extremely facile, both being half-complete (by GLC analysis) within 1 min of mixing the reagent with the sample. The yield of pure **1a** obtained in this reaction is about 60%, although the yield decreases slightly as the proportion of cis isomer in the original mixture increases. For example, the yield of **1a** obtained from a sample of **1b** containing 72% of the cis isomer was only 39%. The implication that the cis isomer is not only isomerized to the trans isomer but is also subject to a cis-selective (vide infra) competing reaction is consistent with the observation that the yield of *trans*-**1a** is decreased by reaction times longer than 15 min.

Isomerization of *trans*-**1a** to an intermediate which is not isolated but is assigned structure **3a** is reported to occur in refluxing 1.25 M sodium methoxide–methanol in 3 h.[4] Hydrolysis of the intermediate to hydroxy lactone **3c** is then achieved by refluxing in aqueous dioxane.[4] Analogous treatment of the mixture of isomers of **1b** obtained on ozonolysis of **2b**, however, did not give significant amounts of the hydroxy lactone despite rapid in situ formation of *trans*-**1a** by transesterification and isomerization. Instead of hydroxy lactone **3c**, the reaction sequence provided ethoxy lactone **3b** in 39% isolated yield. Isolation of this compound despite the hydrolysis step was subsequently shown to be a consequence of its resistance to mild (aqueous acetic acid) hydrolysis conditions, although it can be hydrolyzed to hydroxy lactone **3c** by stirring for 24 h at 25 °C in 0.2 M aqueous HCl.

The structure and stereochemistry of the unexpected lactone **3b** were firmly established by both chemical and spectroscopic methods. Hydrolysis of the product with potassium hydroxide in water gave *trans*-2,2-dimethyl-3-formylcyclopropanecarboxylic acid (*trans*-**1c**), a substance shown subsequently to also be present in the crude mixture from the original isomerization reaction. Reduction with $LiAlH_4$ of the compound assigned structure **3b** yielded **8a**, which in turn gave diacetate **8b**, spectroscopically identical with that reported in the literature.[7]

The spectral data, particularly the proton and ^{13}C NMR results, confirm the structural assignment of **3b** and establish that the ethoxy group is exo to the ring system. This is evident from the small (0.8 Hz) coupling between the cyclopropyl proton (H_a) and the vicinal dioxymethine proton (H_b), a phenomenon consistent[8] with their nearly perpendicular orientation in the *exo*-ethoxide isomer as predicted by molecular models and simple computerized conformational analysis (Figure 1).[10] On the other hand, normal coupling is predicted for these protons in the *endo*-ethoxide isomer. The ethoxymethylene group in **3b** appears in the proton NMR spectrum as a highly complex multiplet due to the diastereotopic nature of H_c and H_d.[9]

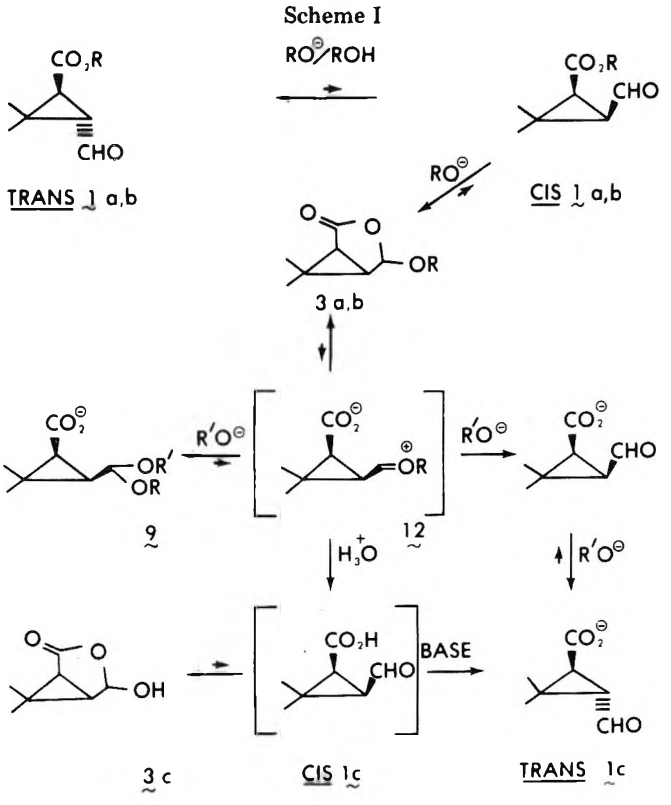
Ethoxy lactone **3b** was an unexpected product because the only ethanol present in the sodium methoxide–methanol promoted isomerization of **1b** was that released by transesterification of the ethyl ester. This very minor ethanol component does not compete successfully with methanol in the lactonization reaction as shown by the presence of only traces of **3b** (GLC analysis) in the reaction mixture prior to workup. Ethoxy lactone **3b** is therefore formed by secondary reaction during workup of a precursor present in the isomerization reaction mixture. One viable explanation for the formation of **3b** during workup is that the higher concentration of ethanol incidentally achieved during solvent removal results in reaction of the ethanol with a labile precursor present in the reaction mixture. The formation of **3b**, possibly through an exchange reaction, was the first indication that methoxy lactone **3a** might not be the base-stable cis intermediate (see Discussion).

Isolation of ethoxy lactone **3b** suggested that conversion of the mixture of isomers of **1b** to **3b** by refluxing in sodium ethoxide–ethanol might represent a more efficient synthesis of **3c**. This reaction, however, only gave intractable products despite the fact that pure *trans*-**1b** could be isolated in 67% yield after 5 min of reaction at room temperature. Extension of the room temperature reaction to 21 h, on the other hand, led to the formation in high yield of *trans*-2,2-dimethyl-3-formylcyclopropanecarboxylic acid (*trans*-**1c**).

In order to suppress the formation of **3b** during workup, the product mixture obtained on isomerization of a mixture of *cis*- and *trans*-**1b** in sodium methoxide–methanol was directly quenched by pouring into a pH 4.1 citrate buffer solution without concentration on a rotary evaporator.[16] The aqueous solution was extracted with ether and the crude product obtained on removal of the ether was subjected to NMR analysis. The crude product mixture depended on the pH of the workup, but usually consisted of approximately 40–60% dimethyl acetal **9** (vide infra), 10% aldehydes **1a** and **1c**, and 5–30% of methoxy lactone **3a**. The remaining material represented various unidentified side products. Crystallization of the crude product from ether–pentane yielded approximately 20% of pure dimethyl acetal **9**. This structure is firmly established by complete analytical and spectroscopic characterization. The complete conversion of **9** to **3b** when the reaction mixture was worked up at pH 2 rather than at pH 4.1 and the observation that **9** slowly loses methanol even in the crystalline state provide a ready explanation for the original identification of **3b** as the essential reaction intermediate.[4]

Wittig condensation of methyltriphenylphosphonium bromide with *trans*-**1a**, using sodium hydride as the base and dimethyl sulfoxide as the solvent,[11] gave ethyl 2,2-dimethyl-3-vinylcyclopropanecarboxylate which was directly hydrolyzed to acid **10** by stirring 2 h in 2 M aqueous ethanolic potassium hydroxide (58% overall yield). Isolation of the ester

Scheme I



was possible, but resulted in lower yields due to its volatility. The acid was spectroscopically identical with that previously described,[11] not only confirming the structure and stereochemistry of **1a** but also providing the precursor for the desired amide **6**. The amide was prepared in good yield by treatment of the acid with thionyl chloride followed by ammonium hydroxide. Condensation of triphenylphosphonium methylide with hydroxy lactone **3c** was also carried out in dimethyl sulfoxide, except that 2 equiv of ylide had to be used due to the acidic proton on **3c**. Attempts to pregenerate the free aldehyde by removal of the hydroxyl proton resulted in rapid isomerization to *trans*-**1c**, and consequently in the formation of **10**. The formation of **11** from **3c** by Wittig reaction[11] confirmed the structure of **3c** and provided the starting material for the synthesis of amide **5**.

Discussion

Transesterification and cis–trans isomerization of 2,2-dimethyl-3-formylcyclopropanecarboxylic acid esters are very facile, providing a simple route for preparation of pure trans isomers starting with isomeric mixtures. Stirring in sodium methoxide–methanol for a few minutes, for example, cleanly converts a mixture of isomers of **1b** into pure *trans*-**1a**. On the other hand, prolonged stirring at room temperature, or refluxing the solution for 3 h, results in accumulation of an intermediate which we have identified as **9** rather than the originally suspected **3a**.[4] In view of the rapidity with which transesterification occurs in this system, it is retrospectively unreasonable to expect that methoxy lactone **3a** would accumulate in a solution in which it could react with methoxide to regenerate *cis*-**1a**, itself in equilibrium with the thermodynamically favored trans isomer. On the other hand, dimethyl acetal **9** should be relatively stable to methoxide, particularly since the carboxyl would bear a negative charge in basic solution. A reasonable mechanism can be written for the formation of **9** from *cis*-**1a**, although it involves **3a** as a transient intermediate. Methoxy lactone **3a**, formed by addition of methoxide to the aldehyde followed by intramolecular lactonization, is likely to be in equilibrium with oxonium zwitterion **12** as well as with *cis*-**1a**. Addition of methoxide at the oxonium carbon then easily accounts for the formation of **9**. Formation of the oxonium ion by internal oxygen elimination, a reaction with ample precedent,[12] is particularly favored in the present case due to the potential for delocalization of the cationic charge into the cyclopropyl ring.[13] Reversion of **9** to the oxonium ion under basic conditions is also possible, but less favored because the leaving group would be an alkoxide rather than a carboxylate anion.

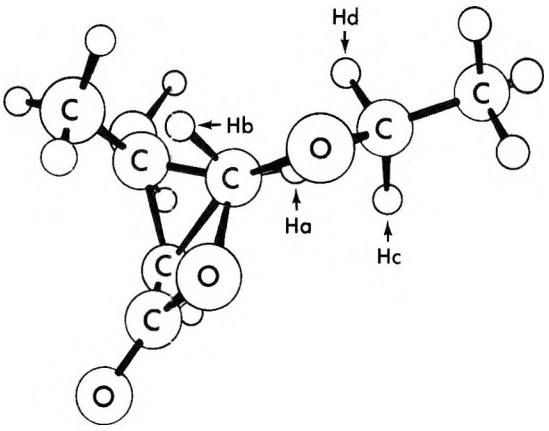


Figure 1. Three-dimensional projection of the calculated conformation of exo-ethoxy lactone **3b**. All unlabeled atoms are hydrogens. The carbon atom bearing Hb conceals the ring carbon bearing Ha, as in a Newman projection.

In view of the ease of formation of **9** with sodium methoxide–methanol, it is significant that the corresponding diethyl acetal is not obtained in sodium ethoxide–ethanol. Under these conditions the only isolable product was trans aldehyde acid **1c**. The change in reaction course was not due to an effect on cis–trans isomerization, or to an inability to form **3b**, since both were shown to occur with ease. The change in reaction product is most reasonably[15] explained by a competition between the two general pathways known for reaction of oxonium salts with nucleophiles, addition to the oxonium carbon atom or displacement of the substituent on oxygen (Scheme I).[12,14] Thus, reaction of **12** with an alkoxide by displacement of the oxygen from group R would yield *cis*-**1c**, which in basic solution rapidly isomerizes to the isolated trans isomer. It is of interest in this context to note that trace amounts of *trans*-**1c** were also observed by NMR and GLC analysis of isomerization reactions run in methanol–sodium methoxide. A summary of the postulated reaction network is given in Scheme I.

Experimental Section

Solvents and Reagents. Anhydrous methanol and ethanol were prepared by distillation of absolute grade alcohols from sodium, dry dimethyl sulfoxide (Me_2SO) was obtained by distillation in vacuo from calcium hydride, while hexane, pentane, and pyridine were dried by allowing reagent grade solvents to stand at least 18 h over 3A molecular sieves. Anhydrous ether, obtained from freshly opened cans, was used without further treatment. Reagents were of the highest quality commercially available and were used as received except where otherwise indicated. Sodium methoxide solutions were prepared by appropriate methanol dilution of the commercially available 25% methanol solution. Ethyl chrysanthemate was obtained from Aldrich Chemical Co.

General Procedures. Infrared spectra were determined on a Perkin-Elmer Model 337 grating infrared spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60A (proton) or on a Varian XL-100 Fourier transform instrument (proton and ^{13}C). All spectra are 60 MHz unless otherwise indicated, with peak positions reported as parts per million shifts from an internal tetramethylsilane standard. Chemical ionization mass spectra were determined on a modified AEI MS-902 spectrometer. Gas chromatography was performed on a Varian 2100 flame ionization instrument, using a 6-ft all-glass column packed with 3% OV-225. Ozone was generated in a Welsbach Model T408 apparatus at an oxygen inlet

pressure of 7 psi and a flow rate of 2.5 L/min (110 VAC). The drying agent used throughout was anhydrous $MgSO_4$. Elemental analyses were performed by the Microchemical Laboratory, University of California, Berkeley.

Computer modeling and conformational calculations were carried out on the PROPHET system, a specialized computer resource developed by the Chemical/Biological Information Handling Program of the National Institutes of Health.[10] Conformational analysis in this system is achieved by minimization of steric interactions using standardized bond lengths and atomic radii, without specific allowance for electronic effects.

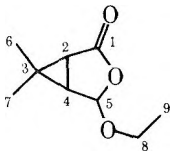
Ethyl 2,2-Dimethyl-3-formylcyclopropanecarboxylate (1b, Cis–Trans Mixture). The procedure of Martel was modified as follows.[4] Ethyl chrysanthemate (100 g, 0.51 mol) was dissolved in 750 mL of absolute ethanol and was cooled with exclusion of moisture ($CaSO_4$ drying tube) in a dry ice–acetone bath. A mixture of ozone in oxygen was bubbled through the cold solution with stirring until a faint blue color persisted in the solution (approximately 5 h). The solution was purged with dry N_2 for 15 min at −78 °C before addition of 100 mL (85 g, 1.4 mol) of dimethyl sulfide. The mixture was stirred overnight at 25 °C, after which time a small aliquot added to aqueous sodium iodide liberated no iodine. The reaction mixture was concentrated on the rotary evaporator and was diluted with 200 mL of ether. The ether solution was washed with water (3 × 100 mL) and brine (100 mL), dried, and filtered. The crude product obtained on solvent removal at a rotary evaporator, presumably diethyl acetal **7** (98 g), was suspended in 700 mL of 30% acetic acid under nitrogen. The mixture was stirred at 75–85 °C until it became homogeneous (approximately 15 min) and was then cooled to 25 °C, diluted with 400 mL of water, and neutralized with solid sodium bicarbonate. The resulting solution was extracted with three 250-mL portions of ether. The combined extracts, washed with water (250 mL) and brine (250 mL), were dried and filtered. Removal of the ether on a rotary evaporator yielded 79 g of crude product which was distilled in vacuo to give 71.6 g (82%) of a 34:66 mixture (by GLC) of *cis*-/*trans*-**1b:** bp 49–53 °C (0.15 torr); IR (film) 2717 (CHO), 1704 and 1722 cm^{-1} (carbonyls); NMR ($CDCl_3$) 1.30 (3 H, t, J = 7 Hz, OCH_2CH_3), 1.33 and 1.37 (6 H, 2 s, ring CH_3), signals at 1.58 (s), 1.7–2.4 (m), and 2.48 (d, J = 2 Hz) due to two ring protons in cis and trans isomers, 4.22 (2 H, q, J = 7 Hz, OCH_2CH_3), 9.67 (m, CHO, trans isomer), and 9.83 ppm (d, J = 6.5 Hz, CHO, cis isomer).

Methyl *trans*-2,2-Dimethyl-3-formylcyclopropanecarboxylate (*trans*-1a). A mixture of isomers of **1b** (35.8 g, 0.21 mol) was dissolved in 300 mL of anhydrous methanol under N_2 and 120 mL of a 25% sodium methoxide–methanol solution (0.53 mol) was added. The mixture was stirred 15 min at 25 °C before being diluted with 525 mL of ice-cold 1 M HCl and extracted with four 250-mL portions of ether. The combined extracts were washed with 250 mL of brine, dried, and filtered. Removal of the ether gave a residue which was distilled in vacuo to yield 19.5 g (60%) of *trans*-**1a** as a clear colorless oil: bp 47–49 °C (0.75 torr) [lit.[4] 96 °C (14 torr)]; IR (film) 2728 (CHO), 1732 (ester C=O), 1700 cm^{-1} (aldehyde C=O); NMR ($CDCl_3$) 1.32 and 1.36 (6 H, 2 s, ring CH_3), 2.49 (2 H, m, ring protons), 3.74 (3 H, s, OCH_3), and 9.67 ppm (1 H, m, CHO).

Ethyl *trans*-2,2-Dimethyl-3-formylcyclopropanecarboxylate (*trans*-1b). A mixture of isomers of **1b** (340 mg, 2.0 mmol) was added in 1 mL of anhydrous ethanol to the solution resulting from dissolving sodium metal (0.12 g, 5.2 mmol) in 3 mL of anhydrous ethanol. The mixture was stirred 5 min under N_2 at 25 °C before being diluted with 25 mL of 0.2 M HCl. Extraction with ether (3 × 25 mL), drying of the combined extracts, solvent removal, and bulb-to-bulb distillation (oven temperature 80–85 °C, 1 torr) gave 227 mg (67%) of pure *trans*-**1b**, a colorless oil: IR (film) 2776 (CHO), 1721 (ester C=O), and 1705 cm^{-1} (aldehyde C=O); NMR ($CDCl_3$) 1.28 (3 H, t, J = 7 Hz, ethoxy CH_3), 1.33 and 1.37 (6 H, 2 s, ring CH_3), 1.65 (2 H, d, J = 2 Hz, ring protons), 4.22 (2 H, q, J = 7 Hz, ethoxy CH_2), and 9.68 ppm (H, m, CHO).

Repetition of the above reaction, except with a reaction time of 21 h instead of 5 min, yielded 271 mg (95%) of virtually pure *trans*-**1c** as the only isolable product.

***cis*-2,2-Dimethyl-3-formylcyclopropanecarboxylic Acid, Lactone–Monoethyl Acetal (3b).** In analogy to Martel's procedure for the isomerization of pure *trans*-**1a**,[4] a mixture of cis–trans isomers of **1b** (25.0 g, 147 mmol) was dissolved in 180 mL of absolute methanol (N_2 atmosphere), 68 mL (0.3 mol) of 25% sodium methoxide in methanol was added, and the mixture was stirred and refluxed for 3 h. The mixture was then concentrated on a rotary evaporator and the residue was taken up in 100 mL of ice cold 3 M HCl. The aqueous solution was extracted with three 50-mL ether portions which were combined, washed with brine (50 mL), dried, and filtered. Removal of the ether on a rotary evaporator gave 21.5 g of viscous yellow oil which was dissolved in 60 mL of tetrahydrofuran. Water (120 mL) and acetic acid (5 mL) were added and the mixture was refluxed with stirring under N_2 for 3 h. The cooled solution was concentrated on a rotary evaporator and the residue was taken up in 150 mL of ether. The ether solution was washed with 1 M $NaHCO_3$ (3 × 50 mL). The combined aqueous fractions were in turn backwashed with ether (6 × 50 mL). The combined ether fractions were dried and filtered. Removal of the ether gave 12.9 g of viscous yellow oil which was distilled under vacuum, yielding 9.67 g (39%) of **3b** as a clear, colorless oil: bp 58.5–60 °C (0.2 torr). A trace of *trans*-**1a** was present in this sample. Analytically pure material was obtained by partitioning the sample between ether and water and bulb-to-bulb distillation of the organic fraction: IR (film) 1757 (lactone carbonyl), 1166 and 1116 cm^{-1} (C–O); NMR ($CDCl_3$, 100 MHz) 1.191 and 1.170 (6 H, 2 s, ring CH_3), 1.250 (3 H, t, J = 7.0 Hz, ethoxy CH_3), 2.046 (H, s, ring proton by C=O), 2.027 (H, d, J = 0.8 Hz, ring proton distal to C=O), 3.985–3.537 (2 H, m, ethoxy CH_2), and 5.156 ppm (H, d, J = 0.8 Hz, OCHO); NMR (^{13}C, $CDCl_3$, 25 MHz) 15.0 (2 C, 2 q, J_{CH} = 130 Hz, C-7 and C-9), 24.4 (1 C, s, C-3), 25.4 (1 C, q, J_{CH} = 130 Hz, C-6), 30.1 (1 C, d, J_{CH} = 180 Hz, C-4), 35.5 (1 C, d, J_{CH} = 180 Hz, C-2), 64.8 (1 C, t, J_{CH} = 140 Hz, C-8), 101.4 (1 C, d, J_{CH} = 175 Hz, C-5), and 173.3 ppm (1 C, s, C-1); CIMS *m/e* 171 (MH^+), 153 ($MH - H_2O$), 127, 125, and 57. Anal. Calcd for $C_9H_{14}O_3$; C, 63.51; H, 8.29. Found: C, 63.50; H, 8.21.



The aqueous $NaHCO_3$ washes from the above procedure were acidified to pH 1.5 with concentrated HCl and then extracted with ether. Solvent removal from the dried ether extracts yielded 3.36 g (16%) of waxy off-white *trans*-**1c** contaminated with a small amount (5%) of **3b:** IR (film) 1695 cm^{-1} (carbonyl); NMR ($CDCl_3$) 1.35 and 1.41 (6 H, 2 s, ring CH_3), 2.51 (2 H, m, ring CH), 9.65 (H, m, CHO), and 11.35 ppm (H, br s, exch. D_2O, CO_2H).

Reduction of 3b with $LiAlH_4$. To 42 mg (1.1 mol) of $LiAlH_4$ in 4 mL of dry ether at 0 °C under N_2 was added 170 mg (1.00 mmol) of **3b** in 1 mL of dry ether. The mixture was stirred 2 h at 25 °C before quenching with 0.12 mL of saturated sodium sulfate solution. After stirring 15 min, filtering, and solvent removal, 133 mg of colorless highly viscous oil was obtained. Bulb-to-bulb distillation of this oil [95 °C (0.05 torr)] gave 114 mg (88%) of pure **8a:** IR (film) 3300 (br, OH stretch) and 1030 cm^{-1} (OH bend); NMR ($CDCl_3$) 1.06 and 1.10 (6 H, 2 s, ring CH_3), 0.8–1.4 (2 H, m, ring CH), and 3.3–4.2 ppm (6 H, m, CH_2OH).

Acetylation of 8a. Acetic anhydride (0.25 mL, 0.27 g, 2.6 mmol) was added to 76 mg (0.58 mmol) of **8a** in 1 mL of dry pyridine under N_2. The mixture, after stirring 24 h at 25 °C, was diluted with 25 mL of ether. Washing the ether solution with 1 M HCl (25 mL), saturated $NaHCO_3$ solution (25 mL), H_2O (25 mL), and brine (25 mL), followed by drying, filtration, and solvent removal, yielded 112 mg (90%) of colorless **8b:** IR (film) 1728 (C=O), 1240 and 1022 cm^{-1} (C–O); NMR spectrum identical with that in the literature.[7]

Hydrolysis of 3b with Aqueous KOH. To 170 mg (1.00 mol) of **3b** in 4 mL of absolute ethanol was added 1 mL of 10 M aqueous KOH. The mixture, after stirring 3 h at 25 °C, was added to 25 mL of 0.5 M aqueous HCl. The pH was brought to a value of 1.5 with concentrated HCl and the resulting solution was extracted with ether (3 × 25 mL). The combined extracts were dried and filtered, and the ether was removed on a rotary evaporator, yielding 165 mg of viscous pale yellow oil whose NMR spectrum identified it as *trans*-**1c.**

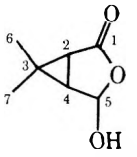
Hydrolysis of 3b with Aqueous HCl. To 170 mg (1.00 mmol) of **3b** in 4 mL of H_2O was added 1 mL of 1 M HCl. The mixture was allowed to stir 24 h at 25 °C before being diluted with 25 mL of brine and extracted with five 15-mL portions of ether. Solvent removal from the combined extracts after drying and filtering yielded 147 mg of white solid, which recrystallized from ether–pentane to give 88 mg (62%) of pure white, granular **3c,** mp 84–86.5 °C, identical with that reported below.

***cis*-2,2-Dimethyl-3-formylcyclopropanecarboxylic Acid, Dimethyl Acetal (9).** A mixture of geometric isomers of **1b** (1.702 g, 10.0 mmol) was dissolved in 15 mL of anhydrous methanol under nitrogen, 5.7 mL (25 mmol) of 25% sodium methoxide in methanol was added, and the mixture was refluxed and stirred for 3 h. After cooling to 15 °C and diluting with 75 mL of ice-cold citrate buffer (1.00 M citric acid in 1.33 M NaOH, pH 4.1),[16] the aqueous solution was extracted with ether (3 × 25 mL), and the combined extracts were

dried. Removal of the solvent on a rotary evaporator gave 1.75 g of yellow semisolid. This crude product, after analysis by NMR, was recrystallized from ether–pentane without heating, yielding 360 mg (19%) of white, granular **9**: mp 87–88.5 °C; IR (KBr) 1670 (C=O), 1231, 1184, and 1141 cm^{-1} (C–O); NMR ($CDCl_3$) 1.23 and 1.35 (6 H, 2 s, ring CH_3), 1.5–1.8 (2 H, m, ring CH), 3.42 and 3.43 (6 H, 2 s, OCH_3), 4.91 (H, d of d, J = 6.5 and 1.5 Hz, OCHO), and 11.75 ppm (H, br s, D_2O exch, CO_2H); CIMS m/e 173 ($MH^+ - 16$, parent itself not observed), 157 (base peak), 139, 125, 113, and 57. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.51; H, 8.58.

***cis*-2,2-Dimethyl-3-formylcyclopropanecarboxylic Acid, Monomethyl Acetal-Lactone (3a).** The mother liquor from the recrystallization of **9** was concentrated on a rotary evaporator, giving a residue which was taken up in 15 mL of dry dimethoxyethane. The solution was refluxed 1 h under N_2, after which the dimethoxyethane was removed by distillation under N_2. Three 15-mL aliquots of dimethoxyethane were added, each one being removed by distillation before addition of the next one. The residue was cooled to 25 °C and diluted with 10 mL of ether. Filtration to remove slight cloudiness, removal of the ether on a rotary evaporator, and bulb-to-bulb distillation [66–71 °C (0.05 torr)] gave 613 mg (45%) of clear, colorless **3a**: IR (film) 1767 (C=O), 1166, 1118, 997, and 938 cm^{-1}; NMR ($CDCl_3$) 1.21 (6 H, s, ring CH_3), 2.03 (2 H, br s, ring CH), 3.55 (3 H, s, OCH_3), and 5.15 ppm (H, s, OCHO); CIMS m/e 157 (MH^+), 143, 139, 125, and 57.

***cis*-2,2-Dimethyl-3-formylcyclopropanecarboxylic Acid, Hemiacetal-Lactone (3c).** The procedure described for the preparation of **9** was repeated using 6.81 g (40 mmol) of **1b** (cis–trans mixture) and 0.1 mol of sodium methoxide in 83 mL of anhydrous methanol, providing 6.15 of the crude yellow semisolid product. The crude product was dissolved in 25 mL of tetrahydrofuran, 50 mL of 0.3 M aqueous HCl was added, and the mixture was refluxed under N_2 for 2 h. The hot mixture was then poured onto 75 g of ice, after which 100 mL of brine was added. The aqueous mixture was extracted with ether (3 × 100 mL), and the combined ether fractions were dried and filtered. Solvent removal on a rotary evaporator gave 4.65 g of viscous yellow oil which, after treatment with activated carbon, crystallized from ether–pentane to yield 1.54 g (27%) of white, granular **3c**: mp 83.5–87 °C (lit.[4] 116 °C from diisopropyl ether); IR (KBr) 3286 (OH), 1705 (C=O), 1206, 1183, and 1112 cm^{-1}; NMR ($CDCl_3$) 1.23 and 1.30 (6 H, 2 s, ring CH_3), 2.11 (H, s, ring CH distal to C=O), 2.13 (H, s, ring CH vicinal to C=O), and 6.72 ppm (2 H, br s, exch. D_2O, OCHOH); NMR (^{13}C, $CDCl_3$, 25 MHz) 14.9 (1 C, q, J = 127 Hz, C-7), 25.9 (2 C, br s + q, J = 125 Hz, C-3 and C-6), 31.2 (1 C, br d, J = 160 Hz, C-4), 37.3 (1 C, br d, J = 170 Hz, C-2), 96.3 (1 C, br d, J = 180 Hz, C-5), and 174.2 ppm (1 C, s, C-1); CIMS m/e 143 (MH^+), 125, 99, 97, 81, 71, 69, and 57. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.11; H, 7.06.



***trans*-2,2-Dimethyl-3-vinylcyclopropanecarboxylic Acid (10).** A modification of the procedure of Okada et al.[11] was used. Sodium hydride (50% in oil, 6.15 g, 128 mmol) was washed with hexane and 80 mL of dry Me_2SO was added to the residue. The resulting suspension was heated at 75–80 °C for 45 min and was then cooled to 0 °C while 44.0 g (123 mmol) of methyltriphenylphosphonium bromide in 130 mL of dry Me_2SO was added over 15 min. The mixture was stirred at 25 °C for 30 min and was then transferred via a metal cannula to a dropping funnel maintained under N_2. The solution was then added over 30 min to 15.4 g (99 mmol) of *trans*-**1a** in 30 mL of dry Me_2SO held at 0 °C with an ice bath. After completing the addition, the mixture was stirred at 25 °C for 1 h and was then poured into 1 L of ice water. The aqueous mixture was extracted with ether (3 × 250 mL), and the combined extracts were washed with water (3 × 250 mL) and brine (100 mL). Most of the ether was removed, after drying and filtering, by distillation through an 8-cm Vigreux column to prevent loss of the volatile ester. Absolute ethanol (250 mL) was added and distillation was continued until a head temperature of 78 °C was obtained. The mixture was then cooled to 25 °C and 50 mL of 10 M aqueous KOH was added. After stirring 2 h 500 mL of H_2O was added and the mixture was extracted with ether (3 × 100 mL). The *aqueous* solution was acidified to pH 1 with 50 mL of concentrated HCl (ice bath) and was then reextracted with pentane (3 × 100 mL). The combined pentane extracts, after drying and solvent removal, yielded 7.98 g (58%) of viscous oily **10** which solidified on standing: mp 39–43 °C; IR (film) 1684 (C=O) and 1634 cm^{-1} (C=C); NMR[11] ($CDCl_3$) 1.19 and 1.33 (6 H, 2 s, ring CH_3), 1.59 (H, d, J = 5.5 Hz, $CHCO_2H$), 1.9–2.4 (H, m, allylic proton), 4.9–6.1 (3 H, m, vinyl H), and 11.51 ppm (H, s, CO_2H).

***trans*-2,2-Dimethyl-3-vinylcyclopropanecarboxamide (6).** Acid **10** (701 mg, 5.00 mmol) was dissolved in 10 mL of dry pyridine and cooled to 0 °C under N_2. Freshly distilled $SOCl_2$ (0.45 mL, 0.75 g, 6.3 mmol) was added slowly via syringe and the mixture was stirred 1 h at 0 °C before pouring into 25 mL of ice-cold concentrated NH_4OH. The mixture was saturated with NaCl and was extracted with ether (3 × 25 mL). The combined extracts were dried and filtered, and the solvent was removed, yielding 729 mg of pale yellow solid. Recrystallization from ether–pentane provided 430 mg (62%) of floculent, off-white crystals of **6**: mp 119.5–120.5 °C; IR (KBr) 3377 and 3173 (NH_2) and 1630 cm^{-1} (C=O); NMR ($CDCl_3$) 1.17 and 1.27 (6 H, 2 s, ring CH_3), 1.38 (H, d, J = 5.5 Hz, CHCO), 1.9–2.2 (H, m, allylic proton), and 4.9–6.2 ppm (5 H, m, vinyl H and NH_2); CIMS m/e 140 (MH^+), 122, and 57. Analytical sample mp 120–121 °C. Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.89; H, 9.24; N, 10.13.

***cis*-2,2-Dimethyl-3-vinylcyclopropanecarboxylic Acid (11).** The procedure cited for the preparation of **10** was used, except that 2 equiv of triphenylphosphonium methylide/equiv of **3c** was used. The reaction mixture from 3.55 g (25 mmol) of **3c** was worked up by pouring it into 500 mL of ice-cold H_2O. The aqueous solution was washed with ether (3 × 100 mL) and then brought to pH 1.5 with concentrated HCl (6 mL). The acidic aqueous solution was extracted with three 100-mL portions of pentane which were combined, washed with H_2O and brine, dried, and filtered. Removal of the pentane on a rotary evaporator gave 3.05 g (87%) of pale yellow viscous oil which solidified on standing, yielding **11** as an off-white solid: mp 47–51 °C; IR (film) 1688 cm^{-1} (C=O); NMR[11] ($CDCl_3$) 1.22 and 1.31 (6 H, 2 s, ring CH_3), 1.6–2.4 (2 H, m, ring CH), 5.0–5.5 (2 H, m, $C=CH_2$), 5.7–6.6 (H, m, –CH=C), and 11.65 ppm (H, br s, CO_2H).

***cis*-2,2-Dimethyl-3-vinylcyclopropanecarboxamide (5).** The procedure reported for the preparation of **6** was used, starting with 2.10 g (15.0 mmol) of **11**. A 59% yield (1.23 g) was obtained of pale yellow crystalline **5**: mp 78.5–80 °C; IR (KBr) 3408, 3316, and 3188 (NH_2), 1633 cm^{-1} (C=O); NMR ($CDCl_3$) 1.18 and 1.31 (6 H, 2 s, ring CH_3), 1.4–2.0 (2 H, m, ring CH), 5.0–5.5 (2 H, m, $C=CH_2$), and 5.8–6.7 ppm (3 H, m, CCH=C and NH_2); CIMS m/e 140 (MH^+), 97, 57. Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.86; H, 9.24; N, 9.95.

Acknowledgments. This project has received support from National Institutes of Health Grants P50 AM-18520 to the Liver Center and RR 00892 from the Division of Research Resources to the UCSF Magnetic Resonance Laboratory. Additional support has been provided by a grant from the University of California Cancer Research Coordinating Committee.

Registry No.—*trans*-**1a**, 41301-44-4; *cis*-**1b**, 38692-38-5; *trans*-**1b**, 38692-37-4; *trans*-**1c**, 67528-52-3; **3a**, 67528-53-4; **3b**, 67488-71-5; **3c**, 67528-54-5; **5**, 67506-07-4; **6**, 67488-72-6; *cis*-**7**, 67488-73-7; *trans*-**7**, 67488-74-8; **8a**, 67528-55-6; **8b**, 67488-75-9; **9**, 67528-56-7; **10**, 67528-57-8; **11**, 67528-58-9; *cis*-ethyl chrysanthemate, 7377-84-6; *trans*-ethyl chrysanthemate, 1802-02-4.

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(15) The formation of **1c** instead of diethyl acetal **9** (R = R′ = Et) could also result from the presence of water in the reaction medium. We do not favor this explanation because strictly anhydrous ethanol was used, because a high water content would be required to account for the high yield of **1c**, and because the hydrolysis reaction was not significant under similar conditions in methanol.
(16) The choice of pH is critical. Acidification of the solution to pH 2 results in complete conversion of **9** to **3b**, whereas at a pH of 5 the acetal–acid is not extracted into the organic phase.

Cyclization of Conjugated Azines. Synthesis and Thermal Rearrangements of 1-Oxo-3,4-diaza-2,4,6,7-octatetraenes (Allenyl Azines)

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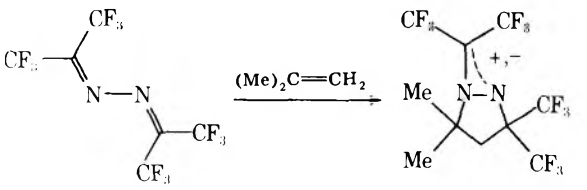
Received May 8, 1978

The Wittig reaction of certain 2-(alkylidenehydrazono)propylidenephosphoranes with ketenes provides a general route to 1-oxo-3,4-diaza-2,4,6,7-octatetraenes (allenyl azines). The allenyl azines undergo a facile intramolecular thermal cycloaddition reaction to yield pyrazolo[5,1-*c*]-1,4-oxazines and/or 4,9-dihydropyrazolo[1,5-*b*]isoquinolines depending on the nature of the substituents introduced via the ketene.

In contrast to all carbon,[2] monoaza,[3] and other diaza[4] dienes, the intra- and intermolecular cycloaddition reactions of acyclic azines (eg., **1** and **8**, Scheme I) or 2,3-diazabutadienes are characterized by the 1,3 reactivity of the C=N—N=C grouping. For example, simple aldehyde and ketone azines (**1**) react with the olefins to yield perhydropyrazolo[1,2-*a*]pyrazoles (**2**), a reaction known as "criss-cross" cycloaddition[5] (Scheme I, eq 1). The intermediacy of azomethinimine 1,3-dipoles has been confirmed by the isolation and characterization[6] of **13** in the reaction of hexafluoroacetone azine (**12**) with isobutylene.

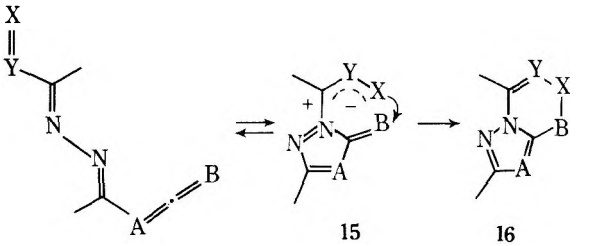


12 **13**

Analogous reactivity has been observed[7,8] with acetylenes, leading to 1,5-dihydropyrazolo[1,2-*a*]pyrazoles (**3**). These azine–acetylene criss-cross cycloadducts are thermally unstable, rearranging to either acyclic azines[7] (e.g., **7**) or N-substituted pyrazoles (e.g., **5** and **6**; Scheme I, eq 2). The key step in these reactions is the ring opening of **3** to a stabilized azomethinimine (**4**).[9] When R = H, **4** can proceed on to the N-substituted pyrazoles (**5**/**6**) by a simple intramolecular proton transfer to the 3-carbon side chain. When R is something other than hydrogen, this proton transfer is not possible and the dipolar intermediate (**4**) decomposes by a second ring opening reaction to yield the acyclic azines **7**.

An analogous intermediate (i.e., **9**) is presumably involved in the thermal rearrangement of certain conjugated azines (**8**) to N-substituted pyrazoles (**10** and **11**). Symmetrical azines derived from α,β-unsaturated aldehydes and ketones[10] (i.e., **8a**) and unsymmetrical azines formed from α-diketone monohydrazones and α,β-unsaturated aldehydes and ketones[11] (i.e., **8b**) rearrange to *N*-propenylpyrazoles (**10a**) and α-pyrazolyl ketones (**11**), respectively (Scheme I, eq 3).

It occurred to us that in a suitably designed system avenues of intramolecular reaction other than proton transfer might be observed in the reactions of azomethinimines such as **4** and **9**. One intriguing system, **14**, has the azine functional group



14 **15** **16**

in conjugation with a cumulene system. If these azines were to react in the same manner as other conjugated azines (**8a** and **8b**), one would expect stabilized azomethinimines such as **15** to be formed. One possible mode of reaction open to **15** would be an internal Michael-type addition to the exocyclic C=B bond, generating bicyclic heterocycles **16**. In theory, a wide variety of heterocyclic systems could be obtained by varying A, B, X, and Y. To establish the feasibility of this reaction concept, we have chosen to study the synthesis and thermal rearrangements of 1-oxo-3,4-diaza-2,4,6,7-octatetraenes (**14**; A = B = Y = carbon, X = oxygen).

Results and Discussion

The required allenyl azines (**14**; A = B = Y = C, X = O) are unknown in the literature. The ready availability[11] of the stabilized phosphorane **17** and the known[12] reaction of phosphonium ylides with ketenes to form allenes suggested the route to the allenyl azines (e.g., **18**) outlined in Scheme II.

As an initial test of the feasibility of this scheme, we investigated the reaction of **17** with diphenylketene (generated in situ by the action of triethylamine on diphenylacetyl chloride,[13] **19**). The reaction proceeds smoothly and rapidly at room temperature in benzene to produce a single product in addition to triphenylphosphine oxide. Although this material proved to be quite thermally labile, by rapidly chromatographing the reaction mixture we were able to isolate it in essentially quantitative yield as an orange solid. Examination of the infrared [1930 (allene) and 1680 cm^{-1} (PhC=O)]

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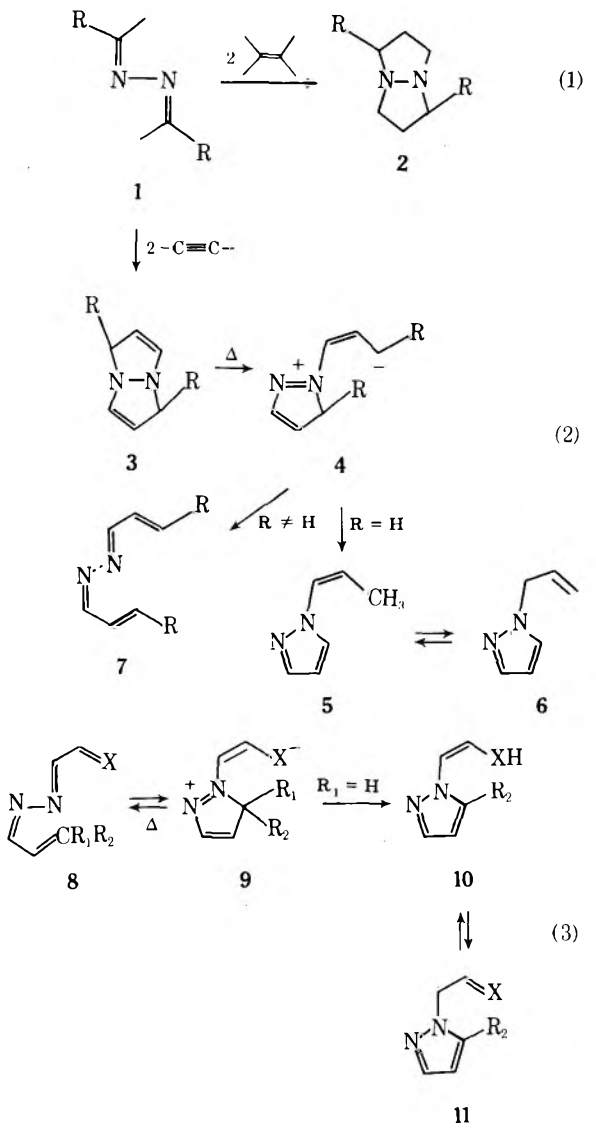
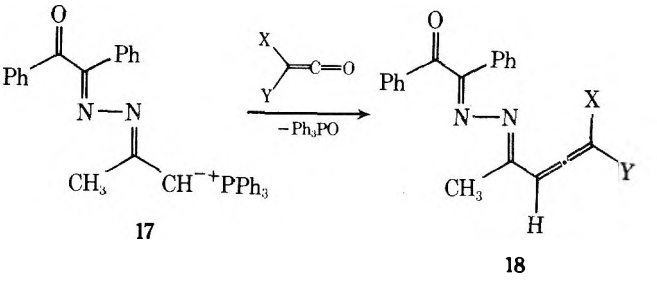
Scheme I

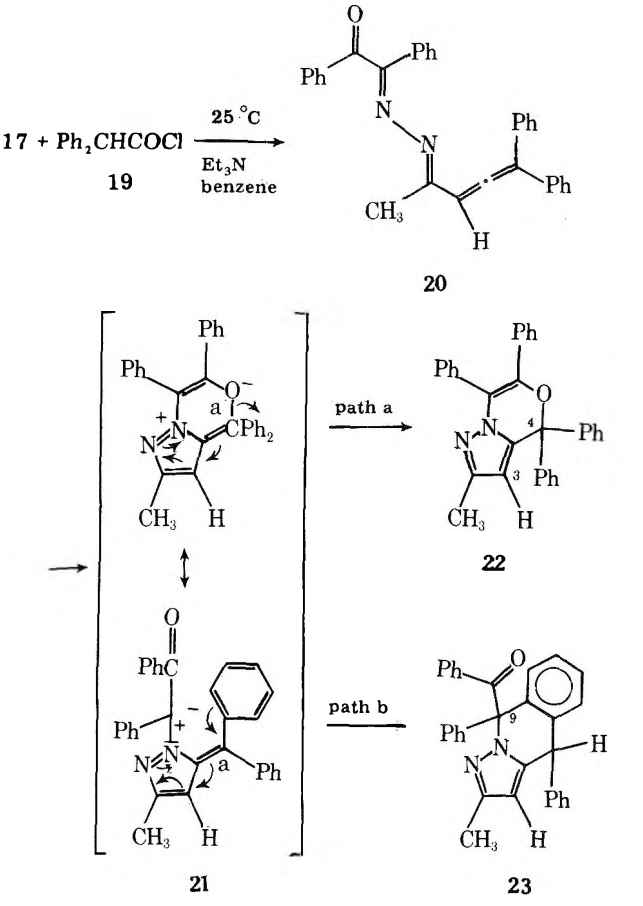


8–11: a, X = CR_1R_2; b, X = O

Scheme II



Scheme III



and ^{13}C NMR [δ 212.1 (C=C=C), 100.2 (C=C=CPh_2), and 197.9 (PhC=O)] spectra confirmed our identification of this orange solid as the allenyl azine **20** (Scheme III).

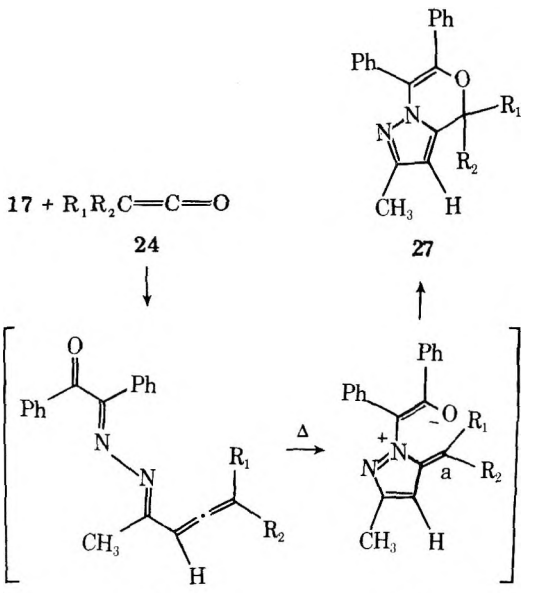
Thermolysis of a benzene solution of **20** (2 h at reflux) led to the formation of two products as determined by thin-layer chromatography (TLC) which were separated by column chromatography. The minor (39% isolated yield) product was a colorless solid isomeric with **20** but lacking a carbonyl in both the IR and ^{13}C NMR spectra. A 3-methylpyrazole ring was indicated by peaks at δ 104.5 (C-3) and 14.0 (CH_3) in the ^{13}C NMR spectrum and at δ 5.62 (s, 1 H, C-3 H)[11] and 2.19 (s, 3 H, CH_3) in the proton NMR spectrum. This data appeared consistent with the 4*H*-pyrazolo[5,1-*c*]-1,4-oxazine structure (**22**), and this was confirmed by a moderate IR band at 1640 cm^{-1} (vinyl ether) and a peak at δ 83.6 in the ^{13}C NMR spectrum[14] assignable to C-4 (Scheme III).

The major product of this thermolysis was also a colorless isomer of **20.** Again the ^{13}C and ^1H NMR spectra indicated a 1,3,5-trisubstituted pyrazole, but a strong band at 1680 cm^{-1} in the IR spectrum suggested a phenyl ketone. In addition to the ^{13}C NMR peak attributable to the 3-methyl carbon (δ 13.6), there were two other "saturated" carbon resonances (at δ 44.5 and 75.2). We assign these two signals to C-4 and C-9, respectively, of the 4,9-dihydropyrazolo[1,5-*b*]isoquinoline **23.** Apparently, **23** is isolated as a mixture of isomers about C-4 although appearing homogeneous by TLC. Two signals are observed for C-4 H (0.5 H each) in the ^1H NMR spectrum as well as for C-3 and the benzoyl carbonyl carbon in the ^{13}C NMR spectrum (Scheme III).

The propensity of conjugated azines to undergo intramolecular cycloaddition reactions via azomethinimines[10,11] (see Scheme I) suggests that the thermolysis of **20** involves a zwitterionic intermediate (**21**), and the products isolated are entirely consistent with this assumption. Intramolecular alkylation of the enolate oxygen by the activated exocyclic Michael acceptor (path a, Scheme III) would lead to the pyrazolooxazine **22,** while conjugate addition of the enolate carbon to one of the phenyl rings (path b, Scheme III) would yield, after rearomatization of the phenyl ring, the pyrazoloisoquinoline **23.**

This same phosphonium ylide (**17**) reacted equally well with phenylketene (**24a**), ketene[15] (**24b**), and vinylketene[16] (**24c**) as outlined in Scheme IV. In these cases, the allenyl azines **25a–c** proved too unstable to isolate, so the thermolyses were carried out directly by briefly heating the crude reaction mixtures. Single products were formed in each case which we isolated and identified (on the basis of spectral and analytical

Scheme IV



	R_1	R_2	yield of 27 (% isolated)
24–27a,	H	Ph	67
b,	H	H	65
c,	H	$-CH=CH_2$	35

analyses) as the pyrazolo[5,1-*c*]-1,4-oxazines **27a–c.** No other products could be detected or isolated.

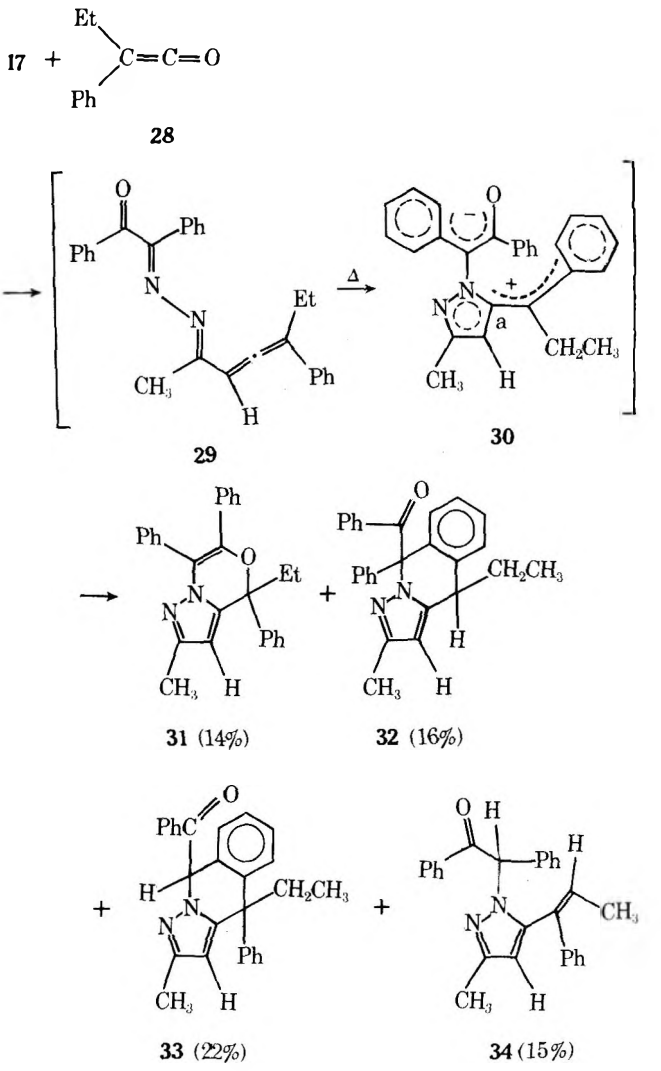
To further probe the effect of substituents at C_a on the course of these rearrangements, we allowed ethylphenylketene (generated in situ from α-phenylbutyryl chloride/Et_3N) to react with **17.** Thermolysis of the resulting allenyl azine (**29,** Scheme V) led to an extremely complex reaction mixture from which we were able to isolate four isomeric heterocycles, **31–34.** Two of the products were the "expected" pyrazolooxazine **31** and dihydropyrazoloisoquinoline **32.** In addition, significant amounts of the isomeric pyrazoloisoquinoline **33** and the monocyclic 5-(1-phenylpropenyl)pyrazole **34** were isolable. As above, all structural assignments were based on and are entirely consistent with spectral and analytical data.

All four products are consistent with a common intermediate, the azomethinimine **30** (Scheme V). Pyrazolooxazine **31** and pyrazoloisoquinoline **32** would result from O- and C-alkylation of the enolate portion of **30** as discussed above in the diphenylketene reaction (Scheme III). The other pyrazoloisoquinoline (**33**) would be the product of attack of the ortho carbon of the phenyl ring α to the pyrazole nucleus on position a. Monocyclic pyrazole **34** can be derived from **30** by a simple intramolecular proton transfer from the methylene group to the anionic portion of the molecule.

The mode of reactivity of these benzoyl stabilized azomethinimines (e.g., **21, 26,** and **30**) is dependent to a large extent on the nature of the substituents on the exocyclic carbon (a). In order to probe the effect of perturbing the anionic portion of these zwitterionic intermediates, we have investigated the reaction of carbethoxy stabilized ylide **35**[11] with several ketenes (summarized in Scheme VI.)

The reaction of **35** with diphenylketene proceeded smoothly to yield a single product after thermolysis of the allenyl azine. This material was isolated in good (80%) yield and identified as the pyrazolo[1,5-*b*]isoquinoline **38** on the basis of spectral and analytical data. No other products could be detected or isolated. However, although **35** reacted with phenyl- and vinylketene, as well as ketene itself, to form the corresponding allenyl azines **40a–c** (as determined by TLC), subsequent

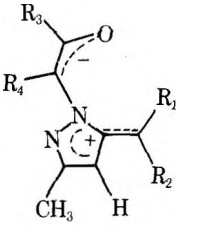
Scheme V



thermolysis led to complex tarry reaction mixtures from which no identifiable products could be isolated.

What was originally envisioned as a rather straightforward extension of known azine chemistry has proven to be another interesting and complex example of the unique cycloaddition chemistry of the azine system. The number and nature of substituents in the allenyl azine molecule have a great effect on the course of its thermal rearrangements. An analysis of the types of products formed as a function of the substituent patterns allows us to make some rational assumptions about both the nature of reactive intermediates and the factors important in determining the course of the rearrangements.

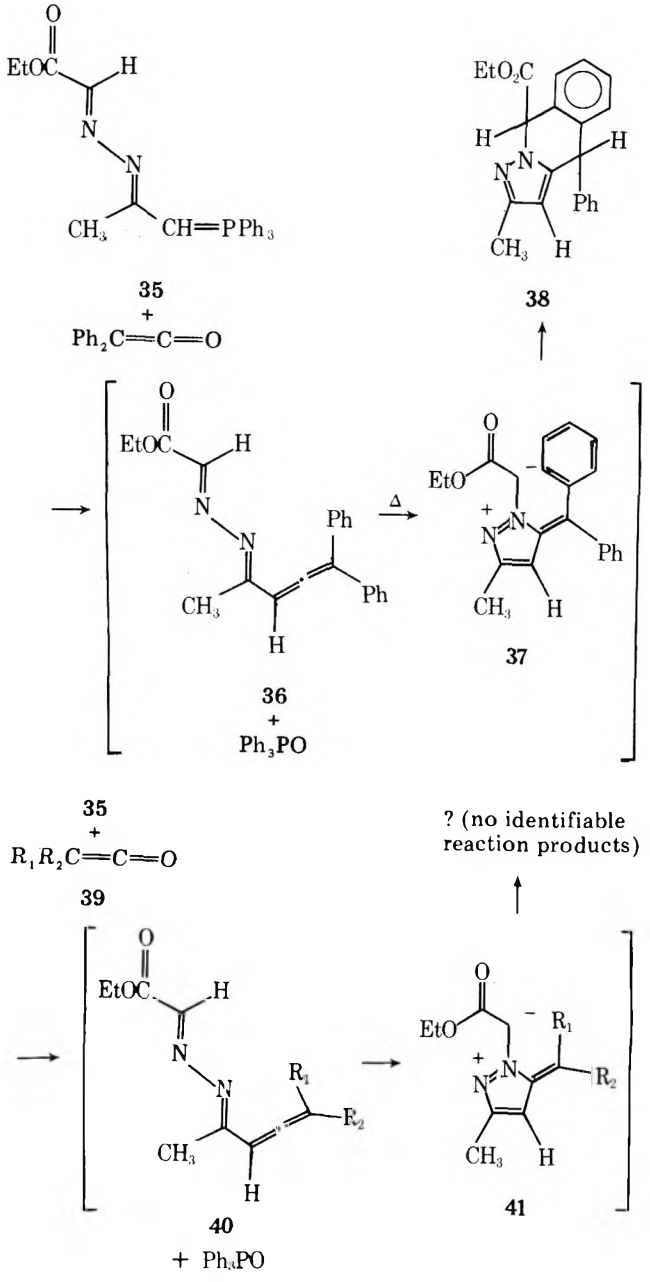
All of the products isolated are consistent with the intermediacy of resonance delocalized azomethinimines such as **42,** which are analogous to intermediates implicated and/or



42

isolated in a number of other azine cycloadditions (see Scheme I). Nearly all of the possible modes of intramolecular reactivity open to **42** have been observed.

Scheme VI

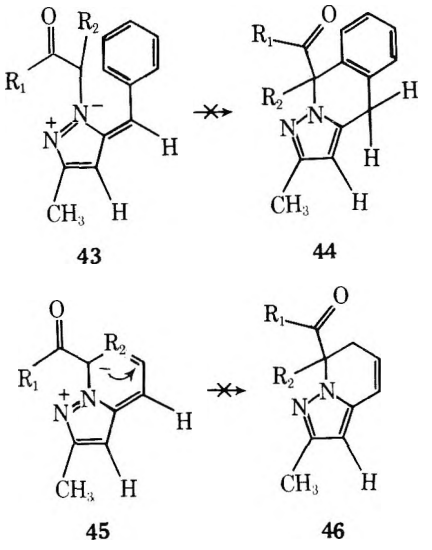


39–41: a, R_1 = H, R_2 = Ph; b, R_1 = H, R_2 = H; c, R_1 = H, R_2 = HC=CH_2

A comparison of the product composition in the thermolysis of the allenyl azine formed from diphenylketene and benzoyl stabilized ylide **17** (**20,** Scheme III) and the carbethoxy stabilized phosphorane **35** (**36,** Scheme VI) supports the intermediacy of dipoles such as **42** in these rearrangements as well as pointing up the effect on reactivity of substituents R_3 and R_4. Pyrazoloisoquinoline **38** is the only product formed when the cabethoxyallenyl azine **36** is thermolyzed (Scheme VI), while nearly equal amounts of the analogous pyrazoloisoquinoline **23** and pyrazolooxazine **22** arise from the benzoylallenyl azine **20** (Scheme III). One would expect a greater preference for C-alkylation (pyrazoloisoquinoline formation) with an ester stabilized carbanion (**42**; R_3 = OEt, R_4 = H) than with a ketone stabilized carbanion (**42**; R_3 = R_4 = Ph).

When R_1 or R_2 is a proton, subsequent reactions of dipole **42** depend on the nature of R_3 and R_4. The reaction of phenyl- and vinylketene with the benzoyl stabilized phosphorane **17** and thermolysis of the allenyl azines **25a** and **25c** (Scheme IV) led to exclusive formation of the pyrazolooxazine derivatives (**27a** and **27c**), that is, O-alkylation of the intermediate dipole. When the benzoyl group is replaced by a carbethoxy substituent, however, the same sequence of reactions leads to complex tarry mixtures, probably the result of intermolecular reactions (oligomerization/polymerization) of the azomethinimine intermediate (**41**, Scheme VI).

In neither of these systems were the products **44** and **46**,



a, R_1 = R_2 = Ph; b, R_1 = EtO, R_2 = H

expected from C-alkylation of the intermediate dipoles **43** and **45,** isolated or detected. This is somewhat surprising since in the systems derived from disubstituted ketenes C-alkylation is actually preferred (see Schemes III, V, and VI). One would certainly expect the pyrazolo[1,5-*a*]pyridine derivatives **46a** and **46b** to be formed readily since the conjugate addition of the anion to the vinyl group involves no loss of aromatic resonance energy. This seems to suggest that when R_1 is a proton in **42** the other substituent is unavailable for reaction with the anionic portion of the dipole. This forces the dipole (**42**) into an alternate mode of reactivity, either O-alkylation when R_3 = R_4 = Ph or unspecified intermolecular reactions when R_3 = EtO and R_4 = H.

When one substituent (R_1 or R_2) in **42** is considerably larger than the other, the prefered conformation of the ground state of the dipole will have the larger group (i.e., R_2) "trans" to the anionic center. This thermodynamically favorable orientation will be maintained as the anionic and cationic centers approach, and a significant amount of energy will be required to bring R_2 into a potentially reactive position. In the benzoyl stabilized systems [e.g., **42** (R_3 = R_4 = Ph)] the dipole has a reasonable alternative (O-alkylation) when faced with the barrier to reaction at R_2. However, since O-alkylation is also a relatively high energy process (see Scheme VI), the carbethoxy stabilized systems (**42**; R_3 = EtO, R_4 = H) have no reasonable intramolecular avenues of reaction available and decompose by complex intermolecular pathways. Further examination of the decomposition products of **41** or of the possible trapping of the azomethinimine **41** and its precursor **40** is underway.

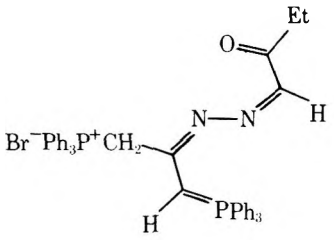
Experimental Section

General. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer and calibrated by comparison with a standard polystyrene film sample. Proton NMR spectra of approximately 10% (w/v) solutions in $CDCl_3$ were obtained on either a Varian A60-A or a Perkin-Elmer R12-b spectrometer. Chemical shifts are reported in parts per million (δ scale) vs. tetramethylsilane as an internal stan-

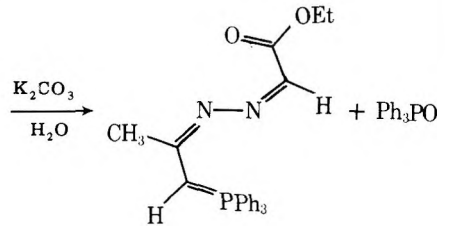
dard, and they were corrected for instrument drift/miscalibration by references to a standard solution containing approximately proton-equivalent amounts of Me_4Si, cyclohexane, acetone, 1,4-dioxane, methylene chloride, and chloroform in $CDCl_3$. In reporting the NMR data, the following abbreviations have been employed: coupling constant in hertz (J), singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), pentet (p), and multiplet (m). The ^{13}C NMR data were collected on a Brüker HFX-90 spectrometer equipped for Fourier transform pulsed NMR with a Nicolet 1085 data system. Electron impact mass spectra were recorded using a duPont CEC21-110D instrument with a resolution of 5000 (20% valley).

Dry (concentrated H_2SO_4 followed by sodium hydroxide and calcium chloride) nitrogen was routinely employed as the reaction atmosphere in all reactions. Eastman Chromagram precoated (silica gel on polyethylene) sheets impregnated with a fluorescent indicator were employed in thin-layer chromatographic operations. Melting points were obtained with a Thomas-Hoover apparatus, and boiling points are uncorrected. Elemental analyses were performed by Micro Analysis Inc. of Wilmington, Del.

Diphenylacetyl chloride,[17] crotonyl chloride,[18] and α-phenylbutyryl chloride[19] were prepared by known methods and distilled prior to use. Phenylacetyl choride was purchased from the Aldrich Chemical Co. and distilled prior to use. Ylide **35** was prepared[11] by mild hydrolysis of the ylide salt **47**, and the resulting mixture with Ph_3PO was used



47



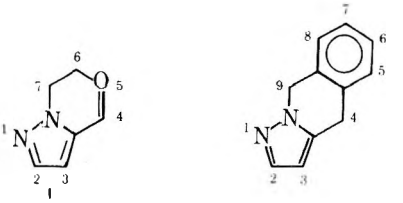
35

as is in further reactions. Both benzene and triethylamine were dried and distilled from sodium metal. In light of its toxicity, benzene should be replaced by toluene or some other suitable aprotic solvent in any attempts to repeat or extend this work. All glassware was baked at 110–120 °C for a minimum of 4 h before use. The numbering systems used in referring to the 4*H*-pyrazolo[5,1-*c*]-1,4-oxazine (**e.g., 48**) and 4,9-dihydropyrazolo[1,5-*b*]isoquinoline (e.g., **49**) systems are shown in Scheme VII.

Reaction of Ylide 17 with Diphenylketene. Isolation of the Allenyl Azine 20 (1-Diphenylvinylidene-2-benzoylbenzylidenehydrazonopropane). To an orange solution of 1.05 g (2.0 mmol) of ylide **17** in 20 mL of benzene was added 0.42 g (4.15 mmol) of triethylamine. The reaction mixture was cooled to ~5 °C with an ice bath (some **17** crystallized but did not hamper the reaction), and a solution of 0.58 g (2.5 mmol) of diphenylacetyl chloride in 5 mL of benzene was added dropwise over 15 min (cooling maintained throughout the addition). The resulting light orange hazy solution was then stirred at 10–15 °C (maintained by intermittent immersion in an ice bath) for 2 h. The solvent was removed in vacuo at less than 35 °C, and the residual orange oil was rapidly chromatographed on a 35 × 350 mm silica gel column eluting with methylene chloride. The mobile orange band was collected in three 125-mL fractions which were combined, and the solvent was evaporated (<35 °C) to yield 0.92 g (theory = 0.88 g) of **20** as an orange solid. Crystallization from warm MeOH afforded an analytical sample: mp 115–115.5 °C; IR (CCl_4) 1930 (C=C=C), 1685 (C=O), 1600, 1580, 1495 cm^{-1}; ^1H NMR δ 2.21 (s, 3 H, CH_3C=N–), 6.28 (br s, 1 H, HC=CPh_2), 7.21 (s) and 7.11–7.48 (m) (total of 16 H, aromatic), 7.51–8.00 (m, 4 H, aromatic ortho to C=N/C=O); ^{13}C NMR δ 14.8 (CH_3), 100.2 (C=C=CPh_2), 162.9, 163.7 (C=N), 197.9 (C=O), 212.1 (C=C=C).

Anal. Calcd for $C_{31}H_{24}N_2O$: C, 84.52; H, 5.49. Found: C, 84.35; H, 5.41.

Scheme VII



48 **49**

Reaction of Ylide 17 with Diphenylketene. In Situ Thermolysis of the Allenyl Azine 20. Preparation of 2-Methyl-4,4,6,7-tetraphenyl-4*H*-pyrazolo[5,1-*c*]-1,4-oxazine (22) and 2-Methyl-4,9-dihydro-9-benzoylpyrazolo[1,5-*b*]isoquinoline (23). To an orange solution of 1.05 g (2.0 mmol) of ylide **17** and 0.23 g (2.28 mmol) of triethylamine in 20 mL of benzene was added 0.48 g (2.08 mmol) of diphenylacetyl chloride in 5 mL of benzene dropwise over 3 min. There was a slight exotherm, the color faded to a pale orange, and a very fine precipitate formed (presumably Et_3N·HCl). The hazy solution was stirred at ambient temperature for 1 h and at reflux (80 °C) for 2 h. Thin-layer chromatography (TLC; CH_2Cl_2, silica gel) showed the formation of two products (along with Ph_3PO). After removal of solvent in vacuo, the crude reaction mixture was chromatographed on a 35 × 350 mm silica gel column eluting with methylene chloride. This yielded the following in order of elution.

(a) **22** (0.34 g, 39%) as a tan solid. Recrystallization from CH_2Cl_2/heptane yielded a colorless analytical sample: mp 233.5–234.5 °C; IR (KBr) 1640, 1540, 1485, 1440 cm^{-1}; ^1H NMR δ 2.19 (s, 3 H, C-2 CH_3), 5.62 (s, 1 H, C-3 H), 6.93 (s, 5 H, C-6 or C-7 Ph), 7.11 (s, 5 H, C-7 or C-6 Ph), 7.18 (s, 10 H, C-4 Ph_2); ^{13}C NMR δ 14.0 (C-2 CH_3), 83.6 (C-4), 104.5 (C-3), 149.4 (C-6); mass spectrum, m/e (% base peak) 440 (2.9, M^+), 336 (30.8), 335 (100), 294 (19.5).

Anal. Calcd for $C_{31}H_{24}N_2O$: C, 84.52; H, 5.49. Found: C, 84.40; H, 5.26.

(b) **23** (0.43 g, 49%) as an amber resinous solid. Crystallization from 95% ethanol afforded a colorless analytical sample: mp 157–172 °C; IR ($CHCl_3$) 1680, 1595, 1540, 1480, 1435 cm^{-1}; ^1H NMR δ 1.98 (s) and 2.01 (s) (total of 3 H, C-2 CH_3), 4.84 (br s, 0.5 H, C-4 H), 5.49 (br s, 1 H, C-3 H), 5.94 (br s, 0.5 H, C-4′ H), 6.46–7.80 (m, 20 H, aromatic); ^{13}C NMR δ 13.6 (C-2 CH_3), 44.5 (C-4), 75.2 (C-9), 104.0 (C-3), 104.6 (C-3′), 193.5 (C=O), 194.2 (C=O′).

Anal. Calcd for $C_{31}H_{24}N_2O$: C, 84.52; H, 5.49. Found: C, 84.55; H, 5.33.

Reaction of Ylide 17 with Phenylketene. Preparation of 2-Methyl-4,6,7-triphenyl-4*H*-pyrazolo[5,1-*c*]-1,4-oxazine (27a). Ylide **17** (1.05 g, 2.0 mmol) was reacted as above with 0.64 g (6.35 mmol) of triethylamine and 0.66 g (4.27 mmol) of phenylacetyl chloride (Aldrich). Column chromatography (35 × 350 mm of silica gel, CH_2Cl_2) of the crude product yielded 0.49 g (67%) of **27a** as a tan solid. Recrystallization from ethanol afforded a colorless analytical sample: mp 211–213 °C; IR (KBr) 1640, 1550, 1495, 1440 cm^{-1}; ^1H NMR δ 2.21 (s, 3 H, C-2 CH_3), 5.78 (s, 1 H, C-3 H), 6.24 (s, 1 H, C-4 H), 7.01 (s, 5 H, C-4 Ph), 7.16–7.66 (m, 10 H, C-6 and C-7 Ph); ^{13}C NMR δ 14.0 (C-2 CH_3), 75.7 (C-4), 102.6 (C-3), 149.6 (C-6); mass spectrum, m/e (% base peak) 365 (16.8, $M^+ + 1$), 364 (56.7, M^+), 260 (21.0), 259 (100).

Anal. Calcd for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.53. Found: C, 82.26; H, 5.34.

Reaction of Ylide 17 with Ketene. Preparation of 2-Methyl-6,7-diphenyl-4*H*-pyrazolo[5,1-*c*]-1,4-oxazine (27b). Ketene was generated by the pyrolysis of acetone according to the method of Williams and Hurd.[15] The apparatus was calibrated by passing the ketene stream (after running for 30 min to thoroughly purge the system) thru a sodium hydroxide solution of known concentration for a known period of time, followed by titration of the residual hydroxide to the phenolpthalein end point. The rate of ketene generation was calculated to be 2.7 mmol/min (average of two runs). The ketene stream was then bubbled through a solution of 1.05 g (2.0 mmol) of ylide **17** in 25 mL of benzene for 5 min (~13.5 mmol of ketene). The resulting solution was stirred for 5 min at ambient temperature and 2 h at reflux. After removal of the solvent in vacuo, crude **27b** (0.38 g, 65%) was isolated as a tan solid by trituration of the residue with cold ethanol. Recrystallization from ethanol afforded a colorless analytical sample: mp 168.5–169.0 °C; IR (KBr) 1645, 1555, 1495, 1450 cm^{-1}; ^1H NMR δ 2.23 (s, 3 H, C-2 CH_3), 5.25 (s, 2 H, C-4 H_2), 5.90 (s, 1 H, C-3 H), 7.10 (s, 5 H, aromatic), 7.30 (br s, 5 H, aromatic); ^{13}C NMR δ 14.0 (C-2 CH_3), 63.2 (C-4), 101.0 (C-3), 149.4 (C-6); mass spectrum, m/e (% base peak) 289 (20.8, $M^+ + 1$), 288 (100, M^+), 259 (23.1), 183 (46.0).

Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59. Found: C, 79.02; H, 5.44.

Reaction of Ylide 17 with Vinylketene. Preparation of 2-Methyl-4-vinyl-6,7-diphenyl-4*H*-pyrazolo[5,1-*c*]-1,4-oxazine (27c). Ylide **17** (1.05 g, 2.0 mmol) was reacted as above with 0.57 g (5.65 mmol) of triethylamine and 0.32 g (3.06 mmol) of crotonyl chloride. Column chromatography (35 × 350 mm of silica gel, CH_2Cl_2) of the crude reaction mixture yielded 0.22 g (35%) of **27c** as a slightly yellow solid, mp 113–116 °C. Recrystallization afforded a colorless analytical sample: mp 118–119 °C; IR (KBr) 1640, 1540, 1495, 1450 cm^{-1}; ^1H NMR δ 2.18 (s, 3 H, C-2 CH_3), 5.13–6.40 (m, 5 H, vinyl, C-4 H, and C-3 H), 7.00 (br s, 5 H, aromatic), 7.20 (br s, 5 H, aromatic); ^{13}C NMR δ 14.0 (C-2 CH_3), 74.2 (C-4), 101.6 (C-3), 119.5 (–CH=CH_2), 149.5 (C-6); mass spectrum, *m/e* (% base peak) 315 (7.1, $M^+ + 1$), 314 (26.4, M^+), 210 (31.3), 209 (100).

Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77. Found: C, 80.30; H, 5.92.

Reaction of Ylide 17 with Ethylphenylketene. A solution of 1.57 g (3.0 mmol) of ylide **17** in 25 mL of benzene was treated as above with 0.55 g (5.45 mmol) of Et_3N followed by 0.74 g (4.05 mmol) of α-phenylbutyryl chloride. After stirring for 1 h at room temperature and 2 h at reflux, the solvent was removed in vacuo and the residue chromatographed on silica gel (35 × 350 mm) eluting with CH_2Cl_2. This yielded the following in order of elution.

(a) 2-Methyl-4,6,7-triphenyl-4-ethyl-4*H*-pyrazolo[5,1-*c*]-1,4-oxazine (**31**; 0.16 g, 14%) as a white solid: mp 109–111 °C (ethanol); IR (KBr) 1640 (m), 1600 (w), 1550 (m), 1500 (s), 1460 (s), 1440 (s) cm^{-1}; ^1H NMR δ 1.06 (br t, $J \simeq 7.5$ Hz, 3 H, –CH_2CH_3), 2.25 (s, 3 H, C-2 CH_3), 2.32 (br q, $J \simeq 7.5$ Hz, 2 H, –CH_2CH_3), 6.01 (s, 1 H, C-3 H), 6.97, 7.05, and 7.12 (s, 5 H each, aromatic); ^{13}C NMR δ 8.6 (–CH_2CH_3), 14.1 (C-2 CH_3), 33.9 (–CH_2CH_3), 82.3 (C-4), 102.2 (C-3), 149.4 (C-6). Calcd for $C_{27}H_{24}N_2O$: *m/e* 392.188. Found: *m/e* 392.191.

(b) 2-Methyl-4-ethyl-9-phenyl-9-benzoyl-4,9-dihydropyrazolo[1,5-*b*]isoquinoline (**32**; 0.19 g, 16%) as a white solid: mp 198–201 °C; IR 1690 (s), 1595, 1575, 1545, 1485, 1445 cm^{-1}; ^1H NMR δ 0.50–1.49 (m, 5 H, –CH_2CH_3), 2.02 (s, 3 H, C-2 CH_3), 3.89 (dd, J = 5.5 and 8.0 Hz, 1 H, C-4 H), 5.82 (s, 1 H, C-3 H), 6.49–7.39 (m, 14 H, aromatic); ^{13}C NMR δ 12.3 (–CH_2CH_3), 13.8 (C-2 CH_3), 31.6 (–CH_2CH_3), 41.6 (C-4), 75.9 (C-9), 104.1 (C-3), 193.3 (C=O).

Anal. Calcd for $C_{27}H_{24}N_2O$: C, 82.62; H, 6.16. Found: C, 82.63; H, 6.15.

(c) A mixture of 2-methyl-4-phenyl-4-ethyl-9-benzoyl-4,9-dihydropyrazolo[1,5-*b*]isoquinoline (**33**) and 1-phenyl-1-[3-methyl-5-(1-phenylpropenyl)pyrazol-1-yl]acetophenone (**34**) (0.44 g, 37.5%) as an amber semisolid. Treatment of the mixture dissolved in 2.0 mL of ethanol with 2.5 mL of a saturated ethanol solution of picric acid yielded the picrate salt of **33** (0.41 g; 22% based on ylide **17**) as a yellow solid, mp 181.5–182 °C.

Anal. Calcd for $C_{33}H_{27}N_5O_8$: C, 63.76; H, 4.38. Found: C, 63.78; H, 4.29.

The free base (**33**) was liberated by treatment of the picrate salt with dilute sodium hydroxide, extracting with ether, drying the organic layer (Na_2SO_4), and evaporation of the solvent in vacuo. This yielded **33** as a colorless oil: IR 1700, 1600, 1580, 1544, 1500, 1450 cm^{-1}; ^1H NMR δ 0.46 (t, J = 7.7 Hz, 3 H, –CH_2CH_3), 2.10 (s, 3 H, C-2 CH_3), 2.43 (q, J = 7.7 Hz, 2 H, –CH_2CH_3), 5.60 (s, 1 H, C-3 H), 6.85 (s, 1 H, C-9 H), 6.89–7.52 (m, 12 H, aromatic), 7.78 (m, 2 H, aromatic ortho to C=O); ^{13}C NMR δ 8.8 (–CH_2CH_3), 13.8 (C-2 CH_3), 37.1 (–CH_2CH_3), 49.0 (C-4), 63.5 (C-9), 102.8 (C-3), 195.4 (C=O).

Neutralization of the filtrate from the picrate formation above with dilute NaOH, extraction with ether, drying of the organic phase (Na_2SO_4), and evaporation of solvent yielded **34** as an amorphous amber solid: IR 1705, 1595, 1580, 1545 cm^{-1}; ^1H NMR δ 1.67 (d, J = 6.6 Hz, 3 H, >C=CHCH_3), 2.03 (C-3 CH_3), 5.73 (q, J = 6.6 Hz, 1 H, >C=C**H**CH_3), 5.86 (s, 1 H, C-4 H), 6.17 (s, 1 H, PhCOCHPh–), 6.52–7.30 (m, 15 H, aromatic); ^{13}C NMR δ 13.8 (C-3 CH_3), 15.3 (>C=C**H**CH_3), 67.0 (PhC**H**CHPh–), 107.4 (C-4), 193.1 (C=O). Calcd for $C_{27}H_{24}N_2O$: *m/e* 392.188. Found: *m/e* 392.184.

Reaction of Ylide 35 with Diphenylketene. Preparation of 2-Methyl-4-phenyl-4,9-dihydropyrazolo[1,5-*b*]isoquinoline-9-carboxylic Acid Ethyl Ester (38). The crude mixture of ylide **35** and Ph_3PO prepared from 3.97 mmol of ylide salt precursor **47** was charged to a 50-mL three-neck round-bottom flask and dissolved in 20 mL of benzene. Triethylamine (1.03 g, 10 mmol) was added, followed by the dropwise addition over 5 min of a solution of 1.39 g (6 mmol) of diphenylacetyl chloride in 10 mL of benzene, which caused a slight exotherm. The reaction was stirred at ambient temperature for 1 h and at reflux for 2 h, the solvent was removed in vacuo, and the crude residue was chromatographed as above to yield 1.05 g (80%) of **38** as a light orange solid. Recrystallization from ethanol afforded a colorless analytical sample: mp 134.5–135.5 °C; IR (KBr) 1750, 1545, 1500, 1455, 1295 cm^{-1}; ^1H NMR δ 1.12 (t, J = 7.0 Hz, 3 H, C**H**$_3$CH$_2$), 2.19 (s, 3 H, C-2 CH_3), 4.03 (q, J = 7.0 Hz, 2 H, CH_3C**H**$_2$), 5.20 (br s, 1 H, C-4 H), 5.75 (s, 1 H, C-3 H), 5.95 (br s, 1 H, C-9 H), 6.85–7.55 (m, 9 H, aromatic); ^{13}C NMR δ 13.8 (**C**H$_3$CH$_2$O– and C-2 CH_3), 44.1 (C-4), 62.1 (CH_3**C**H$_2$O– and C-9), 103.2 (C-3), 169.3 (EtO_2C–); mass spectrum, *m/e* (% base peak) 332 (12.0, M^+), 260 (33.8), 259 (100), 217 (10.6), 216 (16.8).

Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06. Found: C, 75.93; H, 5.98.

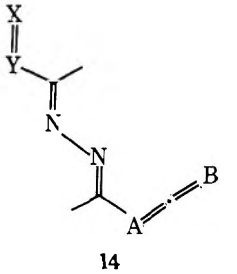
Reaction of Ylide 35 with Phenylketene. The crude mixture of **35** and Ph_3PO prepared from 2.0 mmol of **47** was allowed to react at ambient temperature in 20 mL of benzene with 0.52 g (5.15 mmol) of triethylamine and 0.62 g (4.0 mmol) of phenylacetyl chloride for 1 h. The formation of the allenyl azine **40a** was observed by TLC (CH_2Cl_2, silica gel). When the reaction was heated under reflux for 2 h, it turned very dark and TLC showed the disappearance of **40a** and the formation of a number of non-TLC "mobile" products. The reaction mixture was poured into 50 mL of H_2O, 30 mL of benzene was added, and the layers were thoroughly mixed and separated. The organic layer was extracted two times with 10 mL of 5% HCl and once with 10 mL of water. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo. The dark brown residue was heated with five 20-mL portions of ether (with decantation of the supernatant each time). The hot ether-insoluble portion (0.22 g) was dark brown glass containing at least nine products (by TLC) with similar R_f values. Concentration of the ether solutions (above) to ~20 mL and chilling in ice lead to the crystallization of 0.77 g (70%) of Ph_3PO. The filtrate from this contained at least five products (in addition to some residual Ph_3PO) which again had very similar R_f values. All attempts at separating these complex mixtures proved fruitless.

Reaction of Ylide 35 with Ketene. Ketene, generated as above in the preparation of **27b**, was bubbled through a benzene solution of the crude **35**/Ph_3PO mixture (from 2.0 mmol of **47**) for 3 min (~7.5 mmol of ketene). The reaction was stirred at ambient temperature for 1 h, at which time TLC (CH_2Cl_2, silica gel) indicated the formation of a single product, presumably allenyl azine **40b**. The reaction mixture was then heated under reflux for 2 h, during which time the solution turned extremely dark. Thin-layer chromatography (silica gel, CH_2Cl_2) showed the disappearance of the spot assigned to the allenyl azine **40b** and the formation of a number of (6–10) new spots with very low (<0.3) R_f values (R_f values of 0.5–0.75 would have been expected for the products of this reaction). Removal of the solvent in vacuo and trituration of the dark brown residue with ether allowed the isolation of 0.84 g (78% of theory) of Ph_3PO, identical in all respects with authentic material. The ether-soluble material was a nearly black viscous oil containing at least 6–10 products with very similar R_f values. Attempts at product isolation by crystallization (CH_2Cl_2/heptane, EtOH/water, ether/hexane) failed to give any solid material. Various solvent combinations ($CHCl_3$/MeOH, benzene, EtOAc) failed to improve the TLC separation.

Reaction of Ylide 35 with Vinylketene. The crude mixture of **35** and Ph_3PO prepared from **47** was allowed to react at ambient temperature in 20 mL of benzene with 0.52 g (5.15 mmol) of triethylamine and 0.42 g (4.0 mmol) of crotonyl chloride for 1 h. The formation of the allenyl azine **40c** was observed by TLC. Heating at reflux for 2 h and workup as above yielded 0.89 g (80%) of Ph_3PO and 0.25 g of a dark brown gum containing a number (5–10) of products with similar R_f values in a variety of solvents. All attempts at separation failed.

Conclusions

The thermal rearrangements of 1-oxo-3,4-diaza-2,4,6,7-octatetraenes (allenyl azines) provide another example of the unique cycloaddition behavior and potential synthetic utility of the azine functional group. Our results have confirmed, for the most part, our original hypothesis concerning the reactivity of azines conjugated with cumulene systems. This reaction concept should be readily extended to general azine–cumulene systems such as **14**. Work in these laboratories will



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continue to be directed toward the understanding and synthetic exploitation of the 1,3 reactivity of 2,3-diazabutadienes.

Acknowledgment. The generous support of the National Science Foundation to S.E. is gratefully acknowledged. We would also like to thank Dr. Roger Crecely of the University of Delaware for obtaining the carbon-13 NMR spectra reported in this work.

Registry No.—**17** (charged), 63570-24-1; **17** (unchanged), 63570-25-2; **20**, 67478-68-6; **22**, 67478-69-7; **23**, 67478-70-0; **27a**, 67478-71-1; **27b**, 67478-72-2; **27c**, 67478-73-3; **31**, 67478-74-4; **32**, 67478-75-5; **33**, 67478-76-6; **33** picrate, 67478-77-7; **34**, 67478-78-8; **35**, 63570-22-9; **38**, 67478-79-9; **40a**, 67478-80-2; **40b**, 67478-81-3; **40c**, 67478-82-4; **47**, 63570-20-7; diphenylketene, 525-06-4; phenylketene, 3496-32-0; ketene, 463-51-4; vinylketene, 50888-73-8; ethylphenylketene, 20452-67-9; diphenylacetyl chloride, 1871-76-7; phenylacetyl chloride, 103-80-0; crotonyl chloride, 10487-71-5; α-phenylbutyryl chloride, 36854-57-6.

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Stereoselectivity in Photocycloaddition of Bicyclic Enones to Olefins

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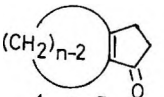
Received May 25, 1978

Stereoselectivity in photocycloaddition of bicyclic enones **1**, **2**, **5**, and **6** to 2-butene and cyclohexene is discussed. In the cases of **1** and **5**, having a five-membered ring fused to the double bond of monocyclic enones, from two to four kinds of cycloadducts were always obtained regardless of the ring size of the enone moieties, and, therefore, stereoselectivity is relatively low. On the other hand, in the cases of **2** and **6**, having a six-membered ring fused to the double bond of monocyclic enones, the formation of cis-anti-trans cycloadducts proceeded stereoselectively. This remarkable effect of fused ring size on stereoselectivity in photocycloaddition is ascribed to the degree of nonbonded hydrogen interaction in 1,4-diradical intermediates and can be associated with differing flexibility and rigidity of cyclohexane and cyclopentane rings.

While the stereochemistry of photocycloaddition and the factors controlling it are the most important and intriguing problems in the field of photocycloaddition of cyclic enones to olefins, relatively few studies have been made. Recently reports on the stereochemical assignment of photocycloadducts of cyclohexenone to cycloheptene,[1a] monocyclic cyclohexenone derivatives to cyclopentene,[1b] and bicyclic cyclohexenone **5** to 2-butene [1c]have appeared. In these reactions, photocycloaddition proceeded nonstereoselectively, and, therefore, two or three stereoisomers of cycloadducts were always formed. Subsequently, we reported that photocycloaddition of bicyclic cyclopentenone **2** to cyclohexene took place stereoselectively to afford cis-anti-trans adduct **15** as a sole cycloadduct, though enones **1**, **3**, and **4** gave mixtures of three or four stereoisomeric cycloadducts.[2] This marked distinction in stereoselectivity in photocycloaddition between these enones was interpreted in terms of differences in steric effects in the alicyclic rings fused to the double bond of cyclopentenone. To further clarify this concept, we have investigated the stereoselectivity in photocycloaddition of bicyclic



1, n=5
2, n=6
3, n=7
4, n=8

15

enones **1**, **2**, **5**, and **6**, composed of five- and six-membered rings, to 2-butene and cyclohexene.

First, we examined the photoreaction with about a 20-fold excess of *cis*- or *trans*-2-butene in methylene chloride at −70 °C. In the case of bicyclic cyclopentenone **1**, four stereoisomeric cycloadducts (**7a–d**)[3] were obtained. With bicyclic cyclohexenone **5**, as also reported by Cargill et al.,[1c] three isomeric cycloadducts (**10a–c**)[3] and keto olefin **11** were given. On the other hand, with enones **2** or **6** one of two kinds of cycloadducts (**8a** or **12a**)[3] was obtained in quantity, respectively, along with small amounts of another cycloadduct (**8b** or **12b**)[3]

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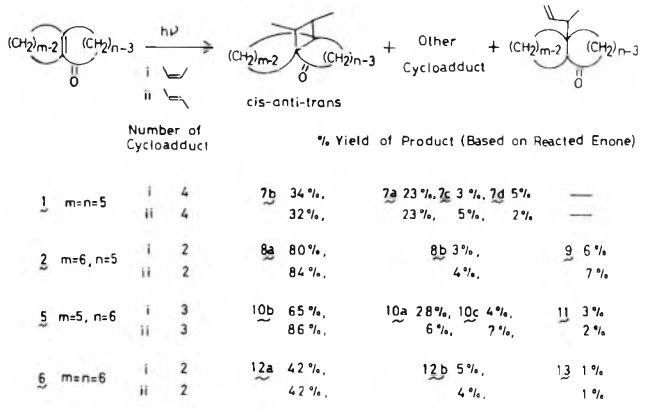
Table I. *S* Values of Methyl Protons in the LIS NMR Spectra of Cycloadducts 7a,b, 8a, 10a,b, and 12a

cycloadduct	registry no.	S^a	
7a	67504-85-2	0.22	0.61
7b	67504-84-1	0.28	0.44
8a	67504-83-0	0.29	0.51
10a	38312-64-0	0.19	0.46
10b	38343-72-5	0.25	0.43
12a	67504-82-9	0.25	0.44

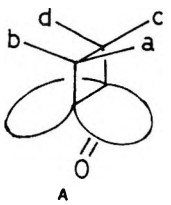
[a] $[Eu(DPM)_3]/[ketone] = 0.2–0.8$.

Chart I



and keto olefin (**9** or **13**). In all cases products obtained from *cis*-2-butene were essentially the same as those from *trans*-2-butene (Chart I).

The configuration of methyl groups in the cycloadducts **7a, 7b, 8a,** and **12a** was confirmed by LIS NMR in the same manner as Cargill's assignment of structure to **10a** and **10b.**[1c] Evidently, for the four possible positions of a methyl group, the degree of deshielding should decrease going from a to d on addition of $Eu(DPM)_3$, as shown in structure A. This is



A

expressed in terms of an *S* value[4] and is summarized in Table I.

Among the *S* values of methyl protons of **10a** and **10b,** one of those of **10a** is the largest (0.46) and the other is the smallest (0.19), and those of **10b** are the two intermediate values (0.25 and 0.43).[5] Consequently, it is reasonable to assign the structures of **10a** and **10b** to cis-syn-trans and cis-anti-trans in a manner similar to Cargill's assignment.[1c] Similarly, one of *S* values of methyl protons of **7a** is the largest (0.61) and the other is the smallest (0.22), and those of **7b** are intermediate (0.28 and 0.44) among *S* values for **7a** and **7b.** Accordingly, the structures of **7a** and **7b** should be assigned to cis-syn-trans and cis-anti-trans, respectively.[6] Methyl protons of **8a** and **12a** show similar *S* values (**8a,** 0.29 and 0.51; **12a,** 0.25 and 0.44) to those of **7b** and **10b,** which suggests that **8a** and **12a** have the cis-anti-trans configuration. The structures of keto olefins **9** and **13** may be assigned in analogy with **11**[1c] since they show vinyl absorption in their IR and NMR spectra.

Next, the photoreaction with cyclohexene was examined. As we reported previously,[2] **1** gave four isomeric cycloadducts (**14a–d**),[3] whereas **2** gave cis-anti-trans adduct **15** as a sole

Chart II

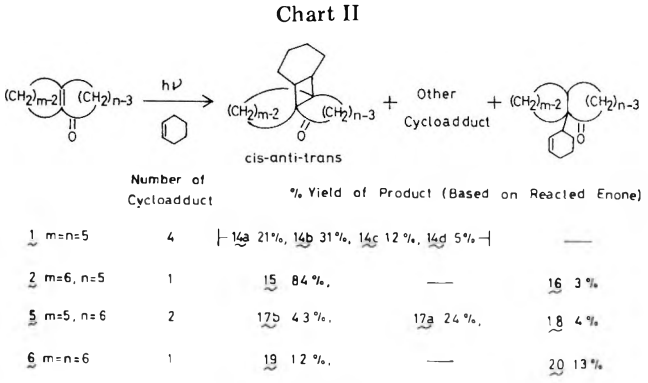
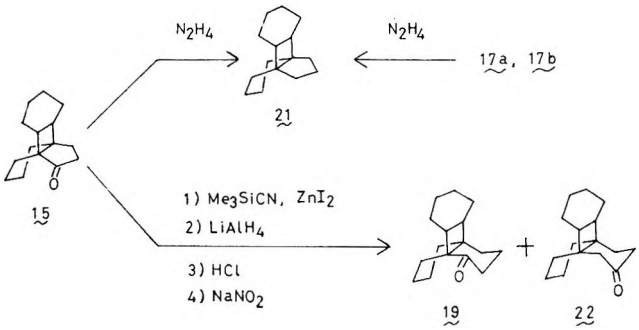


Chart III



cycloadduct along with some minor products. In addition, irradiation of **5** with a 10-fold excess of cyclohexene afforded two kinds of cycloadducts (**17a** and **17b**)[3] together with small amounts of keto olefin **18,** bicyclo[4.3.0]nonan-1-one, and 3,3′-bicyclohexenyl. On the other hand, with **6** only one cycloadduct (**19**) was given, though other products such as keto olefin **20,** bicyclo[4.4.0]decan-1-one, and 3,3′-bicyclohexenyl were formed in substantial amounts in this case (Chart II).

The configuration around the cyclobutane of **17a, 17b,** and **19** was established on the basis of the results of some reactions shown in Chart III. Since Wolff–Kishner reduction of **17a** and **17b** gave the same single hydrocarbon (**21**) in good yields, which was identical with the hydrocarbon obtained by reduction of cis-anti-trans cycloadduct **15** under similar condition,[7] **17a** and **17b** might be cis-syn-trans or cis-anti-trans adducts. Interestingly, the semicarbazone formation of **17b** proceeded quickly on treatment with semicarbazide hydrochloride and potassium acetate at room temperature, but with **17a** it took about 2 days. The above fact probably indicates that the carbonyl group of **17a** is sterically more hindered than that of **17b.**[8] Consequently, it may be reasonable to assume that **17a** has the cis-syn-trans configuration and **17b** the cis-anti-trans one.

Tiffeneau–Demjanov ring enlargement of **15** with retention of configuration around cyclobutane yielded two cyclohexanone derivatives (**22** and **19**) in a ratio of 4:1 in 26% overall yield. Since the minor ring expansion product **19** was identical with obtainable cycloadduct **19** (IR, GLC, and melting point), the structure of **19** should be assigned to cis-anti-trans.

The results in Chart I and II are summarized as follows. In the cases of both olefins with bicyclic enones **1** and **5,** where the five-membered ring fuses to the double bond of cyclopentenone and cyclohexenone, respectively, from two to four kinds of cycloadducts were always obtained in considerable amounts regardless of the ring size of the enone moieties, and therefore stereoselectivity in photocycloaddition is relatively low as well as in the case of stepwise cycloaddition of some cyclic enones to olefins reported previously.[1a,b] On the other hand, in the cases of **2** and **6,** where the six-membered ring fuses to the double bond of the monocyclic enones, the formation of cis-anti-trans cycloadducts, on the whole, proceeded stereoselectively.

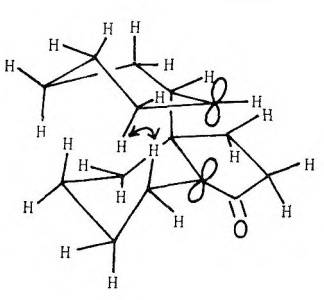
Table II. Phosphorescence Spectra and Lifetimes of Enones 5 and 6[a]

enone	phosphorescence, cm^{-1}	τ, ms
5	25 600 (origin)	39
	21 700 (max)	
	24 900 (10%)	
6	24 800 (origin)	490
	21 900 (max)	
	24 300 (10%)	
	23 100 (sh)	

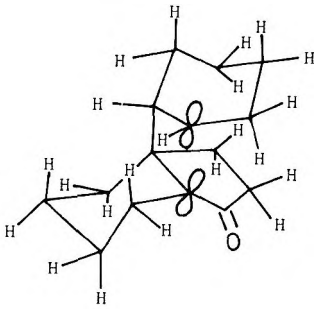
[a] Measured at 77 K in EPA matrix.

Concerning the mechanism of the present photocycloaddition, phosphorescence spectra and lifetimes of **5** and **6** were measured. It is evident from the results listed in Table II that there is no significant difference in the nature of the excited triplet states of **1**,[2] **2**,[2] **5**, and **6**.

Recently, it has been pointed out that in stepwise photocycloaddition reactions, steric effects in diradical intermediates are important in determining product stereochemistry.[9] In the present case, differences in stereoselectivity in photocycloaddition may be interpreted in terms of steric effects in 1,4-diradical intermediates such as **23** and **24**, assuming that



23



24

the initial bond formation occurs at the β position of the enones.[10] Namely, in the cases of **2** and **6**, having a cyclohexane ring fused to the double bond, significant nonbonded interaction between the axial hydrogens of the cyclohexane rings α to the radical centers may be produced in the intermediate **23**. Therefore, reversion to starting material rather than cyclization might occur predominantly from this intermediate.[12] In intermediate **24**, however, unfavorable nonbonded interaction between hydrogens may be reduced, and consequently cis-anti-trans cycloadducts are formed through **24** exclusively.[13] In the cases of **1** and **5**, having a cyclopentane ring fused to the double bond, there may be little difference in nonbonded hydrogen interaction between the two kinds of 1,4-diradical intermediates corresponding to **23** and **24** owing to the planarity of both cyclopentane rings, and therefore at least two isomeric cycloadducts may be formed indiscriminately.

Moreover, the higher stereoselectivity observed with cyclohexene than with *cis*- and *trans*-2-butene is attributable to the rigidity of the cyclohexene ring, which may make the unfavorable nonbonded interaction of allyl hydrogens larger in 1,4-diradical intermediates like **23**.

In conclusion, this work shows that five- and six-membered rings fused to the double bond of alicyclic enones have dramatically different effects on stereoselectivity in photocycloaddition to olefins. This difference is ascribed to the degree of nonbonded hydrogen interaction in 1,4-diradical intermediates and can be associated with the differing flexibility and rigidity of cyclohexane and cyclopentane rings.

Experimental Section[14]

General Irradiation Procedure. Enones **1** and **2** were prepared according to the procedures reported by Kulkarni and Dev[15] and Dev,[16] respectively, and enones **5** and **6** were prepared by the method of Hill and Conley.[17] Irradiation with cyclohexene was carried out as described previously,[2] and with *cis*- and *trans*-2-butene it was carried out with about a 20-fold excess of olefin in methylene chloride at −70 °C. The progress of the reaction was monitored by GLC, and irradiation was continued until the enones were almost consumed (>95%). After removal of olefin and solvent, the residue was distilled under reduced pressure. Products were analyzed by GLC (1 m × 3 mm columns: A, 10% PEG-20M; B, 5% SE-30; C, 10% FFAP; D, 10% DEGS) and isolated by preparative GLC. Yields were estimated based on reacted enones. [Yields and retention times on column C (temperature) are given for each adduct below.] The carbonyl absorptions in the IR spectra of cycloadducts **7a–d** and **8a,b** were at 1710 cm^{-1}, of **12a,b** and **17a** at 1680 cm^{-1}, and of **17b** and **19** at 1670 cm^{-1}. In the mass spectra, cycloadducts to 2-butene showed weak parent peaks with base peaks of molecular ions corresponding to the respective enone, and those to cyclohexene showed base peaks corresponding to the respective enone plus hydrogen. Cycloadducts **17a,b** and **19** showed only aliphatic protons in their NMR spectra. Keto olefins **18** and **20**, bicyclo[4.3.0]nonan-1-one, bicyclo[4.4.0]decan-1-one, and 3,3′-bicyclohexenyl were identified with authentic materials (IR and GLC). Authentic samples of **18** and **20** were prepared from **5** or **6** and 3-bromocyclohexene using the method of Stork et al.[18]

Irradiation of 1 with 2-Butene. Cis-syn-trans adduct **7a**, cis-anti-trans adduct **7b**, and two other cycloadducts (**7c** and **7d**) were obtained. Yields with *trans*-2-butene are given in parentheses. **7a** [23% (23%), 6.2 min (110 °C)]: NMR δ 0.98 (d, 3 H), 1.02 (d, 3 H), 1.20–2.80 (m, 12 H). Semicarbazone, mp 196–197 °C. Anal. Calcd for $C_{13}H_{21}ON_3$: C, 66.35; H, 9.00; N, 17.86. Found: C, 66.09; H, 9.02; N, 17.56. **7b** [34% (32%), 7.6 min (110 °C)]: NMR δ 0.92 (d, 3 H), 0.99 (d, 3 H), 1.20–2.80 (m, 12 H). Semicarbazone, mp 199–200 °C. Anal. Calcd for $C_{13}H_{21}ON_3$: C, 66.35; H, 9.00; N, 17.86. Found: C, 66.07; H, 8.99; N, 17.77. **7c** [3% (5%), 9.8 min (110 °C)]. **7d** [5% (2%), 13.9 min (110 °C)].

Irradiation of 2 with 2-Butene. Cis-anti-trans adduct **8a**, cycloadduct **8b**, and keto olefin **9** were obtained. **8a** [80% (84%), 7.8 min (130 °C)]: NMR δ 0.92 (d, 6 H), 1.00–2.50 (m, 14 H). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.91; H, 10.46. **8b** [3% (4%), 9.5 min (130 °C)]. **9** [6% (7%), 12.1 min (130 °C)]: IR 3060, 1720, 900 cm^{-1}; MS *m/e* 192 (M^+), 137; NMR δ 0.90 (d, 3 H), 1.00–2.80 (m, 14 H), 4.90–6.00 (m, 3 H).

Irradiation of 6 with 2-Butene. Cis-anti-trans adduct **12a**, cycloadduct **12b**, and keto olefin **13** were obtained. **12a** [42% (42%), 9.5 min (140 °C)]: NMR δ 0.82 (d, 3 H), 0.90 (d, 3 H), 1.10–2.60 (m, 16 H). Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.26; H, 10.91. **12b** [5% (4%), 12.6 min (140 °C)]: NMR δ 0.90 (d, 3 H), 1.00 (d, 3 H), 1.10–2.50 (m, 16 H). **13** [4% (5%), 15.6 min (140 °C)]: IR 3070, 1690, 900 cm^{-1}; MS *m/e* 206 (M^+), 151; NMR δ 0.92 (d, 3 H), 1.10–2.80 (m, 16 H), 4.80–6.00 (m, 3 H).

Irradiation of 5 with Cyclohexene. Cis-syn-trans adduct **17a**, cis-anti-trans adduct **17b**, keto olefin **18**, bicyclo[4.3.0]nonan-1-one (3%), and 3,3′-bicyclohexenyl were obtained. **17a** [24%, 10.5 min (160 °C)]. Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.33; H, 10.18. Upon treatment with semicarbazide hydrochloride and potassium acetate in absolute ethanol at room temperature, **17a** afforded semicarbazone after about 2 days, mp 220–222 °C. Anal. Calcd for $C_{16}H_{25}ON_3$: C, 69.78; H, 9.15; N, 15.26. Found: C, 69.54; H, 9.24; N, 15.33.

17b [43%, 13.2 min (160 °C)], mp 97–98 °C. Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.25; H, 10.14. **17b** quickly gave its semicarbazone under similar conditions as above, mp 209–210 °C. Anal. Calcd for $C_{16}H_{25}ON_3$: C, 69.78; H, 9.15; N, 15.26. Found: C, 69.79; H, 9.19; N, 15.36.

18 [4%, 15.2 min (160 °C)]: IR 3030, 1685, 710 cm^{-1}; MS *m/e* 218 (M^+), 138; NMR δ 0.95–2.70 (m, 20 H), 5.10–5.90 (m, 2 H). Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.25; H, 10.35.

Irradiation of 6 with Cyclohexene. Cis-anti-trans adduct **19**, keto olefin **20**, bicyclo[4.4.0]decan-1-one (18%), and 3,3′-bicyclohexenyl were obtained. **19** [12%, 10.0 min (180 °C)] mp 105–106 °C. Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.77; H, 10.54. **20** [13%, 13.8 min (180 °C)]: IR 3030, 1690, 710 cm^{-1}; MS *m/e* 232 (M^+), 152; NMR δ 1.00–2.70 (m, 22 H), 4.90–5.80 (m, 2 H). Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.45; H, 10.27.

Wolff–Kishner Reduction of 17a and 17b. **17a** (0.268 g, 1.23 mmol) and 1.4 g of potassium hydroxide in 20 mL of 85% hydrazine hydrate and 10 mL of diethylene glycol were heated at 150 °C for 3 h. Excess hydrazine hydrate was distilled off, and the mixture was heated at 220 °C for 4 h. After cooling, the mixture was neutralized with dilute hydrochloric acid and extracted with ether. Evaporation of the ether and distillation under reduced pressure gave 0.145 g (58%) of **21**. Reduction of **17b** under similar conditions gave the same hydrocarbon **21** in 70% yield, which was identical with the sample prepared by reduction of **15**[7] (IR and GLC).

Ring Enlargement of 15. To a mixture of 1.0 g (5.0 mmol) of **15** and catalytic amounts of zinc iodide was added dropwise 0.59 g (6.0 mmol) of trimethylsilyl cyanide,[19] and the mixture was stirred at room temperature for 2 h and filtered. The filter was rinsed with dry ether, and the combined filtrate was evaporated to give 1.37 g (86%) of cyanotrimethylsilyloxy compound: IR 2210, 1240, 1100, 830 cm^{-1}.

A 1.37-g (4.31 mmol) amount of the above cyanide in 10 mL of ether was added dropwise to a suspension of 0.25 g (6.6 mmol) of lithium aluminum hydride in 10 mL of ether, and the mixture was refluxed for 2 h. Excess hydride was decomposed by water, and dilute sodium hydroxide solution was added and then filtered. The filtrate was extracted with ether, and the organic layer was washed with saturated sodium chloride solution and dried (Na_2SO_4). After filtration, gaseous hydrogen chloride was bubbled into the ethereal solution for 2 h. The white solid that formed was filtered, washed with ether, and dried to afford 0.775 g (62%) of the hydrochloride salt of the aminomethylhydroxy compound: IR 3350 cm^{-1}.

To a solution of 0.775 g (2.69 mmol) of the above amine hydrochloride salt and 0.232 g (2.89 mmol) of sodium acetate in 25 mL of acetic acid and 10 mL of water was added dropwise 0.186 g (2.69 mmol) of sodium nitrite in 5 mL of water, and the mixture was stirred at room temperature for 2 h. The mixture was poured into water and extracted with ether. The organic layer was washed with dilute sodium bicarbonate solution and saturated sodium chloride solution and then dried (Na_2SO_4). The ether was evaporated and the residue distilled under reduced pressure to afford 0.274 g (44%; 26% from **15**) of a mixture of the two ketones **19** and **22** in a ratio of 1:4. **19** thus prepared was identical with the sample obtained by photocycloaddition of **6** to cyclohexene (IR, GLC, and melting point). **22:** mp 74–75 °C; IR 1690 cm^{-1}; MS *m/e* 232 (M^+), 150; NMR δ 1.00–2.50 (m). Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.57; H, 10.46.

Registry No.—**1,** 10515-92-1; **2,** 22118-00-9; **5,** 22118-01-0; **6,** 18631-96-4; *cis-syn-cis*-**7,** 67452-38-4; *cis-anti-cis*-**7,** 67504-81-8; **7a** semicarbazone, 67452-96-4; **7b** semicarbazone, 67504-80-7; **8b,** 67452-39-5; **9,** 67452-40-8; **12b,** 67452-41-9; **13,** 67452-87-3; **15,** 67504-49-8; **5** cyanotrimethylsilyloxy derivative, 67452-94-2; **15** aminomethylhydroxy HCl derivative, 67452-95-3; **17a,** 67452-88-4; **17a** semicarbazone, 67452-89-5; **17b,** 67504-47-6; **17b** semicarbazone, 67504-48-7; **18,** 67452-90-8; **19,** 67452-91-9; **20,** 67452-92-0; **21,** 63305-46-4; **22,** 67452-93-1; *cis*-2-butene, 590-18-1; *trans*-2-butene, 624-64-6; cyclohexene, 110-83-8.

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(3) Compound numbers a–d were assigned in order of GLC retention times on column C (see Experimental Section) and do not refer to the stereochemistry.

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(5) This result is almost consistent with that reported by Cargill et al.[1c]

(6) *S* values of methyl protons of **7a, 7b,** and **8b** are slightly larger than those of **10a, 10b,** and **12a,** presumably because of the difference in coordination distance between Eu^{3+} and the carbonyl groups of cyclopentanone and cyclohexanone.

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(8) Similarly, cis-anti-trans adduct **7b** readily gave its semicarbazone, but cis-syn-trans adduct **7a** gave it after 3 days.

(9) (a) F. D. Lewis, R. H. Hirsh, P. M. Roach, and D. E. Johnson, *J. Am. Chem. Soc.*, **98,** 8438 (1976); (b) A. J. Wexler, J. A. Hyatt, P. W. Raynolds, C. Cottrell, and J. S. Swenton, *ibid.*, **100,** 512 (1978).

(10) The mechanistic pathway involving the initial bond formation at the β position of the enones is favored in the photocycloaddition of 2-cyclopentenone to 1,2-dichloroethylene[11] and enone **5** to 2-butene.[1c]

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(13) As for the selective cyclization, in the case of cycloaddition to cyclohexene, to form cis-anti-trans adducts which seem to be less favorable than the corresponding cis-syn-cis adducts in the thermodynamic sense, it may be reasonable to assume that the ring closure to give the observed adducts is rapid, though the relative thermodynamic stability of stereoisomers of these tetracyclic compounds is uncertain at present.

(14) Melting points are uncorrected. Infrared spectra were recorded using a JASCO IR-G spectrometer. NMR spectra were obtained on a JEOL JNM-PS-100 spectrometer using CCl_4 as a solvent and Me_4Si as an internal standard. Mass spectra were measured with a Hitachi RMU-6E spectrometer. Analytical GLC was carried out on a Hitachi 163 gas chromatograph, and preparative GLC separation was conducted on a Varian Aerograph 90-P gas chromatograph. Phosphorescence spectra were recorded on a Hitachi MPF-3 spectrometer.

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Preparation and Rearrangement of Bridgehead Phosphorus Ylides and Their Derivatives in the Homocubane Ring System

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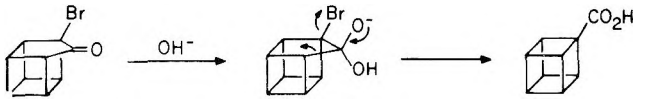
Received May 16, 1978

Experiments are described in which carbanions are generated at the bridgeheads adjacent to phosphorus in phosphonium salt **2** and in phosphine oxide **1**. These experiments were undertaken to find ways to make the intermediates in a proposed scheme (Scheme III) for the synthesis of derivatives of cubane. When attempts are made to prepare the conjugate base of **2** using sodium hexamethyldisilylamide in tetrahydrofuran (THF), the ylide apparently rearranges rapidly to a *syn*-tricyclooctadienyldiphenylphosphine (**5**), a novel example of the electrocyclic process summarized as eq 5. The conversion constitutes a preparation of the tricyclooctadienyl ring system. On oxidation with hydrogen peroxide, **5** gives its phosphine oxide (**21**), but at −2 °C this equilibrates with an isomer (**22**). At 138 °C these isomers rearrange to give **7**. Similarly at 74.5 °C, **5** isomerizes to cyclooctatetraenyldiphenylphosphine (**6**), but shows no evidence of giving an isomer analogous to **22**. Unlike the carbanion **3** derived from **2**, lithiated phosphine oxide **1** is stable in solution at ambient temperature. This lithium derivative can be made from **1** and phenyllithium in THF at room temperature, while at −78 °C the same reagents give **8**. D_2O, CH_3I, and $(C_6H_5S)_2$ react with the lithiated material to introduce substituents adjacent to phosphorus. The thiophenyl substituent can be oxidized to the sulfone (**16**), and this with sodium hexamethyldisilylamide gives **18**. With phenyllithium **16** gives the analogue **20**. These last rearrangements are novel, and since **1** does not undergo them, they reflect the leaving ability of sulfone anions.

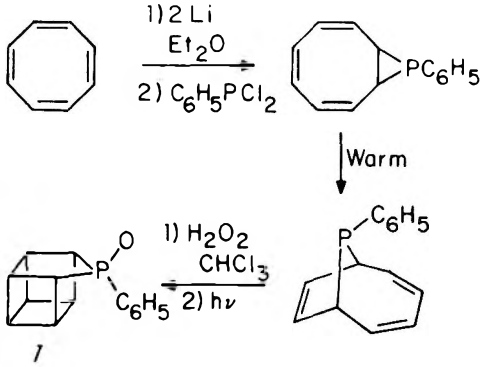
The cubic hydrocarbon C_8H_8, known as cubane, was first synthesized by Eaton and Cole in 1964.[1] Shortly afterwards a related synthesis was reported by Barborek, Watts, and Pettit,[2] and additional ways to arrive at intermediate molecules on the original routes were found by Chin, Cuts, and Masamune[3] and by Eaton and Cole.[4] These syntheses, and all of those developed since for derivatives of cubane,[5] employ as a key step the Favorskii rearrangement[6] of an α-bromohomocubanone (Scheme I), and despite difficulties experienced in some laboratories,[5f,c] although not in others,[5f,h] and despite the length of the synthesis, the original route of Eaton and Cole[1] remains the most effective. Alternative syntheses have not been reported and seem to have been sought only rarely.[7]

The availability of phenylphosphahomocubane oxide from the cyclooctatetraenyl dianion (Scheme II)[8-10] suggested that another route to cubane might be found if a phosphorus analogue of the Favorskii rearrangement could be discovered (Scheme III), and the research described here was toward this goal. A sulfur analogue of such arrangements, the Ramberg–Bäcklund rearrangement,[11] has been applied effectively in many syntheses, but because it proceeds by way of an episulfone and fails when the intermediate three-membered ring is highly strained, path B in Scheme III is unlikely. Path A,

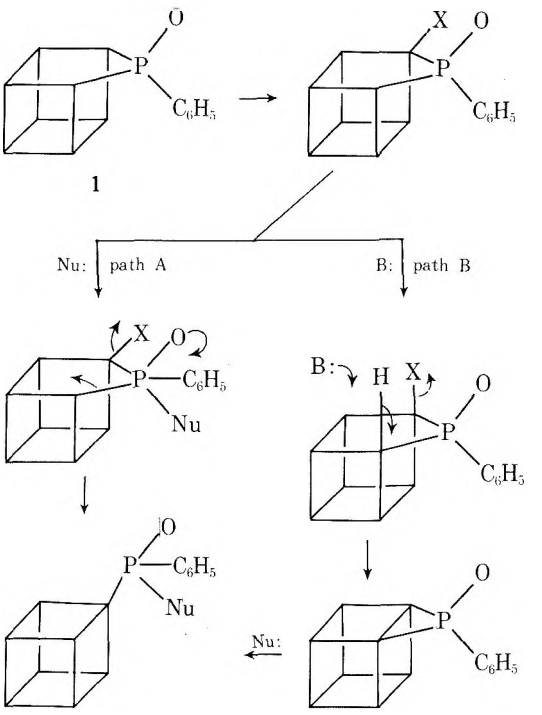
Scheme I



Scheme II



Scheme III



however, seems possible, for although the ring contraction is unprecedented, a number of examples are known of alkaline hydrolyses of α-halo- and α-unsaturated phosphonium salts in which nucleophiles attach to phosphorus and a carbon atom migrates to the α position.[12,13]

The experiments described below show how substituents can be introduced into molecule **1** on the ring carbon next to the phosphorus atom and how derivatives of **1** when combined with bases rearrange.

Results

A. Reactions of Diphenylphosphoniahomocubane Bromide (2). Brominating the ylide **3** derived from the phosphonium salt **2** (Scheme IV) seems a possible way to introduce a halogen at the ring carbon next to phosphorus in the phosphahomocubane ring system, and it seems to be a good way considering the ease with which the salt **2** can be prepared.[10,14] However, although simple phosphonium salts upon

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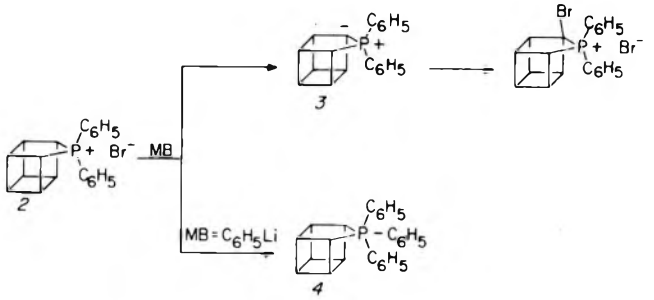
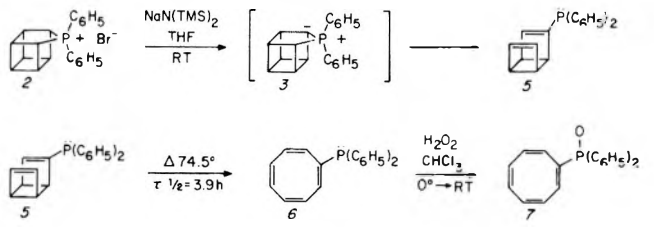
Scheme IV



Scheme V



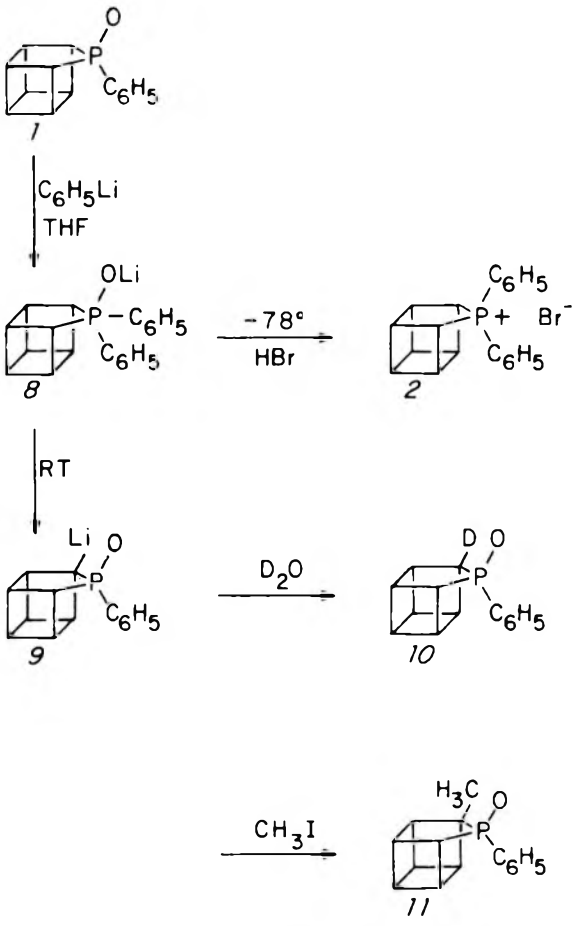
reaction with phenyllithium are generally transformed into their ylide derivatives, the phosphonium salt **2** with this reagent gives the triphenylphosphorane **4** instead.[10,14] Thus, a reagent had to be used that would abstract a proton rather than react irreversibly with the phosphorus, and because of its effectiveness in enolizing ketones,[15] sodium hexamethyldisilylamide, $NaN[Si(CH_3)_3]_2$, was tried.

Surprisingly, when the salt **2** was combined with this reagent in tetrahydrofuran (THF) at room temperature, instead of giving the ylide **3** it gave in good yield (38–74%) the novel *syn*-tricyclooctadienyldiphenylphosphine **5** (Scheme V). As the phosphine probably arises by the expected ylide **3** fragmenting, attempts were made to suppress the fragmentation by lowering the reaction temperature, but these experiments failed, for at 0 °C the formation of the ylide was suppressed also and only the starting salt **2** was obtained when the reaction mixture was quenched with deuterium bromide. When in place of sodium hexamethyldisilylamide two other bases were used that are also noted for their ability to abstract protons rather than bring about other reactions, the results were similar. Lithium 2,2,6,6-tetramethylpiperidide[16] after 3 h at ambient temperature gave a 48% yield of **5** and 26% recovered **2**, and lithium diisopropylamide[17] at either ambient temperature or 0 °C gave **5** completely and at −20 °C only starting salt **2**. Other bases tried[18] brought about either no reaction or partially hydrolyzed salt **2** to the phosphine oxide **1**.

The tricyclooctadienyldiphenylphosphine structure **5** was assigned to the product of the reactions above on the basis of its proton nuclear magnetic resonance (^1H NMR) spectrum (described in the Experimental Section and also in part in this section, below) and because heating converts it into a material identified by its spectra as cyclooctatetraenyldiphenylphosphine (**6**). The half-life for the thermal conversion of **5** to **6** in benzene at 74.5 °C (the kinetics are first order) is 3.9 h, much like that for the conversion of the parent *syn*-tricyclooctadiene to cyclooctatetraene.[19] Phosphine **6** upon oxidation in chloroform with 30% H_2O_2 gives its phosphine oxide (**7**), but the analogous oxidation of **5** is more interesting, and this reaction and other aspects of the chemistry of **5** are discussed further below.

B. Reactions of *P*-Phenylphosphahomocubane Oxide (1). It seems likely that for the conjugate base of phosphine oxide **1** to fragment should be more difficult than for the phosphonium salt **2**, and indeed when **1** is combined in THF with phenyllithium at ambient temperature and the reaction mixture is quenched 20 min later with deuterium bromide in

Scheme VI



deuterated water the phosphine oxide is recovered, but containing one deuterium atom (Scheme VI). Thus, the lithiated phosphine oxide **9**, unlike the ylide **3**, is stable in THF at ambient temperature, but that it forms at all in this reaction is remarkable for when the reaction of phosphine oxide **1** in THF with phenyllithium is conducted at −78 °C and quenched with HBr it gives instead the diphenylphosphonium salt **2**.[10,14] This must mean that at room temperature the oxyphosphorane **8** extrudes phenyllithium and that phenyllithium reacts with **1** quickly at phosphorus but gradually and irreversibly at the α hydrogen. The reaction of triphenylphosphine oxide with methyllithium to yield lithiomethyldiphenylphosphine oxide provides a precedent,[20] although the stabilization of **8** relative to **1** and phenyllithium that should be consequent on the constraints of the ring system[10] might have prevented **8** from following this course.

Further evidence that **9** is formed from **1** and phenyllithium at room temperature is provided by the observation that quenching the reaction mixture with methyl iodide introduces a methyl group into **1** on the carbon next to the phosphorus.

However, procedures effective for other lithiated phosphine oxides could not be found that could be used to convert **9** into an α-halophosphine oxide, although many examples of lithiated phosphine oxides reacting with electrophiles other than halogens, such as aldehydes, ketones, and carbon dioxide, have been published.[21–23] Accordingly, various ways were studied to combine solutions of **9** with bromine by adding the former to the latter or the latter to the former, but all such experiments gave intractable products. Experiments were done with other halogenating agents, including iodine, iodobenzene, phenyliodine dichloride, 1,2-dibromoethane, *N*-bromosuccinimide, *N*-chlorosuccinimide, and 2,2,5-trimethyl-5-bromo-1,3-dioxane-4,6-dione, some of which convert lithiated sulfones to their α-halosulfone derivatives,[24] but they

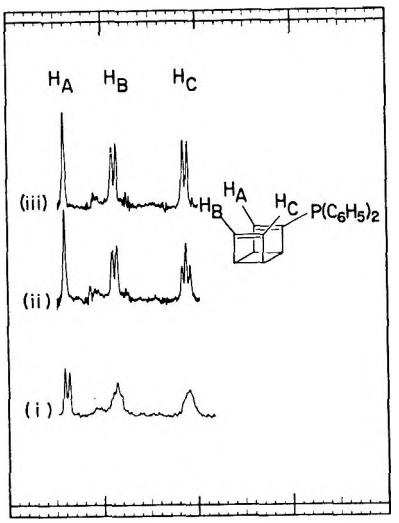
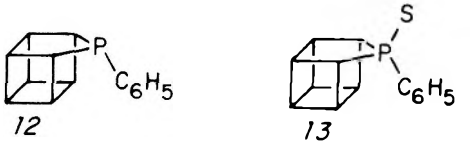


Figure 1. 100 MHz ^1H NMR spectrum of **5** in $CDCl_3$. Only the vinyl proton resonances are displayed: (i) undecoupled; (ii) hydrogens on saturated carbons decoupled; (iii) both hydrogens on saturated carbons and ^{31}P decoupled.

either yielded recovered **1** after aqueous workup or gave intractable materials. No α-halophosphine oxide could be found. Experiments were tried in which in place of the phosphine oxide **1** the corresponding phosphine sulfide **13**, prepared from

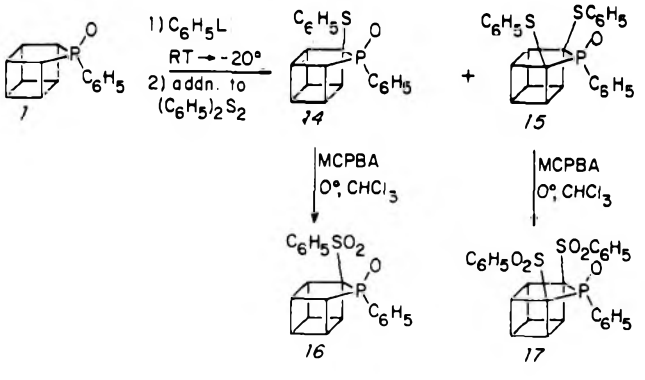


12[9,10] and elemental sulfur, was used, but reaction with phenyllithium in THF followed by bromine at −78 °C also gave only tars. Experiments were tried with phosphine **12** itself plus *N*-chlorosuccinimide or sulfuryl chloride, on the basis of analogy to procedures known to chlorinate sulfides,[25] but these gave mainly phosphine oxide **1**, the product of reaction at phosphorus and not at the α carbon.

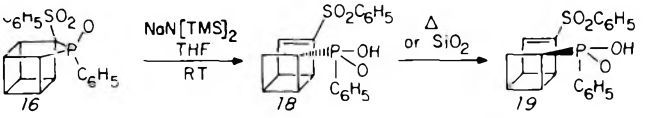
Accordingly, the possibility was considered of introducing into the ring system a leaving group other than a halogen, and as summarized in Scheme VII this could be accomplished by attaching a sulfide group and then oxidizing it. Thus, adding a cold solution of **9** in THF to a solution of diphenyl disulfide in THF at 0 °C gave in up to 68% yield the sulfide **14** together with up to 5% of the disulfide **15**; *m*-chloroperbenzoic acid oxidizes these to their sulfone derivatives (**16** and **17**). Experiments using trifluoromethyl disulfide[26] in place of diphenyl disulfide were also tried, but failed.

Attempts were then made to carry through with sulfone **16** the transformation to a substituted cubane envisioned in Scheme III. However, with sodium hexamethyldisilylamide

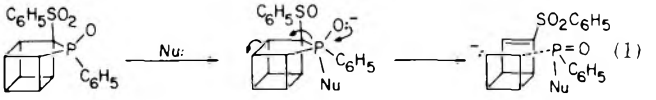
Scheme VII



in THF at ambient temperature, **16** gave a product that still contained the sulfone group and exhibited a single olefin proton resonance. On the basis of this and other spectroscopic data it was assigned structure **19**. When the reaction mixture



was worked up so as to avoid overheating or excessive contact with silica gel, the product isolated was not **19** but a similar material, seemingly **18**. [The two are distinguished by their different mobilities on thin-layer chromatography and by their different olefin proton nuclear magnetic resonance frequencies (δ 6.04 for **18** and δ 5.86 for **19** in CD_3CN).] The formation of these phosphinic acids must reflect the facility with which oxyphosphoranes extrude sulfone anions and the facility with which carbanions cleave adjacent carbon–carbon bonds to relieve ring strain (eq 1). What the nucleophile is that



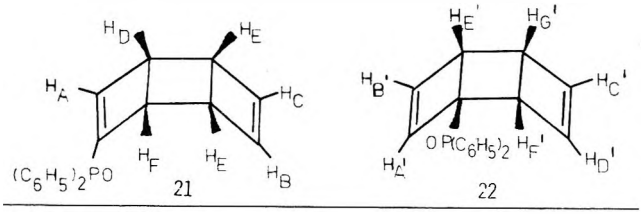
initiates this transformation is, however, uncertain, for although the sulfone **16** had been dried at 56 °C and 0.1 mm pressure for 24–48 h or at 100 °C and 0.1 mm pressure for 24 h, adventitious water might still have been present to form hydroxide anions.

Other nucleophiles bring about similar transformations. Thus, phenyllithium in THF at −78 °C followed by HBr, which might convert **16** to its diphenylphosphonium salt if the oxyphosphorane were stable at −78 °C, instead gives (in 32% yield) the diphenylphosphine oxide **20**, the analogue of **18** or **19** in which the OH on phosphorus is replaced by phenyl. The structure was assigned the phosphine oxide on the basis of its spectra, but whether the stereoisomer characterized was the analogue of **18** or **19** was not analyzed.

C. Chemistry of 5. The preparation of **5** was discussed above, but other aspects of its chemistry are considered here. A portion of the proton nuclear magnetic resonance spectrum, which was used as part of the evidence to assign its structure, is displayed in Figure 1. The figure shows that irradiation at the resonance frequencies of the protons on the saturated carbons simplifies the resonances of the protons on olefinic carbons to a singlet, a doublet, and a triplet. (The coupling constants are 2 Hz.) Further decoupling at the phosphorus resonance frequency collapses the triplet to a 2-Hz doublet. Accordingly, we assign the pair of doublets to H_B and H_C (2 Hz is the magnitude of the proton–proton coupling in other cyclobutenes),[27] but this means that while H_A is not coupled to the phosphorus, either H_B or H_C is.[28]

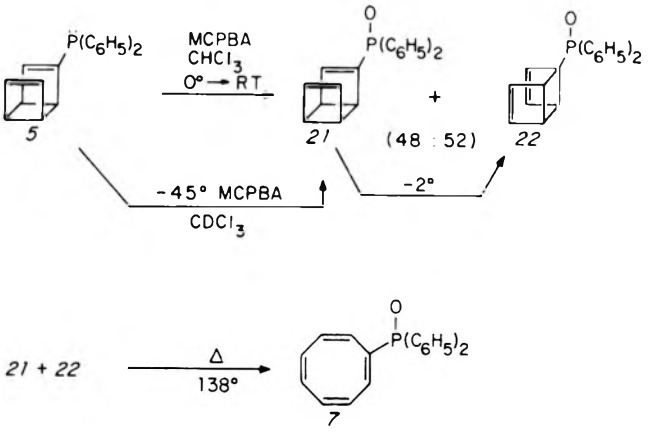
Combining phosphine **5** in chloroform with 30% aqueous hydrogen peroxide at 0 °C oxidizes it to the phosphine oxide, but the ^1H NMR spectrum (Figure 2) of the product, a white crystalline material, mp 109–109.5 °C, homogeneous according to the thin-layer chromatography, is unusually complex. With the help of proton decoupling, the shift reagent tris(dipivaloylmethanato)europium(III), and a 100 MHz ^1H NMR spectrometer, this spectrum could be analyzed (the chemical shifts and coupling constants are collected in Table I) as that of a 48:52 mixture of **21** and **22**, molecules related by a Cope rearrangement (Scheme VIII).[29] Thus, presumably the oxidation initially gives **21**, but this must transform easily into **22**. This last hypothesis is demonstrable for the Cope rearrangement should be suppressed at temperatures that are sufficiently low, and in fact when the oxidation is effected at −45 °C in $CDCl_3$ with *m*-chloroperbenzoic acid, only phosphine oxide **21** is produced. But when the solution of this

Table I. Chemical Shifts (in $CDCl_3$) and Coupling Constants (Absolute Values) for 21 and 22



proton	chemical shift, δ	coupling constant, Hz	proton	chemical shift, δ	coupling constant, Hz
H_A	6.77	J_{PA} = 3.0	$H_{A'}$, $H_{B'}$	6.13–5.96	$J_{PA'}$ = 4–6
H_C	5.91	J_{AD} = 2.0	$H_{C'}$, H_D		$J_{PE'}$ = 11.0
H_B	5.30	J_{BC} = 3.0	$H_{E'}$	3.64	$J_{PF'}$ = 5.0
H_D	3.46	J_{BE} = 2.0	$H_{F'}$	3.48	$J_{A'B'}$ = 2.0
H_E	3.21	J_{CE} = 2.0	$H_{G'}$	3.27	$J_{B'E'}$ = 2.0
					$J_{C'D'}$ = 2.0
					$J_{C'G'}$ = 2.0
					$J_{D'F'}$ = 2.0
					$J_{E'G'}$ = 3.0
					$J_{F'G'}$ = 8.0

Scheme VIII



phosphine oxide is then warmed to −2 °C for 14 min, the transformation takes place to give the characteristic mixture (presumably an equilibrium mixture) of **21** and **22**. When this is heated further in tetrachloroethylene, the rate of interconversion does not increase enough to cause the ^1H NMR spectra to coalesce, but the spectra are slowly replaced by that of cyclooctatetraenyldiphenylphosphine oxide (**7**). This last isomerization is analogous to the thermal conversion of **5** into **6** (see above), except that no Cope rearrangement product is observed by ^1H NMR during that reaction.

The photochemistry of **5**, **21**, and **22** was also explored to see whether ring closures to derivatives of phosphahomocubane would take place. However, instead of rings closing, rings already present opened. Thus, the mixture of oxides **21** and **22** in CD_2Cl_2 when irradiated for 1.0 h with ultraviolet filtered through Vycor (λ > 254 mm) gave cyclooctatetraenyldiphenylphosphine oxide (**7**), and when irradiated for 18.3 h in the presence of Michler's ketone it gave, according to ^1H NMR analysis, a mixture of 66 parts of **7** and 34 parts of starting materials. Phosphine **5** behaved similarly; upon irradiation for 5 h in CD_2Cl_2 with light of 254 nm in wavelength, it gave a mixture of 72 parts of **6** and 28 parts of **5**.

Discussion

The intermediate **3** that must form when strong bases transform **2** into **5** is a rare example of a bridgehead phosphorus ylide, and accordingly it is not known how typical its behavior is. However, the ylide **23**, the only other example known,[10,30] does not fragment so easily (eq 2), and the fragmentation observed for **2** is reminiscent of that which homocubylcarbinyl anions undergo (eq 3)[31] presumably to relieve the ring strain. It is therefore plausible that **3** gives **24** (eq 4), and even more so that **24** gives **5** as phosphines are eliminated by carbanions generated on carbons adjacent to carbon–phosphonium bonds.[32] However, to the extent that **24** violates Bredt's rule, its formation is likely to be avoided, and the transformation in eq 4 would then be concerted. Thus, the reaction would be an example of a novel electrocyclic process, summarized in its essential form in eq 5.[33]

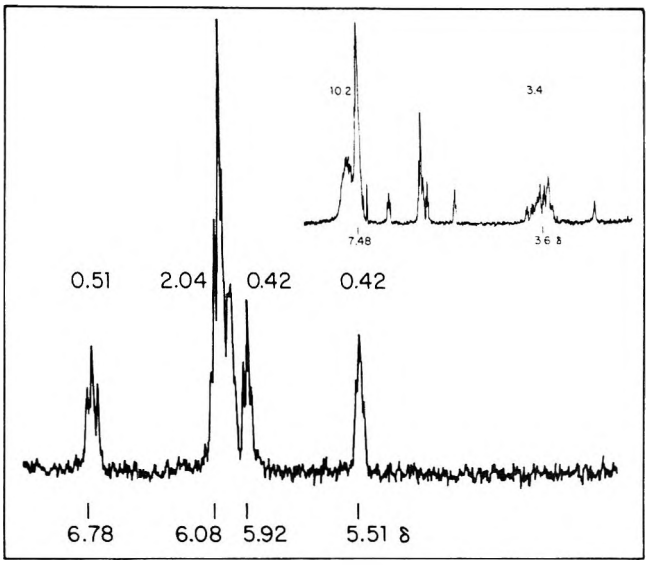
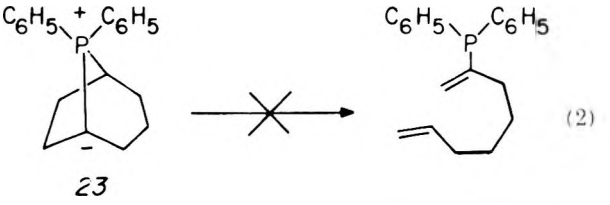
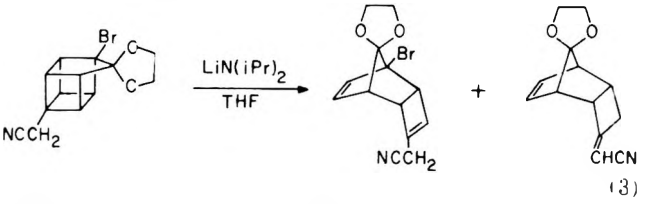
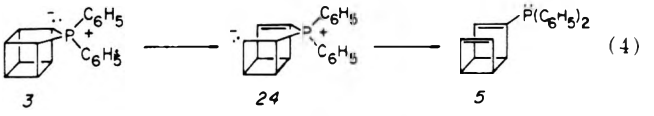
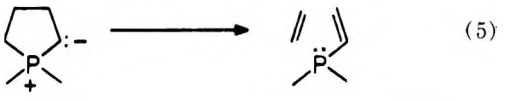


Figure 2. ^1H NMR spectrum (100 MHz) of a mixture of **21** and **22** in $CDCl_3$. Chemical shifts are displayed below and intensities above the resonances. The full spectrum is shown in the insert.







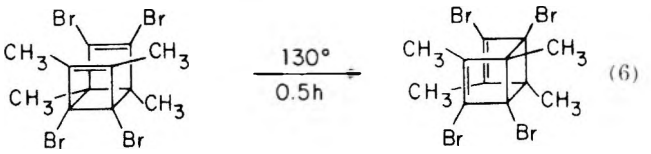


It is interesting that the phosphine oxide analogue of **3**, molecule **9**, does not undergo the analogous fragmentation, presumably because the phosphine oxide does not provide as good as leaving group as the phosphonium salt.

There is also an interesting contrast between the behavior of the intermediate oxyphosphoranes in eq 1 and the parent oxyphosphorane (**8**). The fragmentation in eq 1 undoubtedly reflects the stability of the sulfone anion and the drive to relieve ring strain, exemplified by eq 3.[34] However, the parent (**8**), which also could fragment to relieve ring strain, does not, and this must mean that this relief provides insufficient drive

for the ring carbon–phosphorus bond to cleave. Thus, **8**, as is usual,[35] eliminates phenyllithium rather than alkyllithium, but when the sulfone substituent is present the basicity of the carbanion is decreased,[36] facilitating elimination of the latter. It must be the formation of the ring carbanion that causes the carbon–carbon bond to cleave as summarized in eq 1.

The facility of the Cope rearrangement in converting **21** into **22** (the reaction takes place in minutes at −2 °C) contrasts with the greater difficulty of an analogous transformation (eq 6),[37] which does not take place during recrystallization from



(6)

acetone but does on heating to 135 °C. That phosphine **5** does not seem to undergo the reaction possibly means that it is more stable than its Cope rearrangement product, just as bullvalenes with substituents on their double bonds are almost always more stable than their Cope rearrangement products.[38] Thus, the phosphine oxide **21** might have a driving force for rearrangement that the phosphine **5** does not, and this might be an electronic force driving electronegative substituents to bond with orbitals having little s character.

Experimental Section

Proton nuclear magnetic resonance (^{1}H NMR) spectra were determined with Varian A-60A, T60, or HA-100 spectrometers [tetramethylsilane (Me_4Si) as an internal standard]; infrared (IR) spectra with Perkin-Elmer 137, 727B, and 621 spectrophotometers (calibrated using polystyrene film); ultraviolet (UV) spectra with Cary Model 15 or 17 spectrophotometers; and mass spectra with a Jeol JMS-07 electron impact spectrometer. The mass spectral data listed are the intensities as a percentage of the base peak of the peaks due to the parent ions and of those fragment ions whose abundance is greater than a stated fraction of the base peak. Elemental analyses were performed by Schwartzkopf Microanalytical Laboratory, Woodside, N.Y. Melting points, determined on a Thomas-Hoover melting point apparatus, are uncorrected.

Just prior to its use, tetrahydrofuran (THF) was dried over potassium hydroxide pellets and distilled from $LiAlH_4$ into Linde type 5A molecular sieves. Phenyllithium was obtained from Alfa Inorganics, Beverly, Mass., as a 2.2–2.3 N solution in 70:30 benzene–ether. Dry solvents and reagents sensitive to air or moisture were transferred by syringe.

***P,P*-Diphenyl-*syn*-tricyclo[4.2.0.0^{2,5}]octa-3,7-dien-3-ylphosphine (5).** To a flame-dried, three-neck, N_2-flushed, 50-mL round-bottom flask equipped with a serum inlet, N_2 inlet, stopper, and magnetic stirrer was added 660 mg (1.78 mmol) of *P,P*-diphenylphosphoniahomocubane bromide[10] and 15 mL of dry THF. A solution of 291 mg of sodium hexamethyldisilylamide (1.59 mmol, 1.15 equiv) in dry THF was added by syringe to the slurry and stirred at ambient temperature. The slurry turned a salmon color after 15 min and was allowed to stir for 2.0 h before it was quenched with 3 mL of 24% HBr. Ether (100 mL) was added, and the organic solution was washed successively with 30 mL of 10% HCl, H_2O, and brine and dried over $MgSO_4$. Filtration and removal of solvent gave 330 mg of a yellow oil, which was chromatographed on a 2 × 50 cm column of 35 g of SiO_2 eluting with CH_2Cl_2. A yellow, foul-smelling oil was isolated (217 mg, 69%) and identified as *P,P*-diphenyl-*syn*-tricyclo[4.2.0.0^{2,5}]octa-3,7-dien-3-ylphosphine: ^{1}H NMR (CCl_4) δ 7.38 (m, 10.27 H), 6.24 (d, J = 2.0 Hz, 0.75 H), 5.96 (t, J = 2.0 Hz, 1.04 H), 5.62 (m, 0.81 H), 3.14 (m, 3.96 H); IR ($CHCl_3$) 3074 (w), 3058 (m), 3021 (s), 3008 (m), 1964 (w), 1888 (w), 1812 (w), 1770 (w), 1660 (w), 1584 (w), 1540 (w), 1478 (s), 1442 (s), 1298 (m), 1274 (m), 1244 (m), 1162 (w), 1146 (w), 1094 (w), 1070 (w), 1026 (w), 1000 (w), 954 (w), 914 (w), 838 (w), 820 (m), 692 (s), 662 (m) cm^{-1}; mass spectrum (75 V, peaks ≥ 10%), *m/e* 289 (M$^+$ + 1, 10), 288 (M$^+$, 46), 287 (63), 281 (24), 211 (24), 210 (41), 209 (21), 207 (18), 185 (19), 183 (100), 179 (37), 178 (67), 167 (10), 165 (16), 152 (16), 147 (23), 133 (28), 115 (16), 109 (10), 108 (52), 107 (46), 104 (10), 103 (78), 102 (23), 78 (18), 77 (60), 73 (50), 63 (11), 51 (45), 50 (15), 39 (19); UV (95% EtOH) λ_{max} 251 nm (ϵ 7830).

A second product eluted from the column was a yellow oil (13 mg), later identified as the equilibrium mixture of phosphine oxides **21** and **22** (3%).

Cyclooctatetraenyldiphenylphosphine (6). To a flame-dried, N_2-flushed, 100-mL round-bottom flask equipped with a condenser and a N_2 inlet was added a solution of 285 mg of *P,P*-diphenyl-*syn*-tricyclo[4.2.0.0^{2,5}]octa-3,7-dien-3-ylphosphine (0.99 mmol) in 50 mL of dry benzene. Simultaneously a ^{1}H NMR tube containing 28 mg of the phosphine (0.10 mmol), 1 drop of Me_4Si, 1 drop of CH_2Cl_2 as an internal standard, and benzene-d_6 (total volume = 0.5 mL) was sealed at 0.05 mm pressure. Both the flask and the tube were placed in an insulated oil bath maintained at 74.5 ± 0.2 °C, and the reaction was monitored by observing in the ^{1}H NMR spectrum the disappearance of the resonances of protons on saturated carbons. After 20.0 h the ^{1}H NMR sample was completely isomerized, but heating was continued for an additional 18 h. The samples were combined and the solvents evaporated at 157 °C (0.07 mm), giving 312 mg of bright yellow, viscous, foul-smelling oil (99%). The kinetic data showed the isomerization to be first order, with k = 0.41 h^{-1} ($\tau_{1/2}$ = 3.9 h): ^{1}H NMR ($CDCl_3$) δ 7.45 (m, 10.06 H), 5.82 (s, 7.00 H); IR ($CHCl_3$) 3140 (w), 3083 (m), 3059 (m), 3006 (s), 2973 (m), 2928 (w), 2852 (w), 1954 (w), 1885 (w), 1813 (w), 1750 (w), 1621 (w), 1600 (w), 1585 (w), 1480 (s), 1431 (s), 1365 (w), 1301 (w), 1130 (m), 1091 (m), 1070 (w), 1051 (w), 1022 (w), 995 (w), 865 (w), 630 (m) cm^{-1}; mass spectrum (75 V, peaks ≥ 10%), *m/e* 289 (M$^+$ + 1, 10), 288 (M$^+$, 51), 287 (29), 211 (25), 210 (46), 209 (13), 185 (15), 184 (12), 183 (72), 179 (32), 178 (56), 167 (10), 165 (15), 152 (15), 133 (28), 115 (14), 109 (10), 108 (46), 107 (45), 104 (11), 103 (100), 102 (32), 91 (13), 81 (10), 78 (22), 77 (92), 76 (11), 63 (15), 57 (16), 55 (14), 52 (11), 51 (66), 50 (19), 43 (14), 41 (14), 39 (28), 28 (19), 27 (17); UV (95% EtOH) λ_{max} 253 sh nm (ϵ 12 500).

Cyclooctatetraenyldiphenylphosphine Oxide (7). To a solution of 300 mg of cyclooctatetraenyldiphenylphosphine (1.04 mmol) in 25 mL of $CHCl_3$ at 0 °C contained in a three-neck, 100-mL round-bottom flask equipped with an addition funnel, condenser, stopper, and magnetic stirrer was added 10 mL of 30% H_2O_2 in drops from the addition funnel during 0.5 h. The temperature was then raised to ambient for 0.5 h. Water (30 mL) and $CHCl_3$ (50 mL) were added, the layers were separated, and the organic layer was washed successively with 30 mL of 1 N $NaHSO_3$, H_2O, and brine and dried over $MgSO_4$. Filtration and removal of solvent gave 321 mg of yellow solid, mp 141.5–143.5 °C, which was recrystallized from cyclohexane (Norit, hot filtration) and dried overnight in an Abderhalden apparatus (78 °C, 0.02 mm) to give 267 mg (84%) of a light yellow solid: mp 142.5–144.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (m, 10.29 H), 6.63 (d, 0.84 H, J_{PH} = 20 Hz), 5.92 (s, 5.74 H); IR (KBr) 3052 (w), 3010 (w), 2966 (w), 2928 (w), 1630 (w), 1616 (w), 1590 (w), 1480 (w), 1440 (m), 1370 (m), 1320 (m), 1277 (w), 1260 (w), 1200 (m), 1177 (s), 1113 (s), 1100 (s), 1070 (w), 1058 (w), 998 (w), 931 (w), 887 (m), 811 (m), 780 (w), 762 (m), 750 (m), 738 (s), 720 (s), 699 (s), 676 (m), 662 (m), 636 (m), 553 (s), 540 (s), 492 (w), 448 (w) cm^{-1}; mass spectrum (20 V, peaks ≥ 10% intensity), *m/e* 305 (M$^+$ + 1, 18), 304 (M$^+$, 83), 303 (37), 202 (33), 201 (100), 183 (18), 179 (22), 178 (15), 155 (14), 125 (10), 103 (17), 102 (47), 77 (29), 47 (11); UV (95% EtOH) λ_{max} 273 nm (ϵ 12 100), 266 (14 400), 257 (15 200).

Oxidation of *P,P*-Diphenyl-*syn*-tricyclo[4.2.0.0^{2,5}]octa-3,7-dien-3-ylphosphine. A. Preparation of 21 and 22. To a solution of *P,P*-diphenyl-*syn*-tricyclo[4.2.0.0^{2,5}]octa-3,7-dien-3-ylphosphine (275 mg, 0.95 mmol) in 25 mL of $CHCl_3$ at 0 °C contained in a three-neck, 100-mL round-bottom flask equipped with an addition funnel, condenser, stopper, and magnetic stirrer was added 10 mL of 30% H_2O_2 in drops during 15 min. The mixture was stirred for 0.5 h at 0 °C and 0.5 h at ambient temperature. Water (20 mL) and chloroform (50 mL) were added, and after successive washing with 30 mL of saturated $NaHSO_3$, H_2O, and brine and drying over $MgSO_4$ the solvents were removed and the residue was triturated with ether–petroleum ether, giving 290 mg of a white solid, mp 108–109 °C. Recrystallization from ether–pentane gave 133 mg of white powder, mp 109–109.5 °C (46% yield). The intensities of the vinyl proton resonances in the ^{1}H NMR spectrum (Figure 2) show the ratio of the isomeric phosphine oxides **21** and **22** to be 48:52: ^{1}H NMR ($CDCl_3$) δ 2.40 (m, 9.97 H), 3.23 (t, J = 3 Hz, 0.47 H), 3.98 (m, 2.48 H), 4.68 (m, 0.41 H), 6.60 (m, 3.42 H); IR (KBr) 3090 (w), 3050 (w), 3028 (w), 2980 (w), 2922 (w), 2850 (w), 1652 (w), 1480 (w), 1440 (m), 1285 (m), 1260 (w), 1178 (s), 1110 (m), 1099 (w), 1070 (w), 995 (w), 982 (w), 948 (w), 920 (w), 882 (w), 804 (s), 745 (m), 718 (s), 700 (s), 587 (s), 541 (s), 502 (w) cm^{-1}; mass spectrum (75 V, peaks > 10% intensity), *m/e* 305 (M$^+$ + 1, 11), 304 (M$^+$, 42), 303 (21) 227 (10), 202 (37), 201 (100), 185 (11), 183 (25), 179 (20), 178 (15), 155 (16), 154 (10), 152 (14), 149 (23), 103 (19), 102 (50), 91 (10), 78 (25), 77, (66), 76 (11), 57 (13), 55 (11), 52 (11), 51 (36), 50 (11), 47 (26), 43 (11), 41 (16), 39 (11), 28 (16); UV (95% EtOH) λ_{max} 272 nm (ϵ 941), 265 (1290), 258 (1190), 222 (16 800).

B. Oxidation at Low Temperature and Thermal Rearrangements of the Oxide. A sample of the phosphine (23 mg, 0.08 mmol)

in 0.5 mL of $CDCl_3$ in a ^1H NMR sample tube was cooled to −78 °C, a cold solution of 20 mg of 85% *m*-chloroperbenzoic acid in 0.5 mL of $CDCl_3$ was added, and the mixture was shaken until the solution was homogeneous (~5 s). The ^1H NMR spectrum was then measured at −45 °C. The three olefinic multiplets of phosphine **5** disappeared and were replaced by the three olefinic multiplets of phosphine oxide **21**. Less than 5% of the isomeric phosphine oxide **22** was detected.

The sample was then removed from the spectrometer and stored at −78 °C while the temperature of the spectrometer's probe was raised to −2 °C. The sample was then warmed slightly from −78 °C and reinserted into the spectrometer, and the olefinic region was scanned every 2 min until the equilibrium mixture of **21** and **22** was observed (ca. 14–18 min).

When a mixture of 21 and 22 in tetrachloroethylene was heated to 138 °C, their spectra were slowly replaced by that of 7.

Photolyses of Oxides 21 and 22. A. An evacuated, sealed quartz ^1H NMR tube containing 16 mg of the mixture of oxides **21** and **22** in 0.5 mL of CD_2Cl_2 (1.06×10^{-1} M) was irradiated with a Hanovia medium pressure Hg lamp through a quartz water jacket and Vycor filter ($\lambda > 254$ nm). After 1.0 h, the aliphatic protons clusterd about δ 3.3 had disappeared and a broad singlet at δ 5.86 attributed to cyclooctatetraenyldiphenylphosphine oxide was observed. According to analytical thin-layer chromatography, the photolysis product and an authentic sample were identical.

B. An evacuated, sealed Pyrex ^1H NMR tube containing a 0.5 mL CD_2Cl_2 solution of oxides **21** and **22** (1.0×10^{-1} M) and 1.9 mg of Michler's ketone (1.4×10^{-2} M) was irradiated with a medium pressure Hg Hanovia lamp through a Pyrex water jacket and uranium glass filter ($\lambda > 330$ nm). After 18.3 h the product, according to ^1H NMR analysis, was a mixture of 66% of cyclooctatetraenyldiphenylphosphine oxide and 34% of starting material.

Photolysis of *P,P*-Diphenyl-syn-tricyclo[4.2.0.0^{2,5}]octa-3,7-dien-3-ylphosphine (5). A quartz ^1H NMR tube containing 28 mg of the phosphine (0.097 mmol) in 1 mL of CD_2Cl_2 (degassed and sealed at 10^{-5} mmHg) was photolyzed at 254 mm with an Ultraviolet Products, Inc., lamp (Model PCOXI). After 5.5 min, a singlet attributable to cyclooctatetraenyldiphenylphosphine began to emerge at δ 5.80 at the expense of the proton signals of the starting material. (After 5.5 min, the ratio of product to starting material was 6:94.) The photolysis was continued and monitored after 15, 45, 75, 180, and 300 min, and after 5 h the mixture consisted of 72 parts of cyclooctatetraenyldiphenylphosphine and 28 parts of starting material.

***P*-Phenyl-α-deuteriophosphahomocubane Oxide (10).** To a flame-dried, N_2-flushed, three-neck, 50-mL round-bottom flask equipped with a magnetic stirrer, N_2 inlet, stopper, and serum inlet was added 252 mg of *P*-phenylphosphahomocubane oxide[10] (1.11 mmol) and 15 mL of dry THF. The solution was treated with 0.6 mL of a 2.3 M phenyllithium solution (1.37 mmol, 1.24 equiv) and stirred for 20 min before quenching with 1.5 mL of DBr in D_2O. The organic material in 30 mL of $CHCl_3$ was extracted successively with 30 mL of water and brine and dried over $MgSO_4$. Filtration and removal of solvent gave 263 mg of a light yellow solid. Chromatography on a 2 × 40 cm SiO_2 column eluting with 5% CH_3OH–CH_2Cl_2 gave 214 mg of a white solid (85% yield), and after recrystallization from 7:2 benzene–cyclohexane and sublimation at 150 °C (0.1 mm) 36 mg was obtained. The product differs from the starting material in that the intensity of the ^1H NMR signal at δ 3.5 has decreased to 4.89 H (relative to 12 H total). The 75 eV mass spectrum showed a base peak at *m/e* 105 and peaks at *m/e* 228 (17%) and 229 (15%). The 25 eV mass spectrum of the undeuterated material showed a base peak at *m/e* 104 and peaks at *m/e* 227 (31%) and 228 (8%):[10] ^1H NMR ($CDCl_3$) δ 7.65 (m, 5.16 H), 4.00 (m, 1.95 H), 3.50 (m, 4.89 H); IR ($CHCl_3$) 2990 (s), 2470 (w), 1599 (w), 1490 (w), 1440 (m), 1240 (s), 1210 (s), 1170 (s), 1120 (s), 1070 (m), 1030 (m), 880 (w), 850 (w), 690 (m), 660 (m) cm^{-1}; mass spectrum (75 V, peaks > 20% intensity), *m/e* (relative intensity) 229 (M^+, 15), 228 (17), 149 (98), 106 (44), 105 (100), 104 (69), 97 (28), 85 (21), 83 (26), 81 (20), 79 (39), 78 (35), 77 (27), 71 (36), 69 (27), 57 (62), 56 (26), 55 (42), 51 (30), 50 (21), 47 (20), 44 (62), 43 (65), 41 (57), 39 (32), 36 (35), 32 (54), 29 (37), 28 (99), 27 (38), 26 (27).

***P*-Phenyl-α-methylphosphahomocubane Oxide (11).** To a three-neck, flame-dried, N_2-flushed, 50-mL round-bottom flask equipped with a serum inlet, N_2 inlet, stopper, and magnetic stirrer was added a 15-mL solution of 229 mg of *P*-phenylphosphahomocubane oxide (1.00 mmol) in dry THF. A solution of 0.6 mL of 1.8 M phenyllithium (1.08 mmol) in 70:30 benzene–ether was added by syringe, and the reddish brown solution was stirred for 10 min at ambient temperature. Excess methyl iodide (2.0 mL, 32 mmol) was then syringed into the mixture, and the resulting amber colored solution was allowed to stir for 0.5 h at ambient temperature. Chloroform (100 mL) was added, and the organic layer was washed successively with 3 × 30 mL of H_2O and 30 mL of brine and dried over $MgSO_4$. Filtration and removal of solvent gave 231 mg of a yellow oil. Chromatography on a 2 × 50 cm SiO_2 column (35 g) eluting with 2% CH_3OH–CH_2Cl_2 yielded 136 mg (56.1%) of a yellow oil, and after evaporative distillation (120 °C, 0.1 mm) 97 mg of colorless oil was obtained. Trituration with ether gave 91 mg of white crystals, mp 82–83.3 °C (38% yield), identified as *P*-phenyl-α-methylphosphahomocubane oxide: ^1H NMR ($CDCl_3$) δ 7.56 (m, 5.19 H), 3.94 (m, 1.62 H), 3.55 (m, 4.90 H), 3.14 (m, 0.93 H), 1.58 (d, J = 13.5 Hz,[39] 2.45 H); IR ($CHCl_3$ solution) 3081 (w), 3060 (w), 2987 (s), 2925 (m), 2877 (w), 2467 (w), 1960 (w), 1900 (w), 1815 (w), 1700 (w), 1590 (w), 1483 (w), 1450 (m), 1438 (s), 1375 (w), 1238 (s), 1215 (s), 1162 (s), 1150 (s), 1118 (s), 1105 (s), 1008 (w), 992 (w), 940 (w), 882 (w), 835 (w), 688 (m), 648 (m) cm^{-1}; mass spectrum (75 V, peaks > 10% intensity), *m/e* 242 (M^+, 5), 241 (16), 118 (100), 117 (64) 115 (12), 102 (19), 92 (14), 91 (22), 78 (11), 77 (16), 51 (13), 47 (10) UV (95% EtOH) λ_{max} 272 nm (ϵ 592), 264 (726), 258 (619).

Reaction of *P*-Phenylphosphahomocubane Oxide with Penyllithium and Diphenyl Disulfide. Preparation of 14 and 15. A 200-mL three-neck, round-bottom flask equipped with a serum inlet, N_2 inlet, stopper, and magnetic stirrer was alternately flame-dried under vacuum and flushed with N_2 three times. A solution of 1.528 g (6.71 mmol) of *P*-phenylphosphahomocubane oxide in 100 mL of dry tetrahydrofuran was added and cooled to 0 °C, and a solution of 4.3 mL of 1.7 M phenyllithium (7.31 mmol) in 70:30 benzene–ether was then added. The solution (now brown) was stirred for 5 min at 0 °C and then cooled to −20 °C to prevent decomposition of the anion.

To a second flame-dried three-neck, 500-mL round-bottom flask equipped with a N_2 inlet, addition funnel, serum inlet, and magnetic stirrer was added a solution of 2.244 g of diphenyl disulfide (10.31 mmol) in 50 mL of dry THF. After this solution had been cooled to 0 °C, the phosphine oxide anion was added at a moderate rate from a dropping funnel into which 20-mL aliquots were periodically added. The total time for the addition was 1.0 h. The brown reaction mixture was stirred for 1.0 h at 0 °C and 1.0 h at ambient temperature and then was quenched with 20 mL of H_2O. Chloroform (300 mL) was added, the layers separated, and the organic layer after washing with H_2O (2 × 100 mL) and brine (50 mL) was dried over $MgSO_4$. Removing the solvent left 3.602 g of crude brown oil, which when chromatographed on a 2.5 × 70 cm SiO_2 column eluting with 2% methanol–methylene chloride (v/v) gave two distinct products. The first band isolated from the column contained 1.36 mg of a mixture of compounds A and B. Product A was obtained in other runs as a light yellow oil that yielded white crystals upon trituration with acetone and melted at 210–211 °C after recrystallization from benzene. Its yield ranged between 1 and 4.9%. It was identified as *P*-phenyl-α,α′-bis(benzenesulfenyl)-phosphahomocubane oxide on the basis of the following spectroscopic data: ^1H NMR ($CDCl_3$) δ 7.30 (m, 15.26 H), 3.70 (m, 1.82 H), 3.47 (m, 3.87 H); IR (KBr) 3056 (w), 3012 (w), 2997 (w), 2926 (w), 2852 (w), 1652 (w), 1578 (m), 1479 (s), 1437 (s), 1432 (s), 1235 (w), 1190 (s, P=O str), 1180 (s), 1132 (w), 1100 (m), 1082 (w), 1062 (w), 1039 (w), 1019 (m), 995 (w), 922 (w), 741 (s), 705 (m), 690 (s), 557 (s), 525 (s) cm^{-1}; mass spectrum (75 V, peaks > 10% intensity), *m/e* (relative intensity) 444 (14), 336 (23), 335 (100), 225 (17), 211 (65), 210 (16), 178 (17), 78 (71), 77 (26), 52 (15), 51 (15); UV (95% EtOH) λ_{max} 261 nm (ϵ 6950).

The second, slower moving product, B, was obtained as a light yellow oil that yielded 1.535 g of white crystals after trituration with acetone (67.8%). The crystals were used in the next step, oxidation, without further purification. In experiments conducted at various temperatures, yields ranged between 32 and 68%. The highest yield was obtained in the procedure above, which prevented decomposition of the phosphine oxide anion and suppressed bissulfenylation. When diphenyl disulfide was added to the lithiated phosphine oxide, rather than the other way around, the yield was much lower.

The solid, mp 155.5–157.0 °C, after recrystallization from benzene, was identified as *P*-phenyl-α-benzenesulfenylphosphahomocubane oxide on the basis of the following spectroscopic data: ^1H NMR ($CDCl_3$) δ 7.46–7.18 (m, 10.27 H), 3.86 (m, 1.90 H), 3.50 (m, 4.76 H); IR (KBr) 3058 (w), 2985 (m), 2940 (w), 2000 (w), 1919 (w), 1852 (w), 1754 (w), 1650 (w), 1610 (w), 1488 (m), 1445 (m), 1337 (w), 1325 (w), 1241 (s), 1233 (m), 1215 (m), 1188 (s), 1164 (m), 1121 (s), 1076 (w), 1031 (w), 1004 (w), 968 (w), 956 (w), 928 (m), 916 (w), 886 (w), 863 (w), 853 (w), 791 (w), 757 (s), 747 (s), 741 (s), 713 (s), 694 (s) cm^{-1}; mass spectrum (75 V, peaks > 10% intensity), *m/e* (relative intensity) 337 (10, $M^+ + 1$,), 336 (36, M^+), 227 (16), 213 (19), 212 (100), 211 (23), 179 (13), 178 (10), 149 (10), 135 (11), 134 (12), 126 (13), 110 (10), 104 (10), 103 (71), 102 (11), 78 (45), 77 (26), 52 (10), 51 (16), 28 (16); UV (95% EtOH) λ_{max} 258 mm (ϵ 3960).

An analytical sample was prepared by recrystallizing twice from 1:1 benzene–cyclohexane and once from benzene, subliming at 124

°C (0.04 mm), and drying in an Abderhalden apparatus at 55 °C (0.01 mm) for 48 h. Anal. Calcd for $C_{20}H_{17}OPS$: C, 71.40; H, 5.10; P, 9.21; S, 9.53. Found: C, 71.49; H, 5.12; P, 8.93; S, 9.51.

***P*-Phenyl-α-benzenesulfonylphosphahomocubane Oxide (16).** To a 500-mL three-neck, round-bottom flask fitted with an addition funnel, condenser, stopper, and magnetic stirrer was added 2.352 g (7.0 mmol) of *P*-phenyl-α-benzenesulfenylphosphahomocubane oxide in 200 mL of $CHCl_3$. The solution was cooled to 0 °C, and a solution of 85% *m*-chloroperbenzoic acid (5.210 g, 25.7 mmol, 3.69 equiv) in 100 mL of $CHCl_3$ was added in drops from the addition funnel during 1.0 h. The reaction mixture was stirred for1.0 h at 0 °C and at ambient temperature for 3.0 h. Washing successively with 1 N NaOH (3 × 60 mL), H_2O (35 mL), and brine (50 mL), drying over $MgSO_4$, and removing the solvent gave 2.923 g of white solid, which after recrystallization from benzene and drying in an Abderhalden apparatus (overnight, 55 °C, 0.1 mm) produced 1.699 g (67% yield) of white powder: mp 214–216 °C; ^1H NMR ($CDCl_3$) δ 7.62 (m, 10.21 H), 4.20 (m, 3.12 H), 3.57 (m, 3.66 H); IR (KBr) 3084 (w), 3050 (w), 3022 (w), 2990 (m), 2924 (w), 2850 (w), 1660 (w), 1590 (m), 1584 (m), 1482 (m), 1450 (s), 1436 (s), 1306 (s), 1288 (s), 1236 (s), 1210 (s), 1190 (s), 1149 (s), 1110 (s), 1081 (s), 1017 (s), 970 (m), 916 (s), 764 (s), 750 (s), 740 (s), 720 (s), 710 (s), 692 (s), 610 (s), 552 (s), 540 (s), 505 (s), 488 (s), 460 (m) cm^{-1}; 368 (M^+, 2), 243 (38), 227 (11), 179 (20), 149 (10), 125 (12), 119 (30), 104 (16), 103 (100), 102 (14), 78 (10), 77 (27), 28 (10); UV (95% EtOH) λ_{max} 273 nm (ε 2014), 266 (7020), 259 (2039).

***P*-Phenyl-α,α′-bis(benzenesulfonyl)phosphahomocubane Oxide (17).** To a 100-mL three-neck, round-bottom flask equipped with a condenser, stopper, and addition funnel was added a solution of 87 mg of *P*-phenyl-α,α′-bis(benzenesulfenyl)phosphahomocubane oxide (0.196 mmol) in 20 mL of $CHCl_3$. The solution was cooled to 0 °C, whereupon a solution of 270 mg of 85% *m*-chloroperbenzoic acid (1.34 mmol, 6.82 equiv) in 15 mL of $CHCl_3$ was added in drops from the addition funnel during 0.5 h. The reaction mixture was stirred for 0.5 h at 0 °C and then at ambient temperature for 3.0 h. Chloroform (50 mL) was added, and the solution was washed successively with 30 mL of 1 N $NaHSO_3$, H_2O, and brine and dried over $MgSO_4$. Removing the solvent gave 128 mg of a white solid, which after recrystallization from methanol produced 57 mg (57% yield) of a white powder: mp 300–301 °C; ^1H NMR (Me_2SO-d_6) δ 7.60 (m, 15.20 H), 4.30 (m, 3.42 H), 3.61 (m, 2.40 H); IR (KBr) 3084 (w), 3064 (w), 3028 (w), 3002 (w), 2920 (w), 2841 (w), 1665 (w), 1580 (w), 1475 (w), 1440 (s), 1435 (s), 1310 (s), 1302 (s), 1238 (w), 1210 (s), 1180 (s), 1144 (s), 1130 (m), 1108 (m), 1082 (s), 1060 (w), 1035 (w), 1018 (w), 996 (w), 978 (w), 950 (w), 934 (w), 921 (m), 872 (w), 792 (w), 762 (m), 748 (s), 715 (s), 682 (m), 618 (s), 608 (s), 565 (m), 550 (s), 510 (s), 362 (w) cm^{-1}; mass spectrum (75 V, peaks > 10% intensity), *m/e* (relative intensity) 508 (M^+, 1) 383 (14), 367 (27), 253 (39), 242 (15), 179 (14), 178 (19), 165 (11), 164 (20), 149 (11), 147 (16), 146 (20), 126 (10), 125 (100), 119 (10), 118 (14), 109 (10), 103 (10), 102 (42), 97 (21), 95 (14), 79 (10), 78 (16), 77 (50), 76 (11), 55 (10), 51 (15), 41 (16), 28 (16); UV (95% EtOH) λ_{max} 273 nm (ε 1871), 267 (2339), 262 (1671).

8-Benzenesulfonyl-*syn*-tricyclo[4.2.0.0^{2,5}]oct-7-en-3-yl-*exo*-phenylphosphinic Acid (19). To a flame-dried, N_2-flushed, three-neck, 50-mL round-bottom flask equipped with a serum inlet, N_2 inlet, stopper, and magnetic stirrer was added 202 mg of *P*-phenyl-α-benzenesulfonylphosphahomocubane oxide (0.55 mmol) and 15 mL of dry THF. To this slurry was syringed a 10-mL solution of 126 mg of sodium hexamethyldisilylamide (0.69 mmol) in THF. After 5 min the mixture was a yellow slurry and after 25 min a clear orange solution. The solution was allowed to stir for 1.0 h before it was quenched with 10 mL of saturated aqueous ammonium chloride. Sufficient water was added to dissolve the amine salt, the solution was extracted with 100 mL of $CHCl_3$, and the organic solution was washed successively with H_2O (2 × 30 mL) and brine and dried over $MgSO_4$. The solvent was removed while the flask was warmed, and 175 mg of a white solid was obtained that was almost homogeneous [one major spot, according to thin-layer chromatographic analysis (R_f 0.20, 5% CH_3OH–CH_2Cl_2, SiO_2), with traces of two minor components]. Recrystallization from hot benzene gave 85 mg of a white solid, R_f 0.20, mp 93–94 °C (40% yield), identified as the exo-phosphinic acid: ^1H NMR (100 MHz, CD_3CN) δ 7.95 (m, 1.81 H), 7.76 (m, 8.11 H), 5.84 (s, 0.98 H), 3.93 (m, 1.01 H), 3.72 (m, 6.04 H), 2.89 (m, 1.01 H); IR (KBr) 3609 (s), 3446 (s), 3343 (s), 3246 (s), 3063 (m), 3015 (m), 2990 (s), 2964 (m), 2873 (w), 1904 (w), 1830 (w), 1601 (m), 1483 (m), 1450 (m), 1440 (m), 1312 (m), 1282 (s), 1265 (s), 1223 (m), 1166 (s), 1140 (s), 1114 (s), 1085 (s), 1038 (m), 1022 (w), 995 (w), 970 (w), 908 (s), 838 (w), 776 (w), 750 (s), 688 (s), 582 (s), 535 (s), 512 (w), 437 (w) cm^{-1}; mass spectrum (30 V, peaks > 10% intensity), *m/e* 386 (M^+ < 1%), 244 (53), 227 (30), 167 (18), 166 (24), 150 (21), 149 (13), 141 (48), 140 (100, $C_6H_5PO_2$), 125 (23), 124 (13), 104 (32), 103 (61), 102 (12), 95 (12), 78 (71), 77 (59), 64 (16), 46 (14), 28 (11); UV (95% EtOH) λ_{max} 273 nm (ε 965), 264 (1102), 258 (1011), 252 (459).

8-Benzenesulfonyl-*syn*-tricyclo[4.2.0.0^{2,5}]oct-7-en-3-yl-*endo*-phenylphosphinic Acid (18). To a flame-dried, N_2-flushed, three-neck, 50-mL round-bottom flask equipped with a serum inlet, N_2 inlet, stopper, and magnetic stirrer was added a slurry of 204 mg of *P*-phenyl-α-benzenesulfonylphosphahomocubane oxide (0.55 mmol) in 15 mL of dry THF. A 5 mL THF solution of 112 mg of sodium hexamethyldisilylamide (0.61 mmol, 1.1 equiv) was syringed into the mixture to give an orange-colored slurry. After 25 min, a clear orange solution resulted, which was allowed to stir for an additional 0.5 h before being quenched with 5 mL of saturated aqueous NH_4Cl. Methylene chloride (75 mL) was added, and the mixture was washed successively with H_2O (3 × 20 mL) and brine (30 mL) and dried over $MgSO_4$. Filtration and removal of solvent (bath temperature between 30 and 40 °C to prevent thermal epimerization) gave a light yellow solid. Chromatography on a 2 × 50 cm column of 35 g of SiO_2 eluting rapidly with 5% CH_3OH–CH_2Cl_2 gave 82 mg (39% yield) of a white solid, mp 71–77 °C, identified as 8-benzenesulfonyl-*syn*-tricyclo[4.2.0.0^{2,5}]oct-7-en-3-yl-*endo*-phenylphosphinic acid on the basis of its R_f value (0.40 in 5% CH_3OH–CH_2Cl_2 on SiO_2) and its vinyl proton chemical shift in the ^1H NMR spectrum (δ 6.04 compared with δ 5.86 for the *exo*-phosphinic acid.) Some (15 mg, 7%) 3-*exo*-phosphinic acid was also obtained. The yields of *endo*-phosphinic acid in several runs varied, after chromatography, from 17 to 48%, while the 3-exo-phosphinic acid was obtained in yields ranging from 6 to 14%. The total yields of both epimers ranged between 26 and 57%. A suitable recrystallization solvent system for the *endo*-phosphinic acid could not be found. In one experiment 123 mg of *endo*-phosphinic acid when rapidly recrystallized from hot benzene gave 38 mg of a mixture of 88.5% *endo*- and 11.5% *exo*-phosphinic acids (analysis by ^1H NMR). The endo acid is more soluble than the exo isomer in $CHCl_3$ and CH_3CN: ^1H NMR (100 MHz, CD_3CN) δ 7.92 (m, 2.00 H), 7.54 (m, 8.37 H), 6.04 (s, 0.82 H), 5.86 (s, 0.18 H, from *exo*-phosphinic acid), 3.87 (m, 1.00 H), 3.57 (m, 1.09 H), 3.22 (m, 4.55 H), 2.89 (m, 1.00 H).

Epimerization of 8-Benzenesulfonyl-*syn*-tricyclo[4.2.0.0^{2,5}]-oct-7-en-3-yl-*endo*-phenylphosphinic Acid (18). Into a flame-dried, N_2-flushed, 50-mL round-bottom flask equipped with a condenser, N_2 inlet, and magnetic stirrer was placed 65 mg of 8-benzenesulfonyl-*syn*-tricyclo[4.2.0.0^{2,5}]oct-7-en-3-yl-*endo*-phenylphosphinic acid (0.168 mmol) in 30 mL of dry benzene. The mixture was refluxed, and the disappearance of the *endo*-phosphinic acid TLC spot at R_f 0.40 (5% CH_3OH–CH_2Cl_2, SiO_2) was monitored hourly. Epimerization was complete after 5.0 h. Removing the solvent and recrystallization from benzene gave 22 mg of a white powder, mp 92–93 °C (34%), identified as 8-benzenesulfonyl-*syn*-tricyclo[4.2.0.0^{2,5}]oct-7-en-3-yl-*exo*-phenylphosphinic acid (19).

8-Benzenesulfonyl-*syn*-tricyclo[4.2.0.0^{2,5}]oct-7-en-3-yldi phenylphosphine Oxide (20). To a flame-dried, N_2-flushed, three-neck round-bottom flask equipped with a serum inlet, N_2 inlet, stopper, and magnetic stirrer and containing a slurry of 203 mg of *P*-phenyl-α-benzenesulfonylphosphahomocubane oxide (0.55 mmol) in 10 mL of THF at −78 °C was added 0.40 mL of 1.7 M phenyllithium in 70:30 benzene–ether (0.68 mmol, 1.23 equiv) in drops from a syringe. A yellow slurry resulted, which was allowed to stir for 5.5 h at −78 °C, and then adding 2 mL of 24% HBr at −78 °C gave a clear green solution. Chloroform (100 mL) was added, and the organic solution was washed successively with H_2O (30 mL) and brine and dried over $MgSO_4$. Removing the solvent gave 296 mg of a light yellow solid. Preparative TLC on four SiO_2 plates (20 × 20 cm, 1000 μm) eluting twice with 5% methanol–methylene chloride gave 151 mg of a fluffy white solid (61% yield), which when recrystallized from 3:1 benzene–cyclohexane (v/v) produced 79 mg (32% yield) of a white powder: mp 206–207.5 °C; ^1H NMR (100 MHz, $CDCl_3$) δ 8.00 (m, 2.24 H), 7.50 (m, 12.98 H), 5.95 (s, 0.94 H), 3.64 (m, 4.96 H), 3.40 (m, 1.77 H); IR (KBr) 3094 (m), 3060 (m), 3030 (m), 2982 (s), 2940 (s), 2864 (w), 1980 (w), 1918 (w), 1828 (w), 1783 (w), 1683 (w), 1612 (w), 1598 (w), 1478 (m), 1446 (s), 1438 (s), 1316 (s), 1286 (s), 1266 (s), 1250 (s), 1220 (m), 1186 (s), 1140 (s), 1110 (s), 1084 (s), 1070 (m), 1032 (m), 1018 (s), 990 (m), 966 (s), 948 (w), 932 (w), 850 (w), 834 (s), 774 (m), 754 (s), 740 (s), 714 (s), 700 (s), 620 (w), 590 (s), 550 (s), 460 (w), 435 (w) cm^{-1}; mass spectrum (30 V, peaks > 10% intensity), *m/e* (relative intensity) 446 (M^+, 1), 306 (11), 305 (48), 228 (27), 227 (26), 203 (11), 202 (66), 201 (82), 183 (10), 155 (17), 125 (28), 104 (22), 103 (15), 78 (100), 77 (61), 52 (32), 51 (33), 50 (21), 39 (16), 28 (17); UV λ_{max} (95% EtOH) 553 nm (ε = 707), 273 (1305), 265 (1577), 258 (1142).

***P*-Phenylphosphahomocubane Sulfide (13).** To a 100-mL three-neck, flame-dried, N_2-flushed round-bottom flask equipped with a condenser with a N_2 inlet, two stoppers, and magnetic stirrer was added a solution of 481 mg (2.26 mmol) of phenylphosphahomocubane[10] in 40 mL of dry benzene. One stopper was replaced by a Gooch tube attached to a 50-mL Erlenmeyer flask containing 1.753

g (6.59 mmol) of S_8 under N_2. The sulfur was added at ambient temperature over 20 min. Clouding was noted. The reaction mixture was stirred for 1.0 h at room temperature and refluxed for 3.0 h. Methylene chloride (75 mL) was added, and after filtration, washing with H_2O (30 mL) and brine, and drying over $MgSO_4$, removal of solvent gave 1.952 g of yellow solid. Trituration with CH_2Cl_2 and two filtrations removed 874 mg of sulfur. Chromatography on 38 g of SiO_2 (2 × 50 cm column) eluting with 20% ether–hexane and sublimation (130 °C, 0.05 mm) gave 265 mg of phenylphosphahomocubane sulfide (48% yield): mp 162–162.5°C; ^1H NMR ($CDCl_3$) δ 7.61 (m, 4.97 H), 3.82 (m, 9.01 H); IR (KBr) 3050 (w), 3018 (w), 2998 (m), 2970 (w), 1665 (w), 1588 (w), 1470 (w), 1430 (s), 1383 (w), 1312 (w), 1248 (s), 1235 (s), 1185 (w), 1150 (w), 1110 (s), 1095 (s), 1062 (m), 1020 (w), 990 (s), 955 (m), 928 (s), 872 (w), 848 (m), 790 (w), 750 (s), 720 (s), 695 (s), 655 (s), 510 (s), 472 (m) cm^{-1}; mass spectrum (75 V, peaks > 10% intensity), *m/e* (relative intensity) 244 (M^+, 24), 211 (13), 179 (12), 140 (11), 134 (13), 133 (21), 108 (15), 107 (20), 105 (10), 104 (100), 103 (37), 78 (38), 77 (30), 63 (25), 51 (32), 50 (12), 44 (12), 39 (18), 32 (27), 28 (81); UV (95% EtOH) λ_{max} 253 nm (ϵ 3310).

Acknowledgment. We are grateful to the National Institutes of Health for support under grant GM19173, to Badische Anilin und Sodafabrik, A. G., for gifts of cyclooctatetraene, and to Mr. Iwao Miura for some of the ^1H NMR spectra.

Registry No.—**1,** 28051-32-3; **2,** 43017-02-3; **5,** 67452-71-5; **6,** 67452-72-6; **7,** 67452-73-7; **10,** 67452-74-8; **11,** 67452-75-9; **12,** 25881-31-6; **13,** 67452-76-0; **14,** 67452-77-1; **15,** 67452-78-2; **16,** 67452-79-3; **17,** 67452-80-6; **18,** 67452-81-7; **19,** 67504-86-3; **20,** 67452-82-8; **21,** 67452-83-9; **22,** 67452-84-0; diphenyl disulfide, 882-33-7.

Supplementary Material Available: Decoupled spectra (7 pages). Ordering information is given on any current masthead page.

References and Notes

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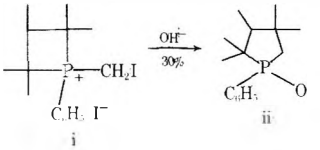

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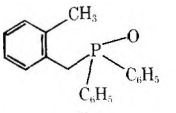

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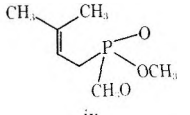

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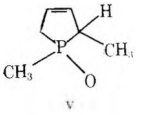

v

Structural Studies of Carbanionic Species Formed from Phosphonates: Anions of Diethyl Benzyl- and Cyanomethylphosphonates

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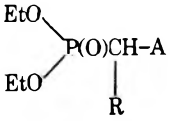
Received April 11, 1978

The structure of anionic species formed from diethyl benzyl- and cyanomethylphosphonates (2 and 3) has been determined by ^1H, ^{13}C, ^{31}P, and ^7Li NMR. From $^1J_{PC}$, $^1J_{CH}$, and δ_{C_1} values, as well as the sign of $^2J_{PH}$, it appears that the anionic carbon is planar and bears a high negative charge, as the corresponding carbon of salt-free P ylides. Some charge delocalization into the phenyl ring takes place for the benzylic derivative **2A**,Li^+; however, such a conjugation with the CN group is less efficient for **3A**,M^+. In the nitrile case, the cation and solvent effect study shows that loose ion pairs are formed in Me_2SO while in THF and pyridine more or less aggregated tight ones exist. On going from tight ion pairs to loose ones, there is no loss of C_1 planarity as the decrease in $^1J_{CH}$ is accompanied by an increase in $^1J_{PC}$.

The reaction of anionic species formed from phosphonates **1** toward aromatic aldehydes or α-enones has been



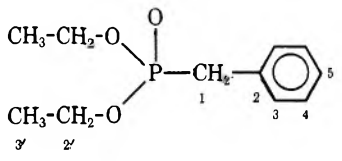
1, R = H, CH_3; A = CN

studied in one of our laboratories.[1] It has been observed that the stereoselectivity and regioselectivity of these reactions are highly dependent upon the nature of the cation associated to the base used to generate the anionic species. Therefore, the possibility of the presence of different structural forms has been raised.

Moreover, the structure of phosphorus ylides, which leads to the same type of reactions with carbonyl compounds, has been widely investigated recently. It has been shown that the carbon atom adjacent to phosphorus of these reagents is planar or nearly so by X-ray determination.[2] However, ^{13}C NMR and photoelectron spectroscopy[3-7] studies indicate a substantial negative charge on this adjacent carbon, which was quite unexpected.

Therefore, it seemed interesting to investigate the structure of anionic species formed from diethyl phosphonates to determine both if there is any relationship between the reagent structure in solution and its chemical reactivity and if the structure of these species is as peculiar as the ylidic one.

In the present paper, we study two types of anionic species in solution by ^1H, ^{13}C, ^{31}P, and ^7Li NMR spectroscopy: one is formed from diethyl benzylphosphonate (**2**) in order to point



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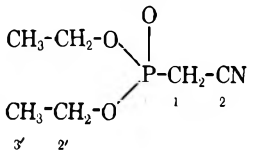

3

out the influence of the $(EtO)_2P(O)$ moiety on the charge delocalization into a phenyl ring; the other is formed from diethyl cyanomethylphosphonate (**3**), which was used in our previous studies.[1] In this latter case, we shall examine the associated cation (Li^+, K^+, cryptated K^+) and the solvent (THF, pyridine, Me_2SO) influences on the anionic species structures.

Previously, from a ^1H NMR study in pyridine and IR in the solid state, Kirilov and Petrov[8] concluded that several different anionic species can coexist from **3**. We have recently published a preliminary communication[9] on the structure of related anionic species formed from diethyl carbomethoxymethylphosphonate; this study is still under investigation.

Results

The anionic species have been prepared in the same way as for the chemical study: by the action of *n*-BuLi on **2** and *n*-BuLi, LiO*t*-Bu, or KO*t*-Bu on phosphonate **3** dissolved in the required protio or deuterated solvent (THF, Me_2SO, or pyridine). [2.2.2]cryptand (1.2 equivalents) was eventually added after formation of the K^+ associated anion. Solution concentrations are from 0.25 to 0.5 M; no important change is observed in this range. Furthermore, these solutions are generally stable at room temperature under anhydrous conditions in an argon atmosphere (up to 5 days), though in some cases precipitation is observed after several hours in THF.

(A) ^1H, ^{13}C, and ^{31}P NMR Spectra. ^{31}P chemical shifts were determined by double resonance $^1H\{^{31}P\}$ experiments.[10] By irradiation at a single ^{31}P frequency, the H_1 doublet and $H_{2'}$ multiplet give rise, respectively to a singlet and a quartet. In some cases, the relative signs of $^1J_{PC_1}$ and $^2J_{PCH_1}$ have been obtained by off-resonance $^{13}C\{^1H\}$ experiments.[11] From ^{13}C proton-coupled and off-resonance decoupled spectra, it is evident that C_1 bears one proton in the anion.

(1) Anionic Species 2A from Diethyl Benzylphosphonate. Using *n*-BuLi in THF or in THF-HMPA (5 or 8 equiv), a single species is observed. ^1H, ^{31}P, and ^{13}C chemical shifts are summarized in Table I and the coupling constants in Table II. Our figures for diethyl benzylphosphonate (**2**) are very close to those published by Ernst[12] and Gray,[13] though the spectra were run in a different solvent.

The main features of our results are the following. On going from **2** to **2A**, one can notice (a) an upfield shift in H_5, H_1, C_3, and C_5, a small change in the C_1 chemical shift according to the solvent, and a downfield shift in ^{31}P resonance and (b) a great increase in $^1J_{PC_1}$ and $^1J_{C_1H}$, an increase in $^2J_{PC_2}$ and $^3J_{PC_3}$, and a slight change in $^2J_{PC_{2'}}$ and $^3J_{PC_{3'}}$. The $^2J_{PCH_1}$ and $^1J_{PC_1}$ coupling constants bear the same sign in **2A** and have opposite signs in **2**.

In the presence of HMPA, the signals are better resolved so that a $^4J_{PC_4}$ coupling can be observed.

(2) Anionic Species 3A from Diethyl Cyanomethylphosphonate. Using a hexane solution of *n*-BuLi, dried or sublimated LiO*t*-Bu, or KO*t*-Bu, a single species is formed

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Table I. Chemical Shifts [a] of Diethyl Benzylphosphonate (2) and Anionic Species 2A,Li$^+$

compd	solvent (base)	$\delta_{^{31}P}$	δ_{H_1}	δ_{H_5}	$\delta_{H_{2'}}$	δ_{C_1}	δ_{C_2}	δ_{C_3}	δ_{C_4}	δ_{C_5}	$\delta_{C_{2'}}$	$\delta_{C_{3'}}$	concn, M: ^{1}H	concn, M: ^{13}C
2	THF	25.0	3.06_6	~7.24	3.91_2	34.1_3	133.4_3	130.5_6	128.7_3	127.0_2	61.9_6	16.6_7	0.5	0.5
2A,Li$^+$	THF	44.7	2.24_2	6.00	3.87_7	34.4_7	149.4_1	119.5_7	128.0	112.2_4	60.2_7	17.0_8	0.25	0.5
	(*n*-BuLi)	(+19.7)	(−0.82_4)	(~−1.24)	(−0.08_5)	(+0.34)	(+15.9_8)	(−1.1)	(−0.7_3)	(−14.7_8)	(−1.6_9)	(+0.41)		
2A,Li$^+$	THF–HMPA [b]	40.1	2.29_2	5.74	3.85	38.7_7	151.5_3	118.7_3	127.3_0	108.6_2	58.36	17.36	0.4	0.4
	(*n*-BuLi)	(+15.1)	(−0.77_4)	(−1.50)	(−0.06_2)	(+4.64)	(+18.1_0)	(−11.8_3)	(−1.43)	(−18.4_0)	(−3.60)	(+0.69)		

[a] δ_H and $\delta_{^{13}C}$ are in parts per million from internal Me_4Si; $\delta_{^{31}P}$ is in parts per million relative to external H_3PO_4 (85%). Positive δ values are in the direction of increasing frequency. [b] 8 equiv.

in the three solvents used.[40] By addition of a few drops of water anion **3a** is not protonated, though addition of two drops of CF_3COOH in the NMR tube gives back only **3**. ^{1}H, ^{31}P, and ^{13}C chemical shifts are summarized in Table III and the coupling constants in Table IV. The ^{13}C parameters of the nitrile **3** are similar to those previously published without solvent.[13]

In pyridine-d_5, the ^{1}H spectrum exhibits a well-resolved upfield doublet which has been assigned to H_1 by a ^{31}P decoupling experiment. Such a doublet is not observed in Me_2SO-d_6; this lack of signal is due to an H–D exchange with solvent, as (a) the formation of partially protiated Me_2SO is observed, (b) the ^{13}C spectrum shows that the C_1 doublet is further split into 1:1:1 triplets due to a C–D coupling, and (c) when the anion is generated in protiated Me_2SO, the H_1 doublet is effectively observed; it collapses into a singlet by ^{31}P irradiation.

In THF or THF-d_8, the H_1 signal is never observed; the C_1 doublet is observed only when noise decoupling of protons is performed. This phenomenon is due to proton exchange, as a broad doublet of doublets can be detected when the ^{13}C proton-coupled spectrum is run at −40 °C (**3A**,Li$^+$) or at room temperature (**3A**,K$^+$). This exchange process did not allow the accurate determination of $^1J_{C_1H_1}$ in this solvent. As it is not possible to run high temperature spectra in THF, we could not determine if such an exchange involves traces of starting material, dianion, or some species formed from the solvent. Up to our knowledge, such an exchange has not been observed for any lithiated species in THF.

In the presence of [2.2.2]cryptand, all of the different signals can be observed either in the ^{1}H or ^{13}C spectra. Let us quote that in these conditions a better resolution is achieved, and the nonequivalence of the two $H_{2'}$ protons can be seen in pyridine (ABK_3 system with ^{31}P irradiation).

On going from **3** to **3A** the main features of our results are the following: (a) a large upfield H_1 shift in pyridine and Me_2SO even when K$^+$ is cryptated; (b) an upfield shift in C_1, and a downfield shift in ^{31}P and C_2, the latter being weakly affected by cation and solvent changes; and (c) a great increase in $^1J_{PC_1}$ (90–100 Hz depending on the associated cation and the solvent), a great increase in $^1J_{C_1H}$ (25–30 Hz), but no noticeable change in $^2J_{PC_2}$. As previously, there is a slight change in $^2J_{PC_{2'}}$ and $^3J_{PC_{3'}}$. Furthermore, $^1J_{PC_1}$ and $^2J_{PCH_1}$ are of opposite sign in **3** while they bear the same sign in **3A**.

(B) ^{7}Li NMR Spectra. The ^{7}Li chemical shifts of **2A**,M$^+$, **3A**,M$^+$, and **9A**,M$^+$ (M$^+$ = Li$^+$) for comparison are reported in Table V in THF and Me_2SO, except for **2A** as the anion could not be generated by the action of *t*-BuOLi on **2** in the latter solvent. All of the signals appear at higher field than the reference values (external LiCl in D_2O 1 M), though they are at lower field than $LiClO_4$(0.5 M) in the same solvent. While the three species have different chemical ^{7}Li shifts in THF, though very close, **3A** and **9A** have the same chemical shift in Me_2SO.

$$[(C_2H_5O)_2P(O)CH\text{–}COOCH_3]^-\ Li^+$$

9A

Discussion

Due to the high concentration used in this work, the species observed are mainly ion pairs which can be more or less aggregated. The improved resolution of the signals in the presence of either HMPA or cryptand suggests the breaking of these aggregates.

It is generally admitted[14] that $^1J_{CH}$ values mainly depend upon carbon hybridization. For instance, when comparing hydrocarbons and the corresponding organolithium compounds, a flattening of the lithiated carbon induces an increase in $^1J_{CH}$ ($Ph_2CH_2 \rightarrow Ph_2CHLi$). However, a decrease in $^1J_{CH}$

Table II. Coupling Constants (Hz) of Diethyl Benzylphosphonate (2) and Anionic Species 2A,Li$^+$

compd	solvent (base)	$^1J_{PC_1}$	$^2J_{PC_2}$	$^3J_{PC_3}$	$^4J_{PC_4}$	$^5J_{PC_5}$	$^2J_{PC_{2'}}$	$^3J_{PC_{3'}}$	$^2J_{PH_1}$	$^1J_{C_1H_1}$	concn, M ^{1}H	concn, M ^{13}C
2	THF	+137.4[a]	8.7	7.2	2.5	3.6	6.2	5.9	−21.7[a]	127.0	0.5	0.5
2A,Li$^+$	THF	+224.8[b]	13.5	15.7	[c]	<1.2	3.7	8.1	+17.8[b]	150.5	0.25	0.5
	(*n*-BuLi)	(+87.4)	(+4.8)	(+8.5)			(−2.5)	(+2.2)	(+39.5)	(+23.5)		
2A,Li$^+$	THF–HMPA	+226.6[b]	12.8	16.0	1.8	<1.2	4.0	8.1	+17.8		0.4	0.4
	(*n*-BuLi)	(+89.2)	(+4.1)	(+8.8)	(−0.7)		(−2.2)	(+2.2)	(+39.5)			

[a] From ^{13}C {^{1}H} off-resonance experiments, $^1J_{PC_1}$ and $^2J_{PH_1}$ are of opposite sign in phosphonate **2**. [b] From ^{13}C {^{1}H} off-resonance experiments, $^1J_{PC_1}$ and $^2J_{PH_1}$ bear the same sign in anionic species **2A**,Li$^+$. [c] Unresolved.

has been interpreted in terms of no hybridization change but an increase of effective nuclear charge ($CH_4 \rightarrow CH_3Li$). This conclusion is in agreement with X-ray determinations, which indicate that the lithiated carbon is indeed pyramidal for C_2H_5Li.[15]

The ^{13}C NMR data concerning tetracoordinated phosphorus compounds indicate that $^1J_{PC}$ is mainly dependent upon carbon hybridization,[3-6,10a,16] more specifically, a comparison of phosphonium salts with the corresponding ylides, the C_1's of which are planar,[2] shows a great increase in $^1J_{PC}$.[3-6] By theoretical calculations, Albright[16] directly related the magnitude of this coupling constant with the percent *s* character in the hybrid orbital on the carbon comprising the P–C bond.

Furthermore, literature data[3a,17] indicate that the sign of $^2J_{PCH}$ depends upon the central carbon hybridization: if this carbon is sp^3 hybridized, $^2J_{PCH}$ is negative;[17a] if it is sp^2 hybridized, $^2J_{PCH}$ is positive.[17b-d] As for tetracoordinated phosphorus derivatives, $^1J_{PC}$ is positive, whatever the carbon hybridization is[3a,10a,17a,18] it follows that $^1J_{PC}$ and $^2J_{PCH}$ will be of opposite sign if the carbon is sp^3 hybridized and of the same sign if it is sp^2 hybridized.[3a]

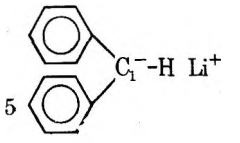
Therefore, we have three criteria at our disposal to evaluate the planar or pyramidal geometry of the anionic carbon: Δ^1J_{PC}, Δ^1J_{CH}, and the sign of $^2J_{PCH}$.

For a carbon atom, in a given hybridization state, numerous attempts have been made to correlate ^{13}C shift with electron density.[19] However, this has been strongly questioned recently, but it seems that the validity of such a correlation is well established for para carbons of aromatic rings;[20] we shall then discuss the values of the other ^{13}C chemical shifts in a qualitative way.

(A) Lithiated Diethyl Benzylphosphonate (2A). The three criteria, based on coupling constants, all indicate that the carbanionic C_1 is planar. Therefore, it can safely be compared with diphenylmethyllithium (**4**),[21a,b] lithiated sulfoxide **5**[22] or sulphone **6**,[22] and phosphorus ylide **7**,[5c,6d] for which C_1 is also planar. For a comparison of these various species, we shall examine the chemical shift differences ($\Delta\delta$) between the lithiated or ylidic species and the parent protonated ones.

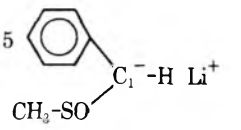
If the chemical shifts variations in C_1 and C_5, as indicated, are very similar for **2A**, **6**, and **7**, slightly different for **5**, they are quite different from those of diphenylmethyllithium (**4**). In this latter case, C_1 is strongly shifted to lower field while the high field shift of the two equivalent para carbons suggests that the negative charge is strongly delocalized into the aromatic rings ($2\Delta\delta_{C_5} = -38$ ppm). For **2A**, **5**, and **6**, it seems that charge delocalization from C_1 to the aromatic ring is rather limited; the C_1 chemical shifts of **2A**, **5**, and **6**, imply that these sp^2 hybridized carbons should bear a large amount of negative charge.

In the case of **2A**, the loosening of anion–cation interaction by HMPA addition induces a slight low field shift in C_1 and a high field shift in C_5, but smaller than that observed by Eliel[23] for dithiane anion **8**. Therefore, the presence of a



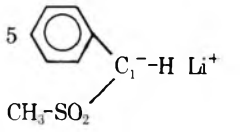
$\Delta\delta_{C_1}$ = +34.4 ppm (THF)
$\Delta\delta_{C_5}$ = −19 ppm (THF)

4



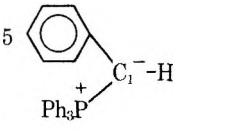
$\Delta\delta_{C_1}$ = +6.7 ppm (THF–C_6D_6, 4:1)
$\Delta\delta_{C_5}$ = −15 ppm (THF–C_6D_6, 4:1)

5



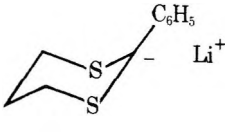
$\Delta\delta_{C_1}$ = −1.9 ppm (THF–C_6D_6, 4:1)
$\Delta\delta_{C_5}$ = −14.4 ppm (THF–C_6D_6, 4:1)

6



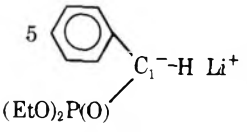
$\Delta\delta_{C_1}$ = ~0 ppm (C_6D_6)
$\Delta\delta_{C_5}$ = −15 ppm (C_6D_6)

7



$\Delta\delta_{C_5}$ = −14 ppm (THF)
$\Delta\delta_{C_5}$ = −23 ppm (THF–HMPA)

8



$\Delta\delta_{C_1}$ = +0.34 ppm (THF)
$\Delta\delta_{C_1}$ = +4.64 ppm (THF–HMPA)
$\Delta\delta_{C_5}$ = −14.8 ppm (THF)
$\Delta\delta_{C_5}$ = −18.4 ppm (THF–HMPA)

2A

phosphoryl moiety α to the carbanionic carbon inhibits somewhat charge delocalization into an aromatic ring, an effect which is reminiscent of the ylidic case **7**[5c,6d] and might suggest a P$^+$–C$^-$ type of stabilization of these two kinds of species as proposed by Bernardi, Wolfe, and co-workers by ab initio calculations.[24] Such an analogy is in line with the ^{31}P chemical shift, as we observe an important downfield shift on going from **2** to **2A** (+20 ppm), which could partly be attributed to a positive charge increase. On going from a phosphonium salt to the corresponding ylide, where no P hybridization or important charge changes occur, one observes a slight high field ^{31}P shift (−5 to −10 ppm).[5c,25]

The HMPA addition effect shows that in THF there is an interaction of Li$^+$ with the p C_1 orbital which polarizes the π

Table III. Chemical Shifts [a] of Diethyl Cyanomethylphosphonate (3) and Anionic Species 3A,M$^+$

compd	solvent (base)	$\delta_{^{31}P}$	δ_{H_1}	$\delta_{H_{2'}}$	δ_{C_1}	δ_{C_2}	$\delta_{C_{2'}}$	$\delta_{C_{3'}}$	concn, M ^1H	concn, M ^{13}C
3	THF	15.0	3.13	4.17$_4$	15.8$_8$	113.9$_6$	63.6$_9$	16.5$_9$		
	py-d_5	15.4	3.67	4.22$_2$	16.3$_0$	114.5$_5$	63.5$_9$	16.3$_4$	0.26	0.51
	Me_2SO-d_6	15.9	3.55	4.12	14.9$_5$	114.4$_6$	62.8$_1$	16.0$_3$	0.25	0.47
3A,K$^+$	THF (*t*-BuOK)	44.1 (+29.1)		3.89$_4$ (−0.28)	3.4$_9$ (−12.3$_9$)	135.1$_6$ (+21.2)	60.8$_2$ (−2.8$_7$)	16.7$_6$ (+0.1$_7$)	0.25	1.0
	py-d_5 (*t*-BuOK)	44.7 (+29.3)	1.51 (−2.16)	4.11$_6$ (−0.10$_6$)	3.9$_1$ (−12.3$_9$)	134.9$_9$ (+20.4$_4$)	60.5$_6$ (−3.0$_3$)	16.6$_1$ (+0.2$_7$)	0.25	0.5
	py-d_5 [c] (*t*-BuOK)	43.0 (+27.6)	1.61 (−2.06)	4.35$_4$ [b] (+0.13$_2$) 4.31$_8$ (+0.09$_6$)	4.4$_3$ (−11.8$_7$)	131.9$_3$ (+17.3$_8$)	59.6$_0$ (−3.9$_9$)	17.0$_8$ (+0.7$_4$)	0.25	0.5
	Me_2SO (*t*-BuOK)	41.9 (+26.0)	0.66 (−2.89)	3.76$_5$ (−0.35$_5$)	3.5$_7$ (−11.3$_8$)	131.3$_6$ (+16.9)	58.8$_0$ (−4.0$_1$)	16.3$_9$ (+0.3$_6$)	0.37	0.5
	Me_2SO [c] (*t*-BuOK)	41.8 (+25.9)		3.74 (−0.38)	3.5$_7$ (−11.3$_8$)	130.8$_2$ (+16.3$_6$)	58.5$_6$ (−4.2$_5$)	16.4$_5$ (+0.4$_2$)	0.37	0.5
3A,Li$^+$	THF (*n*-BuLi)	42.8 (+27.8)		3.94$_1$ (−0.23$_3$)	3.3$_7$ (−12.5$_1$)	132.8$_0$ (+18.8$_4$)	60.5$_9$ (−3.1$_0$)	16.8$_4$ (+0.2$_5$)	0.5	0.37
	THF (*t*-BuOLi)	42.4 (+27.4)		3.93 (−0.24$_4$)	3.5$_1$ (−12.3$_7$)	132.6$_2$ (+18.6$_5$)	60.6$_2$ (−3.0$_7$)	16.8$_7$ (+0.2$_8$)	0.25	0.37
	Me_2SO (*t*-BuOLi)	41.6 (+25.7)	0.70$_4$ (−2.84$_6$)	3.79$_5$ (−0.32$_5$)	3.3$_8$ (−11.5$_7$)	130.6$_4$ (+16.1$_8$)	59.0$_4$ (−3.7$_7$)	16.3$_4$ (+0.3$_1$)	0.37	0.5

[a] $\delta_{^1H}$ and $\delta_{^{13}C}$ are in parts per million from internal Me_4Si; $\delta_{^{31}P}$ is in parts per million relative to external H_3PO_4 (85%). Positive δ values are in the direction of increasing frequency. [b] Inequivalent; $^2J_{AB} = -10.2_7$ Hz. [c] Run in the presence of 1.2 equiv of [2.2.2]cryptand.

system toward this carbon,[26] thus accounting for its shielding in the absence of HMPA. However, from ^{7}Li chemical shifts, the possibility of an interaction with the aromatic π system, according to literature data for benzyllithium,[14b] can be ruled out as a high field ^{7}Li shift for related compounds is not observed in the present case.[14b,27]

Therefore, in THF a structure analogous to α-lithio sulfoxides[28] can be assigned, probably involving an O···Li interaction, as evidenced by the upfield ^{31}P chemical shift observed when weakening ion pair interaction which occurs on HMPA addition.

(B) Anionic Species 3A from Diethyl Cyanomethylphosphonate. The results, on the whole, especially the very large increase in $^1J_{PC}$ (90–100 Hz) and $^1J_{CH}$ (25–30 Hz) when compared to starting material **3** as well as the $^2J_{PC_1H}$ sign change, show that C_1 is planar or nearly so in **3A,M$^+$**.

The large upfield shift of this sp^2 carbon atom (δ_{C_1} 3.5, $\Delta\delta$ = −12 ppm) indicates that C_1 bears a large electron density. A further confirmation that the high shielding of C_1 is mainly due to a charge increase and not to a ΔE variation comes from the fact that H_1 proton shielding also increases ($\Delta\delta H_1 = -2$ to −3 ppm). The C_1 negative charge appears to be higher in **3A** than in **2A** ($\Delta\delta_{C_1}$ = +4 to ~0 ppm, $\Delta\delta$ H_1 = −0.8 ppm). This result is suggesting that the CN moiety is less efficient than Ph in delocalizing the negative charge; it is also less efficient than the ester group, as we have shown[9] that for chelate **9A**

9A

9

C_1 is shifted downfield (+5–6 ppm) when compared to starting material **9**. Such a poor electron-withdrawing effect for the CN moiety has already been observed in the ^{13}C NMR spectrum of the cyanobenzyl carbanion.[29]

From the C_2 chemical shift in **3A,M$^+$**, it appears that the contribution of the resonance allenic form **10**, as suggested by Kirilov and Petrov,[8] seems to have a negligible weight since this carbon should be strongly deshielded.[30]

10

An ab initio calculation of species **11** also indicates that when

11

C_1 is planar, the nitrile bond remains short, as expected for a triple bond (1.17Å).[32] The ^{31}P chemical shift variation to low field ($\Delta\delta$ = 25–30 ppm) suggests that there is some positive charge on this atom, though an angular change can also intervene.[39] The fact that the screening constants decrease for ^{31}P, C_2, and $C_{3'}$ but increase for C_1 and $C_{2'}$ favors a charge alternating structure[33] such as **12**.

Table IV. Coupling Constants (Hz) of Diethyl Cyanomethylphosphonate (3) and Anionic Species 3A,M⁺

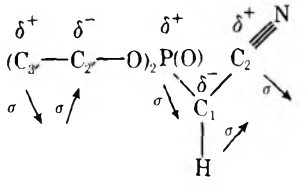
compd	solvent (base)	$^1J_{PC_1}$	$^2J_{PC_2}$	$^2J_{PC_{2'}}$	$^3J_{PC_{3'}}$	$^2J_{PH_1}$	$^1J_{C_1H_1}$	$^2J_{C_2H_1}$	concn, M ^{1}H	concn, M ^{13}C
3	THF	+141.7	11.3	6.1	5.3	−21.1	135.4			
	py-d_5	+140.4	11.3	6.2	5.3	−20.8			0.26	0.51
	Me_2SO-d_6	+138.8[a]	11.1	6.3	6.0	−20.8[a]			0.25	0.47
3A,K⁺	THF (t-BuOk)	233.5 (+91.8)	12.4 (+1.1)	4.9 (−1.2)	7.5 (+2.2)		166 (+30.6)		0.25	1.0
	py-d_5 (t-BuOK)	234.0 (+93.6)	12.0 (+0.7)	5.0 (−1.2)	7.5 (+2.2)	+5.1 (+25.9)	163.8 (+28.4)		0.25	0.5
	py-d_5[c] (t-BuOK)	+236.5[b] (+96.1)	10.8 (−0.5)	5.0 (−1.2)	7.5 (+2.2)	+5.0[b] (+25.8)	160.8 (+25.4)	2.8	0.25	0.5
	Me_2SO (t-BuOK)	+235.5[b] (+96.7)	11.0 (−0.1)	5.0 (−1.3)	7.2 (+1.2)	+5.0[b] (+25.8)	161.3 (+25.9)	2.9	0.37	0.5
	Me_2SO[c] (t-BuOK)	235.7 (+96.9)	10.3 (−0.8)	5.0 (−1.3)	7.2 (+1.2)		160.4 (+25.0)		0.37	0.5
3A,Li⁺	THF (n-BuLi)	242.5 (+100.8)	12.5 (+1.2)	4.9 (−1.2)	7.5 (+2.2)				0.5	0.37
	THF (t-BuOLi)	241.8 (+100.1)	11.7 (+0.4)	4.5 (−1.6)	7.5 (+2.2)				0.25	0.37
	Me_2SO (t-BuOLi)	238.7 (+99.9)	11.2 (+0.1)	5.2 (−1.1)	7.5 (+1.5)	+4.9 (+25.7)	161.5 (+26.1)	3.1	0.37	0.5

[a] From ^{13}C {^{1}H} off-resonance experiments, $^1J_{PC_1}$ and $^2J_{PH_1}$ are of opposite sign in phosphonate **3**. [b] From ^{13}C {^{1}H} off-resonance experiments, $^1J_{PC_1}$ and $^2J_{PH_1}$ bear the same sign in anionic species **3A,K⁺**. [c] Run in the presence of 1.2 equiv of [2.2.2]cryptand.

Table V. ^{7}Li Chemical Shifts[a] of 2A,Li⁺, 3A,Li⁺, and 9A,Li⁺

compound	$LiClO_4$		2A,Li⁺	3A,Li⁺		9A,Li⁺	
solvent	THF	Me_2SO	THF[b]	THF[b]	Me_2SO[c]	THF[b]	Me_2SO[c]
δ	−1.0	−1.3	−0.5	−0.9	−0.3	~0	−0.3
$W_{1/2}$ (Hz)	2.5	2.5	11	6.5	8.5	<5	7

[a] $\delta_{^7Li}$ *is in parts per million from external LiCl/D_2O (c = 1 M). Negative* δ *values are in the direction of decreasing frequency.* Concentrations are 0.5 M in the indicated solvent. [b] n-BuLi was used to generate the anion. [c] t-BuOLi was used to generate the anion.



12

This fits with Bell's proposal[31] that anions α to nitriles should be stabilized by an electrostatic $>C^{\delta-}—^{\delta+}C{\equiv}N^{\delta-}$ interaction rather than by charge delocalization into the triple bond. However, the infrared vibration ν P → O is nearly the same for **3** and **3A,M⁺**;[34] this lack of variation is not in accordance with a P^+–O^- structure for the **3A,M⁺** phosphoryl moiety. This disagreement between NMR and IR results remains still unexplained.

The cation and solvent effects are not very large, but it is known that NMR parameters are not very sensitive to these phenomena.[26,38]

(1) In the case of K⁺ as the associated cation, the NMR parameters of the anionic moiety are similar in Me_2SO in the absence and presence of [2.2.2]cryptand as well as in pyridine in the presence of [2.2.2]cryptand. Therefore, in these cases, the anion–cation interaction is weak, indicative of a loose ion pair in Me_2SO. In THF and pyridine, the variations of the parameters suggest the presence of more or less aggregated tight ion pairs.

$^1J_{PC}$ and $^1J_{CH}$ variations indicate that for loose ion pairs Δ^1J_{PC} is maximum (+97 Hz) while Δ^1J_{CH} is minimum (+25 Hz); the reverse is true for tight ion pairs (Δ^1J_{PC} = +92 Hz, Δ^1J_{CH} = +30.6 Hz). At first sight, the decrease in $^1J_{CH}$ on going from tight ion pairs to loose ones could have been attributed to a pyramidalization of C_1.[14b] However, the parallel increase in $^1J_{PC}$ is not consistent with such an interpretation.[2b,16] Both variations indicate a change in the valency angles around C_1, which still remains planar.

The C_2 and ^{31}P chemical shift variations on going from loose to tight ion pairs might be due either to deaggregation phenomena or to intramolecular effects, and they are difficult to discuss at the present time.

(2) In the case of Li⁺ as the associated cation, the parameters of the anionic species in Me_2SO are very close to those of **3A,K⁺** in the same solvent; one is also dealing with loose ion pairs, a fact which is confirmed by ^{7}Li chemical shifts, which are independent of the associated anion nature. However, $^1J_{PC}$ is a little larger than with K^+ (3 Hz). It is even larger in THF, although it is minimum when M = K^+. This anormal behavior is in contrast with C_2 chemical shift variation, the $\Delta\delta$ of which increases for both **3A,Li⁺** and **3A,K⁺** on going from Me_2SO to THF. Both trends suggest that the cation–anion interaction is different for the two kinds of tight ion pairs; the interaction of Li^+ with the CN group should probably be stronger than with K^+, in line with previous results of the literature on Li^+ affinity for nitriles[35] and on the effect of the CN moiety on the structure of Na^+ and Li^+ 9-cyanofluorenyl ion pairs in THF or DME.[36]

Conclusion

From NMR results, it appears that the stable phosphonate carbanions formed from benzyl- (**2**) and cyanomethyl phosphonates (**3**) have structures which are analogous to P ylides; C_1 is planar and bears a high negative charge, with the pπ–dπ interaction, if it exists, being unable to promote an effective charge delocalization.[5c] The stabilization of these species seems to involve a P^+–C^- interaction.[24] Such a structure is rather unexpected in light of the usual concepts of organic chemistry as it is generally admitted that the stability of charged species increases with charge delocalization.

The benzylic species **2A,Li⁺** structure is very similar to the

lithiated benzyl sulfoxide one[22,28] in THF. Though the C_1 carbon is planar, its negative charge is only partly delocalized into the aromatic ring, even in the presence of HMPA.

In the nitrile case, the anion keeps nearly the same geometry whatever the associated cation and solvent are. The $C_1^{-}-{}^{\delta+}C_2{\equiv}N^{\delta-}$ moiety has a structure which is very reminiscent

$$>C_1{=}C{=}O \leftrightarrow >C_1^{-}{-}C{\equiv}O^{+}$$

of ketenes and diazoalkanes,[30] with the C_1 nucleus nearly as strongly shielded as that of ketene (δ_{C_1} 2.5).

In Me_2SO, **3A**,M^+ are loose ion pairs, while in pyridine and THF they are tight and more or less aggregated in the range of concentrations used.

In THF, the location of the cation seems to be different for Li^+ and K^+. This leads to an interpretation of the different stereoselectivities we previously observed when reacting a cyanomethylphosphonate anion with benzaldehyde[1b,c] using either Li^+ in THF and K^+ in HMPA or K^+ in THF. In the first two cases, the cation is unable to participate in the approach of the aldehyde to the anionic site, as it is too far from the reactive carbon; in the later case, a cationic bridge can take place between the aldehyde carbonyl and the anion so that the relative orientation of the two approaching reagents can be different.[37]

Experimental Section

NMR Spectra. ^1H and ^{13}C spectra were recorded on a Varian XL-100-12 W.G. spectrometer. The temperature of the probe was 31 ± 2 °C. ^1H and ^{13}C chemical shifts were measured with Me_4Si as an internal reference. ^1H spectra (100 MHz, 5-mm tubes) were studied using the CW mode. The ^1H resonance of Me_4Si was used to provide the field frequency lock. Heteronuclear double resonance experiments ^1H-{^{31}P} were performed by irradiating ^{31}P at 40.5 MHz with the XL gyrocode decoupler. The ^{31}P irradiating frequency was determined using an Eldorado-Varian frequency counter, and ^{31}P chemical shifts relative to H_3PO_4 were calculated as previously described.[10]

^{13}C spectra (25.17 MHz, 10-mm tubes, ^2H lock) were collected using the Fourier transform technique. The instrument was equipped with a 620 L-100-16 K on line computer. A capillary filled with D_2O served as an internal lock when using protio solvents. Spectral widths of 5000 or 2500 Hz were used (digital resolution, 1.25 or 0.68 Hz/point). Proton-coupled ^{13}C spectra were obtained with gated proton decoupling.

^7Li spectra were recorded on a Varian FT-80 spectrometer (30.912 MHz, 10-mm tubes, ^2H lock) using the Fourier transform technique. A 4-mm tube filled with a 1 M solution of LiCl in D_2O, located inside the 10-mm tube, was used for the ^2H internal lock and ^7Li external reference. No magnetic susceptibility correction was applied. A spectral width of 2000 Hz was used (digital resolution, 0.5 Hz/point).

Materials. Tetrahydrofuran (Merck pure) was distilled over $LiAlH_4$ and kept under argon. Me_2SO was freshly distilled over CaH_2. Merck *n*-BuLi solutions (1.6 M in hexane) were standardized by acid–base titration before use. *t*-BuOK (Merck) was sublimated before use; *t*-BuOLi was prepared from Li and freshly distilled *t*-BuOH, vacuum dried after solvent evaporation, and kept under an argon atmosphere. Deuterated solvents were commercial.

Preparation of Solutions. Starting material (0.001 mol) was weighed in a drybox into a carefully dried tube containing a small magnetic rod. It was then septum-capped after argon introduction. Solvent (2 mL, or 1.4 mL if the base used was *n*-BuLi) was introduced by a syringe, and the solution was then magnetically stirred. *n*-BuLi (0.7 mL) in hexane was added by a syringe or 0.0012 mol of *t*-BuOK or *t*-BuOLi under argon. The solution was stirred again for 45 min and then centrifugated. A 0.5-mL amount of this solution was taken via a syringe and introduced under an argon atmosphere into a 5-mm NMR tube containing Me_4Si. A 60 MHz ^1H NMR spectrum was run to check the solution, and the remaining 1.5 mL of solution was similarly transferred into a 10-mm NMR tube for a ^{13}C NMR spectrum. Similar procedures were run in half amounts for the 100 MHz ^1H NMR spectra.

Acknowledgment. We are indebted to S. A. Varian and Dr. S. Altenburger-Combrisson for the ^7Li spectra. We thank Mrs. A. Cordaville for running some control ^1H NMR spectra at 60 MHz.

Registry No.—**2**, 1080-32-6; **2A**, 67393-38-8; **3**, 2537-48-6; **3A** (M^+ = K^+), 67393-39-9; **3A** (M^+ = Li^+), 67393-40-2; **4**, 881-42-5; **5**, 29284-50-2; **6**, 60188-42-3; **7**, 21655-89-0; **7** (uncharged form), 16721-45-2; **8**, 53178-41-9; **9A** (M^+ = Li^+), 67393-41-3.

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(40) However, using non freshly sublimated KOt-Bu, one can see another species (δ_{31P} 7.8 ppm) together with ethyl alcohol, both being formed in the same amount, which increases with time. Thus, this second species is certainly an artifact due to the breaking of a EtO–P bond.

Stereostructures of Neurolenins A and B, Novel Germacranolide Sesquiterpenes from *Neurolaena lobata* (L.) R.Br.[1]

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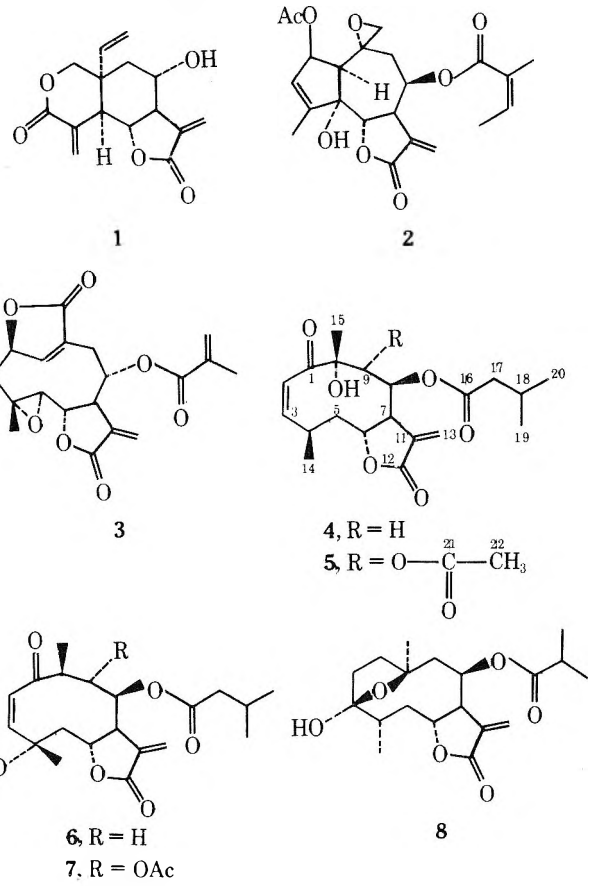
Received June 19, 1978

Two novel germacranolide sesquiterpenoids, neurolenins A (**4**) and B (**5**), have been isolated from *Neurolaena lobata* (L.) R.Br. (Compositae) and their stereostructures determined from spectral and X-ray crystallographic analyses; **4** and **5** possessed the α-methylene-γ-butyrolactone moiety, but were inactive against sarcoma-180 in rats.

A number of sesquiterpenoids possessing the α-methylene-γ-butyrolactone moiety are known to exhibit significant cytotoxic and, if a second α,β-unsaturated group is also present, in vivo antitumor activities.[2] Examples of these compounds are vernolepin (**1**),[3] euparotin acetate (**2**),[4] and elephantopin (**3**).[5] Based on in vitro experiments, particularly



those in which the α-methylene lactone group has been shown to react rapidly and preferentially with the sulfhydryl group, Kupchan has suggested that these sesquiterpenoids probably act by selective alkylation of growth-regulatory biological macromolecules, via a Michael-type reaction of the α-methylene lactone group.[6] In addition, the report by Loeb[7] that there are present in certain DNA polymerases sulfhydryl groups which are susceptible to inhibition by thiol reagents (e.g., *p*-mercurichlorobenzoate) lends some credence to Kupchan's suggestion and also to the speculation that these sesquiterpenoids probably inhibit DNA replication.[8] Despite extensive isolation[2] and synthetic[9] studies in this area, to the best of our knowledge no therapeutically acceptable compound has yet emerged.

In this article we report the isolation and structural elucidation of two novel sesquiterpenoids, neurolenins A (**4**) and B (**5**), both of which possess the aforementioned structural requirements for cytotoxic and antitumor activities, but were inactive against sarcoma-180 in rats.[10]

The neurolenins, extremely bitter substances, were isolated from a methylene chloride extract of the West Indian medicinal plant *Neurolaena lobata* ("zeb-a-pique", "herbe-a-pique", "cow-gall bitter", Compositae),[11] a plant apparently used in the Antilles for the treatment of cancer,[12] but which had not been studied previously. A curious feature of this plant is that its fresh leaves and stems impart a yellow stain to the skin when handled.

Neurolenin A (**4**), $C_{20}H_{28}O_6$, mp 127–128 °C, had IR ($CHCl_3$, cm^{-1}) absorptions indicative of the following functional groups: hydroxyl (3500), γ-lactone (1763), ester (1737), α,β-unsaturated ketone (1685), and terminal methylene (1630). Because absorption in the 235-nm region appeared as a barely discernible shoulder on the main peak at 208 nm, the UV spectrum of **4** was not definitive about the presence of an α,β-unsaturated ketone; however, cogent evidence for the presence of this functionality was readily adduced from inspection of the ^1H and ^{13}C NMR spectra. Thus, absorptions due to an AB quartet (J = 11 Hz) at δ 5.80 and 6.55 in the ^1H NMR spectrum are attributed to protons α (on C-2) and β (on C-3), respectively, to a carbonyl group; corresponding absorptions in the ^{13}C NMR spectrum (see Table I) appeared as doublets at 125.3 (C-2) and 146.6 (C-3) ppm, with absorptions due to the ketone carbonyl (C-1) as a singlet at 205.7 ppm. Other significant absorptions in the ^1H NMR spectrum of neurolenin A include those assigned to an isopropyl group (6 H doublet at δ 0.89, J = 7 Hz), a secondary methyl group (3 H doublet at δ 1.31, J = 7 Hz), a methyl group on a fully substituted carbon atom bearing an oxygen function (3 H singlet at δ 1.44), a one-proton multiplet at δ 3.09 due to H-18, and a one-proton doublet of doublets at δ 4.50 (J = 11 and 2 Hz) ascribed to H-6. As there was only one D_2O exchangeable proton (at δ 4.15) in neurolenin A, it was inferred that a single hydroxyl group was present, and since it was resistant to acetylation (acetic anhydride–pyridine), it was considered tertiary.

Further scrutiny of the extract led to the isolation of a second, closely related sesquiterpenoid, neurolenin B (**5**), $C_{22}H_{30}O_8$, whose IR spectrum showed hydroxyl (3500 cm^{-1}) but only two carbonyl absorptions (1760 and 1690 cm^{-1}). The Raman spectrum, however, disclosed absorptions due to four carbonyl groups (1780, 1745, 1710, and 1690 cm^{-1}), whose presence was fully substantiated by inspection of the ^{13}C NMR spectrum (singlets at 204.3, 170.8, 170.0, and 168.6 ppm; see Table I). The ^1H NMR spectrum of neurolenin B was very similar to that of neurolenin A, and additionally indicated that the extra carbonyl in the former was part of a secondary acetyl group (3 H singlet at δ 2.09 and 1 H singlet at δ 5.50).

The foregoing spectral evidence is compatible with either **4** or **6** for neurolenin A and either **5** or **7** for neurolenin B. Formulas **6** and **7** both contain an oxygen function at C-4, a

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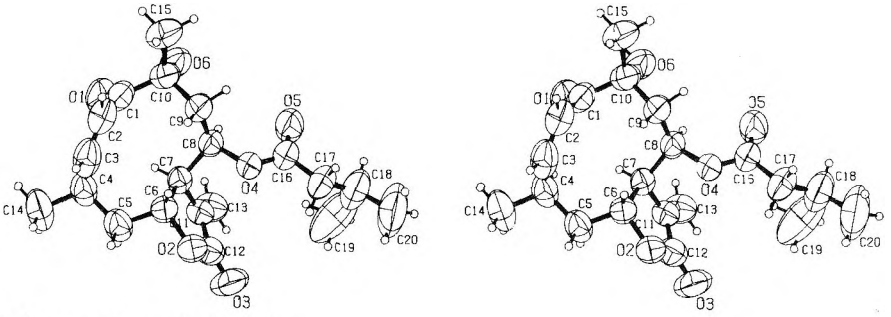

Figure 1. A stereoscopic drawing of neurolenin A (**4**).

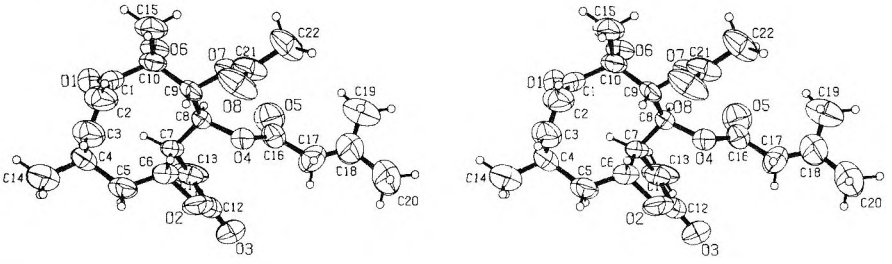

Figure 2. A stereoscopic drawing of neurolenin B (**5**).

Table I. ^{13}C NMR Data[a]

carbon atom[b]	4	5
1	205.7 (s)	204.3 (s)
2	125.3 (d)	125.3 (d)
3	146.6 (d)	147.9 (d)
4	25.4 (d)	24.9 (d)
5	40.2 (t)	40.2 (t)
6	75.9 (d)	76.3 (d)
7	42.4 (d)	41.2 (d)
8	73.9 (d)	73.9 (d)
9	40.4 (t)	73.8 (d)
10	76.5 (s)	79.3 (s)
11	136.1 (s)	134.8 (s)
12	171.3 (s)	170.8 (s)
13	124.5 (t)	126.2 (t)
14	19.9 (q)	19.6 (q)
15	28.1 (q)	23.6 (q)
16	169.0 (s)	170.0 (s)
17	43.0 (t)	42.5 (t)
18	28.3 (d)	28.2 (d)
19	22.2 (q)	22.3 (q)
20	22.2 (q)	22.3 (q)
21		168.6 (s)
22		20.5 (q)

[a] Determined at 25.2 MHz in $CDCl_3$. Chemical shifts are in parts per million with Me_4Si as an internal standard. [b] Assignments are based on chemical shifts and off-resonance decoupled spectra, and are tentative.

Table II. X-Ray Crystallographic Data and Experimental Details

	4	5
formula	$C_{20}H_{28}O_6$ (364.44)	$C_{22}H_{30}O_8$ (422.47)
space group	$P2_1$	$P2_1$
a, Å	12.826 (2)	13.984 (2)
b, Å	7.238 (1)	6.862 (1)
c, Å	12.148 (1)	12.706 (2)
β, deg	116.26 (1)	106.07 (1)
Z	2	2
d_{calcd}, g cm^{-3}	1.196	1.197
μ (Cu Kα), cm^{-1}	7.3	7.6
crystal size, mm	0.10 × 0.15 × 0.6	0.05 × 0.08 × 0.5
max θ, deg	57	57
no. of reflections	1489	1744
no. of obsd reflections	1158	1485
absorption correction	none	none
least-squares refinement	full matrix	full matrix
heavier atoms	anisotropic	anisotropic
hydrogen atoms	iso (fixed)	iso (fixed)
final R	0.048	0.056
final R_w	0.048	0.066
final difference map largest peak, e Å^{-3}	0.1	0.2

feature (or its equivalent such as an epoxide or double bond) that is common to most known germacranolide sesquiterpenoids,[13] and were therefore considered likely structures for neurolenins A and B, respectively. Definitive proof of the structures for the neurolenins was subsequently obtained from X-ray crystallographic analyses, which established structure **4** for neurolenin A and **5** for neurolenin B. Pertinent X-ray crystallographic data are listed in Table II, and stereoscopic drawings for **4** and **5** are displayed in Figures 1 and 2, respectively. As can be seen from the drawings, **4** and **5** contain an α-methylene-γ-butyrolactone trans-fused at C-6 and C-7 to a ten-membered ring, an isopentanoate ester at C-8, and an α,β-unsaturated ketone between C-1 and C-3; the double bond normally present at C-4 has presumably migrated into conjugation with the ketone (vide infra). The acetate group in **5** was located at C-9.

Perusal of the literature[2] indicates that those germacranolide sesquiterpenoids with confirmed antitumor and cytotoxic activities possess, in addition to the α-methylene-γ-butyrolactone moiety, an oxygen function or double bond at C-4. The significance of this additional structural feature in determining the biological activities of these sesquiterpenoids is not immediately apparent, but it is of some interest to note that tirotundin (**8**), recently isolated from *Tithonia rotundifolia* by Herz, had no confirmed activity in the P388 lymphocytic leukemia screen and was inactive in the B 16 melanocarcinoma and Lewis lung screens.[14] As in the case of the neurolenins, tirotundin lacked oxygenation at C-4.

Experimental Section

General. Melting points were determined in capillaries on a Thomas-Hoover melting point apparatus and are uncorrected. Unless otherwise indicated, infrared (IR) and nuclear magnetic resonance spectra (NMR) were determined in $CHCl_3$ and $CDCl_3$, respectively. ^1H and ^{13}C NMR spectra were recorded at 100 and 25.2 MHz, respectively. Chemical shifts are expressed in parts per million (ppm) with tetramethylsilane as an internal standard and coupling constants (J) in hertz (s = singlet, d = doublet, t = triplet, m = multiplet). Mass spectra (MS) were determined using a direct inlet system with an ionization energy of 70 eV; m/e values are given with relative intensities (%) in parentheses. Thin-layer chromatograms (TLC) were made from Merck (Darmstadt) silica gel G, and spots were made visible by spraying with 10% ceric sulfate in 10% H_2SO_4 and heating the plates to 110 °C.

Extraction of *Neurolaena lobata* (L.) R.Br. (syn. *Conyza lobata*, Compositae). Finely ground, dried leaves (2.0 kg) of *N. lobata*, collected in Trinidad (July 1977), were steeped in 12 L of CH_2Cl_2 for 6 days. The mixture was filtered, and the filtrate was evaporated to give 48 g of a green gum, which was dissolved in 1 L of ethyl acetate and stirred 5 times with 20 g of neutral charcoal (4 h each time). Removal of the charcoal and solvent gave 15 g of a light brown gum, which was chromatographed on 300 g of neutral alumina (Woelm, Grade II, dry pack) with 50% ethyl acetate in hexane as eluent. Fractions containing **4** and **5** (ascertained by TLC using 50% ethyl acetate in hexane as eluent) were combined and the solvents removed to give 3.3 g of a gum. The latter was separated by preparative-scale TLC (5 mm thick PF_{254} silica gel plates with 55% ethyl acetate in hexane as eluent, short wavelength UV light) into crude neurolenin A (**4**; R_f 0.66, 800 mg) and crude neurolenin B (**5**; R_f 0.60, 264 mg).

Neurolenin A (4). The preceding crude sample of **4** was crystallized first from a mixture of ethyl acetate (1 mL) and hexane (6 mL) at 0 °C overnight and then from ethyl acetate (0.5 mL) in hexane (3.0 mL) at 0 °C to give 320 mg of **4** as colorless crystals: mp 127–128 °C; $[\alpha]^{25}_D$ −257.7° ($CHCl_3$, c 1.00); UV 208 nm (ε 14 050), 235 sh (~6000), 305 (76); ORD (MeOH) $[\Phi]_{238}$ −47 813, $[\Phi]_{200}$ +60 000; CD (MeOH) $[\theta]_{345}$ −88, $[\theta]_{321}$ +124, $[\theta]_{296}$ −269, $[\theta]_{262}$ +3400, $[\theta]_{219}$ −77 000; IR 3500, 1763, 1737, 1685, 1630 cm^{-1}; Raman (neat) 1780, 1760, 1685, 1640 cm^{-1}; ^1H NMR δ 0.89 (6 H, d, J = 7 Hz), 1.12 (3 H, d, J = 7 Hz), 1.44 (3 H, s), 2.26 (2 H, d, J = 7 Hz), 3.09 (1 H, m), 3.70 (1 H, br s, exchangeable with D_2O), 4.50 (1 H, d of d, J = 12 and 5 Hz), 5.32 (1 H, d of t, J = 7 and 2 Hz), 5.77 (1 H, d, J = 1 Hz), 5.96 (1 H, d, J = 11 Hz), 6.27 (1 H, d, J = 1 Hz), 6.52 (1 H, d, J = 11 Hz); MS m/e 364 (M^+, 0.01).

Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.92; H, 7.74. Found: C, 66.25; H, 7.85.

Neurolenin B (5). Crude **5** isolated above was crystallized from ethyl acetate–hexane (1:5) at 0 °C to give colorless crystals: mp 165–166 °C; $[\alpha]^{25}_D$ −350.0° ($CHCl_3$, c 0.76); UV 207 nm (ε 15 650), 235 sh (~6200), 305 (75); ORD (MeOH) $[\Phi]_{327}$ −9000, $[\Phi]_{240}$ −59 531, $[\Phi]_{200}$ +112 500; CD (MeOH) $[\theta]_{310}$ −4000, $[\theta]_{264}$ +2000, $[\theta]_{215}$ −100 000; IR 3500, 1760, 1690, 1625 cm^{-1}; Raman (neat) 3500, 1780, 1745, 1710, 1690, 1640 cm^{-1}; ^1H NMR δ 0.86 (6 H, d, J = 7 Hz), 1.13 (3 H, d, J = 7 Hz), 1.34 (3 H, s), 2.09 (3 H, s), 2.63 (1 H, s), 3.12 (1 H, m), 4.19 (1 H, exchangeable with D_2O), 4.57 (1 H, d of d, J = 11 and 5 Hz), 5.57 (2 H, s), 5.82 (1 H, d, J = 2 Hz), 6.02 (1 H, d, J = 11 Hz), 6.31 (1 H, d, J = 2 Hz), 6.61 (1 H, d, J = 11 Hz); MS m/e 422 (M^+, 0.01).

Anal. Calcd for $C_{22}H_{30}O_8$: C, 62.55; H, 7.16. Found: C, 62.47; H, 7.12.

X-Ray Crystallography. The crystallographic data for **4** and **5**, which were collected on a fully-automated Hilger-Watts diffractometer (Cu Kα radiation, θ–2θ scans, pulse height discrimination), are summarized in Table II. Listings of final atomic parameters, final anisotropic thermal parameters, bond lengths, bond angles, and torsion angles are given in Tables III–XII as supplementary material. The structure and relative stereochemistry of **4** and **5** were solved by a multiple solution procedure.[15]

Acknowledgment. We are most grateful to Dr. C. D. Adams and Mr. M. Bhorai Kalloo (The Herbarium, University of the West Indies, Trinidad) for the identification of *Neurolaena lobata* and to Mr. M. Hasmathullah for his assistance in the collection of plant material. We are also indebted to the following members of our Physical Chemistry Department for some of the spectral data: Dr. V. Toome (UV, ORD, CD), Mr. S. Traiman (IR), Mr. R. Pitcher (^{13}C NMR), Dr. W. Benz (MS), and Dr. F. Scheidl (elemental analyses).

Registry No.—**4**, 67506-31-4; **5**, 67506-30-3.

Supplementary Material Available: Listings of final atomic parameters, final anisotropic thermal parameters, bond lengths, bond angles, and torsion angles are given in Tables III, IV, V, VI, and VII, respectively, for **4** and Tables VIII, IX, X, XI, and XII for **5** (10 pages). Ordering information is given on any current masthead page.

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Spectinomycin Chemistry. 1. Characterization of a 5a,9a-*epi*-4(*R*)-Dihydrospectinomycin Derivative

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Received May 15, 1978

The identification of a diastereomeric derivative of 4(*R*)-dihydrospectinomycin, having the reversed absolute stereochemistry in the cyclitol ring, is reported. The chemical transformations providing the unequivocal proof of structure **11** for this compound (Schemes II and III) take advantage of the instability of the diastereomeric skeleton relative to that of spectinomycin.

Spectinomycin (**1a**)[1,2] has a structure unique among aminocyclitol antibiotics in that its single sugar component (actinospectose) is fused to the cyclitol portion (actinamine) by both a β-glycosidic bond as well as a hemiketal bond.

As depicted in Scheme I, opening of the hemiketal bond of **1a** would generate the hydrated diketone **2a,** which then could be expected to be in equilibrium with the three isomeric compounds **3a, 4a,** and **5a,** as well as with spectinomycin (**1a**). Such interconversions would also be conceivable for the dihydrospectinomycins **1b** and **1c**.[3] However, to date, only compounds possessing skeleton **1** have been reported.[2-5]

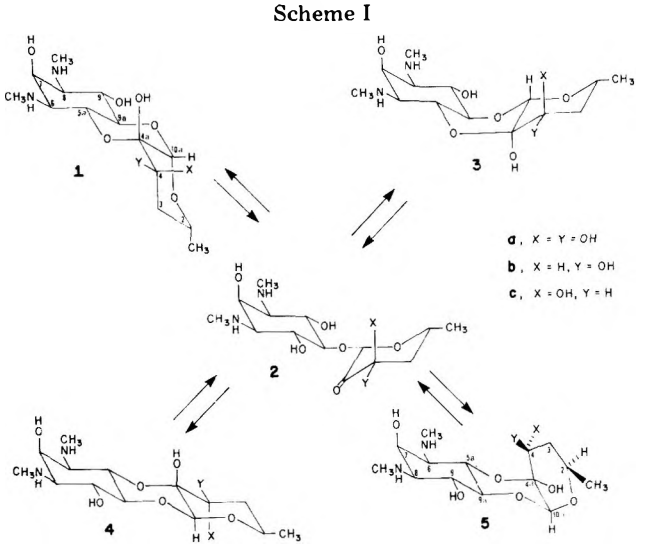
The instability of structure **3** relative to **1** is most likely due to the presence of the high energy boat conformation in its central 1,4-dioxin ring. The predominance of **1** over **4** and **5** may reflect, in addition to steric interactions, the configurational preferences arising from the "anomeric effect".[6]

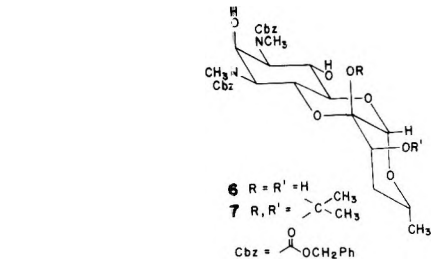
Despite the obvious preference for structure **1,** we continued to seek compounds derived from structures **4** and **5** and now report the isolation and structure determination of the dihydrospectinomycin diastereomer **11,** a derivative of structure **5.**

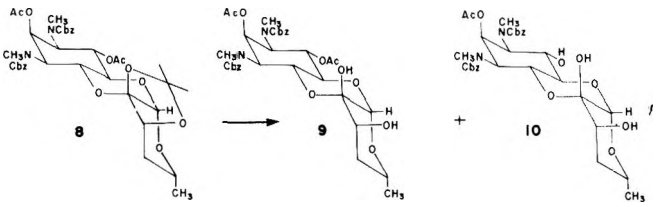
Acid-catalyzed reaction of *N,N'*-dicarbobenzoxy-4(*R*)-dihydrospectinomycin (**6**)[7] with 2,2-dimethoxypropane in dimethylformamide gave, in addition to the reported product **7**,[4b] a small amount of a second acetonide in crystalline form (subsequently shown to be **11**). Acid hydrolysis of both **7** and the unknown acetonide generated the same tetrol **6**.

The 7,9-di-*O*-acetyl-*N,N'*-dicarbobenzoxy-4(*R*)-dihydrospectinomycin acetonide (**8**), prepared by treatment of **7** with excess acetic anhydride in pyridine, on acid hydrolysis yielded the diol **9** in addition to 7-*O*-acetyl-*N,N'*-dicarbobenzoxy-4(*R*)-dihydrospectinomycin (**10**). Both were characterized as their acetonide derivatives. Under identical conditions, the diacetate derived from the unknown acetonide afforded a diol

Scheme I







different from **9** as well as the triol **10**. Further hydrolysis of either diol, **9** or that obtained from the unknown acetonide, gave only the known triol **10,** also characterized as its acetonide derivative.

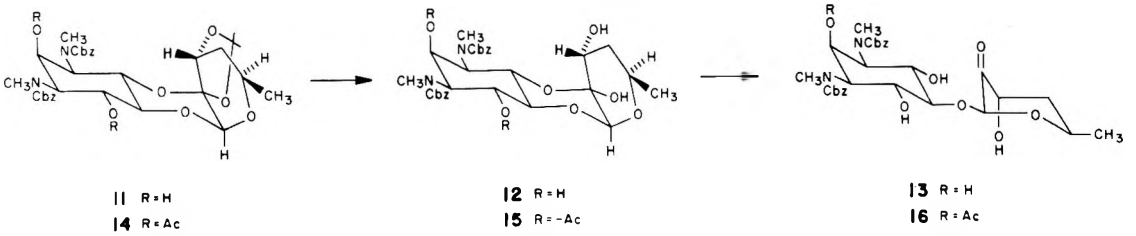
These results suggest that the structure of the unknown acetonide is that of the dihydrospectinomycin diastereomer **11**. Thus, it is evident that hydrolysis of the diastereomeric acetonide **11** resulted in the rearrangement of its skeleton back to the more stable one of the dihydrospectinomycin **6**. Presumably this transformation involved the intermediacy of the tetrol **12** and the ketone **13,** of which the latter upon rotation about the glycoside bond underwent recyclization to the hemiketal **6** (Scheme II). The diacetate **14** afforded, upon acidic hydrolysis, a mixture of the novel diol **15** and the triol **10** (formed via **16**).

The chemistry outlined in Scheme III allowed the establishment of the regioisomeric nature of the cyclitol hydroxyl groups involved in the hemiketal linkages in the dihydrospectinomycin derivative **7** and the diastereomeric acetonide **11**. Thus, if the structure of **11** is correct, the isomeric cyclic carbamates **21a** and **22a** would be expected to afford the rearrangement products **17a** and **18a,** respectively.

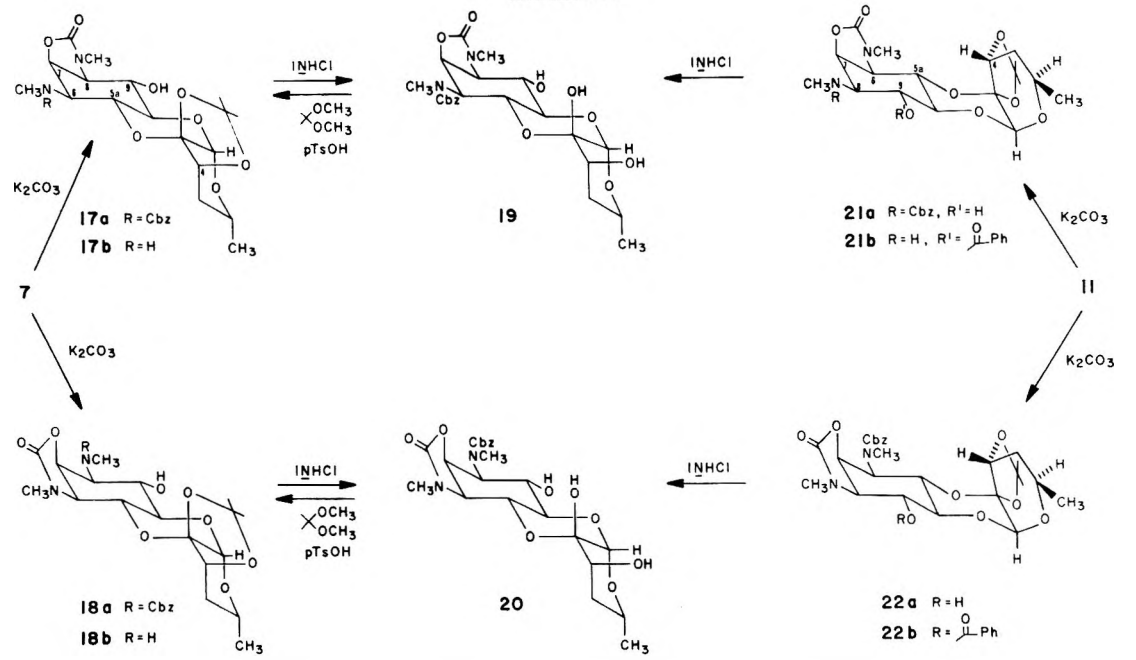
The *N,N'*-dicarbobenzoxy-4(*R*)-dihydrospectinomycin acetonide (**7**) on treatment with potassium carbonate in dimethylformamide at 90 °C yielded a mixture of the 7,8- and 6,7-cyclic carbamates **17a** and **18a**. Spin decoupling experiments carried out on **17b** and **18b,** the hydrogenolysis products of **17a** and **18a,** allowed the unequivocal assignment of the 6,7-cyclic carbamate structure **18a** to the less polar component and confirmed the 7,8-cyclic carbamate structure **17a** of the more polar compound.[8] The pure cyclic carbamates **17a** and **18a** were separately hydrolyzed to yield the triols **19** and **20,** respectively. Reintroduction of the isopropylidene group regenerated only the corresponding starting cyclic carbamates **17a** and **18a,** without evidence of rearrangements or side reactions.

0022-3263/78/1943-4355$01.00/0

Scheme II



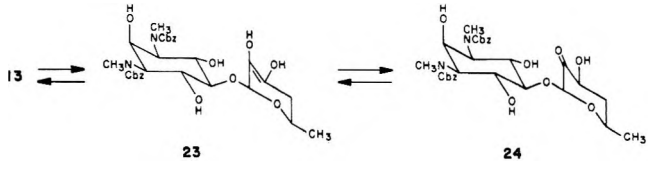
Scheme III



Analogous base treatment of the diastereomeric acetonide **11** resulted in the formation of a mixture of the two new cyclic carbamates **21a** and **22a**. Conversion of the more polar component into the 9-*O*-benzoyl derivative **22b** allowed definitive structure assignment by spin decoupling experiments.[8] Again the more polar compound was found to be a 7,8-cyclic carbamate, in this case **22a**. Confirmation of the 6,7-cyclic carbamate structure **21a** for the less polar component by spin decoupling required the preparation of **21b** by treatment with benzoyl chloride in pyridine followed by the hydrogenolysis of the remaining carbobenzoxy group.[8]

The pure 7,8-cyclic carbamate **22a** was hydrolyzed with 1 N hydrochloric acid in refluxing methanol to yield a triol. Without purification this crude triol was reacted with 2,2-dimethoxypropane in dimethylformamide to generate the expected 6,7-cyclic carbamate **18a**. As anticipated, similar treatment of the 6,7-cyclic carbamate **21a** resulted in formation of the 7,8-cyclic carbamate **17a**. These reactions, as outlined in Schemes II and III, together with the preservation of the 4*R* stereochemistry throughout these transformations firmly established the proposed structure **11**[9] for the novel dihydrospectinomycin diastereomer and ruled out an alternative structure derived from **4**.

The absence of products with 4*S* configuration makes it unlikely that the keto alcohol **13** is in equilibrium with the enediol **23**, which in turn would be expected to produce the keto alcohol **24**.[10] Failure to observe this interconversion or the rearrangement to the 2-hydroxy-3-ulose derivative is indeed surprising in view of the well-known isomerization of 3-hydroxy-2-uloses to the more stable 2-hydroxy-3-uloses via an intermediate enediol.[11,12]



These findings also cast doubt on a proposed biosynthetic scheme for spectinomycin involving the rearrangement of a 2-hydroxy-3-ulose to a 3-hydroxy-2-ulose via an enediol similar to **23**.[13] Additionally, the observation that a symmetrical cyclitol intermediate, such as **2**, will preferentially cyclize to form the spectinomycin skeleton greatly simplifies any synthetic approach to this molecule.

Experimental Section

General. Melting points were taken on a Kofler hot stage melting point apparatus (Reichert) and are uncorrected. Infrared (IR) spectra were recorded on a Digilab FTS 14 spectrometer. Proton NMR spectra were obtained with Varian XL-100 and HA-100 instruments and are reported in parts per million downfield from internal tetramethylsilane. Mass spectra (MS) were obtained on a CEC-110 mass spectrometer. Rotations were measured on a Perkin-Elmer 241 polarimeter.

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 (TLC), respectively. Silica gel PF-254 was used for preparative TLC.

Pyridine and dimethylformamide (DMF) were dried by prolonged storage over Davidson 4A molecular sieves and filtered just prior to use.

p-Toluenesulfonic acid was dried at 80 °C at 10 mm for 4 h prior to use.

Hydrogenolyses were carried out in the Parr apparatus at the pressures noted.

(2*R*)-2α,4β,4aβ,5aβ,6β,7β,8β,9α,9aα,10aβ-Decahydro-2-methyl-6,8-bis[*N*-(benzyloxycarbonyl)-*N*-methylamino]-2*H*-pyrano[2,3-*b*][1,4]benzodioxin-4,4a,7,9-tetrol 4,4a-Acetonide (7) and (2*R*)-2α,4β,4aβ,5aα,6α,7α,8α,9β,9aβ,10aβ-Decahydro-2-methyl-6,8-bis[*N*-(benzyloxycarbonyl)-*N*-methylamino]-2*H*-pyrano[2,3-*b*][1,4]benzodioxin-4,4a,7,9-tetrol 4,4a-Acetonide

(11). The pure 4(R)-dihydrospectinomycin derivative 6[4b] (14.8 g, 0.025 mol) was dissolved in dry DMF (65 mL) and 100 mL of 2,2-dimethoxypropane (84.8 g, 0.814 mol) and p-toluenesulfonic acid (0.2 g) were added. The resulting solution was stirred at room temperature for 21 h. The low boiling solvents were then removed in vacuo, and the residue was treated with AG 1-X8 (OH^-) (30 mL) in MeOH (100 mL). After stirring for 15 min, the resin was filtered off and the filtrate concentrated in vacuo to leave 18.5 g of a white foam. Chromatography on a column containing 900 g of silica gel and development with n-hexane–EtOAc (3:7) gave 15.0 g (95%) of the known N,N′-dicarbobenzoxy-4(R)-dihydrospectinomycin 4,4a-acetonide (7):[4b] R_f 0.68; $[\alpha]^{25}_D$ +31.17° (1.0167, $CHCl_3$).

Later fractions contained the diastereomeric acetonide **11**. Crystallization from MeOH gave 0.21 g (1.3%) as very fine needles: mp 232–233 °C; R_f 0.50; $[\alpha]^{25}_D$ +3.90° (0.9989, $CHCl_3$); IR (KBr) 3490, 1683 cm^{-1}; NMR ($CDCl_3$–D_2O) δ 1.28 (d, 3 H, C-2 CH_3), 1.38 and 1.49 [2s, 6 H, $C(CH_3)_2$], 1.80–2.40 (m, 2 H, H-3), 3.04 and 3.10 (2 s, 6 H, N–CH_3), 3.30–4.60 (m, 8 H), 4.85 (s, 1 H, H-10a), 5.12 (s, 4 H, CH_2Ph), 7.33 (s, 10 H, arom); MS *m/e* 642 (M^+), 627 (M − CH_3).

Anal. Calcd for $C_{33}H_{42}N_2O_{11}$: C, 61.67; H, 6.59; N, 4.36. Found: C, 61.68; H, 6.51; N, 4.59.

Rearrangement of 11 to Give 7. A solution of 11.4 mg (0.018 mmol) of **11** in MeOH (1 mL) and 1 N HCl (1 mL) was heated to reflux on a steam bath for 1 h. Concentration of the reaction solution in vacuo gave 11 mg of a glass, identical to **6** by IR and TLC. This glass was dissolved in a mixture of dry DMF (1 mL), 2,2-dimethoxypropane (5 mL), and p-toluenesulfonic acid (1 mg), and this solution was stirred at room temperature for 24 h. The total reaction solution was concentrated in vacuo, and the residue was dissolved in 10 mL of MeOH and stirred with AG 1-X8 (OH^-) (1 mL) for 5 min. The resin was filtered off and the filtrate concentrated under vacuum to afford 11 mg of a glass, whose IR, TLC, and MS data were identical to those of **7**.

(2R)-2α,4β,4aβ,5aβ,6β,7β,8β,9α,9aα,10aβ-Decahydro-2-methyl-6,8-bis[*N*-(benzyloxycarbonyl)-*N*-methylamino]-7,9-bis(acetyloxy)-2*H*-pyrano[2,3-*b*][1,4]benzodioxin-4,4a-diol4,4a-Acetonide (8). A solution of the acetonide **7** (37.5 g, 0.058 mol) in dry pyridine (400 mL) and acetic anhydride (30 mL) was stirred at room temperature for 4 days. The total reaction solution was diluted with toluene (400 mL) and concentrated in vacuo. The remaining oil was redissolved in 500 mL of toluene and reconcentrated. The residue was dissolved in CH_2Cl_2 and washed twice with H_2O. Drying and concentration of the CH_2Cl_2 solution gave 36.7 g of crude product. Purification of 27 g by column chromatography on 865 g of silica gel using n-hexane–EtOAc (1:1) gave 17 g of 7,9-di-O-acetyl-N,N′-dicarbobenzoxy-4(R)-dihydrospectinomycin 4,4a-acetonide (**8**) as a glass: IR (KBr) 1755 and 1710 cm^{-1}; NMR ($CDCl_3$) (two rotamers present) δ 1.24 (d, 3 H, C-2 CH_3), 1.46 [broad s, 6 H, $C(CH_3)_2$], 1.60–2.10 (m, 2 H, H-3), 1.97 and 2.08 (2s, 6 H, Ac), 2.73, 2.86, and 2.91 (3s, 6 H, N–CH_3), 3.60–4.50 (m, 6 H), 4.59 (s, 1 H, H-10a), 5.10 (broad s, 4 H, CH_2Ph), 5.46 (t, 1 H, *J* = 10 Hz, H-9), 5.74 (broad s, 1 H, H-7), 7.34 (s, 10 H, arom); MS *m/e* 726 (M^+), 711 (M − CH_3), 683 (M − Ac), 591 (M − $OCOCH_2Ph$).

Anal. Calcd for $C_{37}H_{46}N_2O_{13}$: C, 61.15; H, 6.38; N, 3.85. Found: C, 61.04; H, 6.45; N, 3.76.

(2R)-2α,4β,4aβ,5aβ,6β,7β,8β,9α,9aα,10aβ-Decahydro-2-methyl-6,8-bis[*N*-(benzyloxycarbonyl)-*N*-methylamino]-7,9-bis(acetyloxy)-2*H*-pyrano[2,3-*b*][1,4]benzodioxin-4,4a-diol (9) and (2R)-2α,4β,4aβ,5aβ,6β,7β,8β,9α,9aα,10aβ-Decahydro-2-methyl-6,8-bis[*N*-(benzyloxycarbonyl)-*N*-methylamino]-7-acetyloxy-2*H*-pyrano[2,3-*b*][1,4]benzodioxin-4,4a,9-triol (10). A mixture of 0.2 g (0.28 mmol) of the diacetate **8** in MeOH (4 mL) and 1 N HCl (3 mL) was heated to reflux on a steam bath for 0.5 h. Concentration of the total reaction solution in vacuo followed by purification by preparative TLC on silica gel using n-hexane–EtOAc (3:7) gave 0.15 g of 7,9-di-O-acetyl-N,N′-dicarbobenzoxy-4(R)-dihydrospectinomycin (**9**) as a glass: IR (KBr) 3460, 1756, 1710, 1460, 1385, 1350, 1220, 1175, 1085, 1060, 950, 780, 750, 740, 705 cm^{-1}. 7-O-Acetyl-N,N′-dicarbobenzoxy-4(R)-dihydrospectinomycin (**10**) was also obtained as a glass (0.04 g): IR (KBr) 3440, 1754, 1700, 1455, 1350, 1220, 1180, 1060, 950, 780, 750, 740, 705 cm^{-1}.

Reintroduction of the isopropylidene group by treatment of **9** with 2,2-dimethoxypropane in DMF containing a catalytic amount of p-toluenesulfonic acid (as described for **7** above) regenerated **8**.

Similar treatment of **10** (0.51 g, 0.79 mmol) gave 0.51 g (94%) of the 7-O-acetyl-N,N′-dicarbobenzoxy-4(R)-dihydrospectinomycin 4,4a-acetonide as a glass: IR (KBr) 3590, 1752, 1698 cm^{-1}; NMR ($CDCl_3$–D_2O) (two rotamers present) δ 1.25 (d, 3 H, C-2 CH_3), 1.45 and 1.49 [2s, 6 H, $C(CH_3)_2$], 2.70–2.90 (m, 2 H, H-3), 2.04 (s, 3 H, Ac), 2.86, 2.90, and 2.92 (3s, 6 H, N–CH_3), 3.70–4.50 (m, 7 H), 4.67 (s, 1 H, H-10a), 5.16 (broad s, 4 H, CH_2Ph), 5.78 (broad s, 1 H, H-7), 7.26 (s, 10 H, arom); MS *m/e* 684 (M^+), 669 (M − CH_3), 549 (M − $OCOCH_2Ph$).

Anal. Calcd for $C_{35}H_{44}N_2O_{12}$: C, 61.39; H, 6.48; N, 4.09. Found: C, 61.63; H, 6.52; N, 3.92.

(2R)-2α,4β,4aβ,5aα,6α,7α,8α,9β,9aβ,10aβ-Decahydro-2-methyl-6,8-bis[*N*-(benzyloxycarbonyl)-*N*-methylamino]-7,9-bis(acetyloxy)-2*H*-pyrano[2,3-*b*][1,4]benzodioxin-4,4a-diol 4,4a-Acetonide (14). A solution of the diastereomeric acetonide **11** (23 mg, 0.036 mmol) in pyridine (2 mL) containing distilled acetic anhydride (0.5 mL) was stirred at room temperature for 3 days. The total reaction solution was concentrated in vacuo, and the residue was dissolved in $CHCl_3$ and washed once with H_2O. Drying and concentration of the $CHCl_3$ solution gave 35 mg of an oil. Pure **14**, 25 mg (96%), was obtained by preparative TLC on silica gel using n-hexane–EtOAc (3:7): IR (KBr) 1753, 1708 cm^{-1}; NMR ($CDCl_3$) δ 1.24 (d, 3 H, C-2 CH_3), 1.40 and 1.48 [2s, 6 H, $C(CH_3)_2$], 1.90–2.20 (m, 8 H, H-3 and 2Ac), 2.76 and 2.92 (2s, 6 H, N–CH_3), 3.50–4.70 (m, 6 H), 4.73 (s, 1 H, H-10a), 5.10–5.20 (m, 4 H, CH_2Ph), 5.50 (t, 1 H, *J* = 10 Hz, H-9), 5.74 (broad s, 1 H, H-7), 7.33 (s, 10 H, arom); MS *m/e* 726 (M^+), 711 (M − CH_3), 683 (M − Ac).

Anal. Calcd for $C_{37}H_{46}N_2O_{13}$: C, 61.15; H, 6.38; N, 3.85. Found: C, 60.88; H, 6.45; N, 3.54.

Hydrolysis of the Diacetate 14 to Give the Diol 15 and Triol 10. A solution of 37 mg (0.051 mmol) of **14** in 1.5 mL of MeOH containing 1 mL of 1 N HCl solution was heated to reflux for 20 min. The reaction solution was concentrated, and preparative TLC on silica gel using n-hexane–EtOAc (3:7) gave the diol **15** (23 mg) as a glass (IR (KBr) 3505, 3460, 1755, 1705, 1455, 1380, 1350, 1335, 1220, 1165, 1140, 1120, 1080, 1065, 945, 780, 755, 705 cm^{-1}) and the triol **10** (6 mg) (IR (KBr) 3440, 1754, 1700, 1455, 1350, 1220, 1180, 1060, 950, 780, 750, 740, 705 cm^{-1}).

Treatment of the diol **15** in dry DMF with 2,2-dimethoxypropane and a catalytic amount of p-toluenesulfonic acid (as described for **7** above) afforded a glass identical in all respects with the starting diacetate **14**.

Identical treatment of the triol **10** yielded the monoacetate acetonide, identical in all respects with that obtained from **8**.

(2R)-2α,4β,4aβ,5aβ,6β,7β,8β,9α,9aα,10aβ-Decahydro-2-methyl-6-[*N*-(benzyloxycarbonyl)-*N*-methylamino]-8-methylamino-2*H*-pyrano[2,3-*b*][1,4]benzodioxin-4,4a,7,9-tetrol 4,4a-Acetonide 7,8-Cyclic Carbamate (17a) and (2R)-2α,4β,4aβ,5aβ,6β,7β,8β,9α,9aα,10aβ-Decahydro-2-methyl-8-[*N*-(benzyloxycarbonyl)-*N*-methylamino]-6-methylamino-2*H*-pyrano[2,3-*b*][1,4]benzodioxin-4,4a,7,9-tetrol 4,4a-Acetonide 6,7-Cyclic Carbamate (18a). A solution of 2.0 g (3.11 mmol) of the acetonide **7** in dry DMF (10 mL) containing K_2CO_3 (0.4 g) was heated in an oil bath at 90 °C for 24 h. After cooling to room temperature, the solids were filtered off and washed with toluene. Concentration of the combined filtrates in vacuo gave 1.85 g of a foam.

Chromatography on a silica gel column (80 g) developed with n-hexane–EtOAc (3:7) gave pure 6,7-cyclic carbamate **18a**, 0.5 g (30%), as a glass: R_f 0.55; IR (KBr) 3460, 1773, 1700 cm^{-1}; NMR ($CDCl_3$–D_2O) δ 1.26 (d, 3 H, C-2 CH_3), 1.96 [s, 6 H, $C(CH_3)_2$], 1.60–2.10 (m, 2 H, H-3), 2.98 and 3.03 (2s, 6 H, N–CH_3), 3.54 (dd, 1 H, $J_{5a,6}$ = 8 Hz, $J_{6,7}$ = 6 Hz, H-6), 3.60–4.10 (m, 4 H), 4.14 (m, 1 H, H-4), 4.44 (dd, 1 H, $J_{7,8}$ = 5 Hz, $J_{8,9}$ = 11 Hz, H-8), 4.60 (s, 1 H, H-10a), 4.70 (dd, 1 H, $J_{6,7}$ = 6 Hz, $J_{7,8}$ = 5 Hz, H-7), 5.15 (s, 2 H, CH_2Ph), 7.34 (s, 5 H, arom); MS *m/e* 554 (M^+), 519 (M − CH_3), 427 (M − OCH_2Ph), 399 (M − $OCOCH_2Ph$).

Anal. Calcd for $C_{26}H_{34}N_2O_{10}$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.35; H, 6.62; N, 5.33.

Further elution gave the 7,8-cyclic carbamate **17a**, 1.0 g (60%), as a glass: R_f 0.37; IR (KBr) 3450, 1770, 1700 cm^{-1}; NMR ($CDCl_3$–D_2O) δ 1.26 (d, 3 H, C-2 CH_3), 1.44 and 1.47 [2s, 6 H, $C(CH_3)_2$], 1.60–2.00 (m, 2 H, H-3), 3.03 (broad s, 6 H, N–CH_3), 3.53 (dd, 1 H, $J_{7,8}$ = 6.5 Hz, $J_{8,9}$ = 8 Hz, H-8), 3.60–4.30 (m, 5 H), 4.45 (dd, 1 H, $J_{5a,6}$ = 11 Hz, $J_{6,7}$ = 4 Hz, H-6), 4.61 (s, 1 H, H-10a), 4.70 (dd, 1 H, $J_{6,7}$ = 4 Hz, $J_{7,8}$ = 6.5 Hz, H-7), 5.17 (s, 2 H, CH_2Ph), 7.36 (s, 5 H, arom); MS *m/e* 534 (M^+), 519 (M − CH_3), 443 (M − CH_2Ph), 427 (M − OCH_2Ph).

Anal. Calcd for $C_{26}H_{34}N_2O_{10}$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.59; H, 6.39; N, 5.29.

(2R)-2α,4β,4aβ,5aβ,6β,7β,8β,9α,9aα,10aβ-Decahydro-2-methyl-6,8-bis(methylamino)-2*H*-pyrano[2,3-*b*][1,4]benzodioxin-4,4a,7,9-tetrol 4,4a-Acetonide 7,8-Cyclic Carbamate (17b). Hydrogenolysis of the 7,8-cyclic carbamate **17a** (67.5 mg, 0.0126 mmol) in 2-propanol (30 mL) using 5% Pd/C (58 mg) at room temperature and 50 psi of hydrogenation for 4 h gave, after filtration of the catalyst and concentration of the filtrate, 50 mg of **17b** as a glass: IR (KBr) 3325, 1763 cm^{-1}; NMR ($CDCl_3$–D_2O) δ 1.27 (d, 3 H, C-2 CH_3), 1.47 [s, 6 H, $C(CH_3)_2$], 1.65–2.10 (m, 2 H, H-3), 2.54 (s, 3 H, C-6 N–CH_3), 2.82 (dd, 1 H, $J_{5a,6}$ = 10 Hz, $J_{6,7}$ = 4.5 Hz, H-6), 3.02 (s, 3 H, C-8 N–

CH_3), 3.47 (dd, 1 H, $J_{7,8}$ = 6 Hz, $J_{8,9}$ = 8 Hz, H-8), 3.66 (dd, 1 H, $J_{8,9}$ = 8 Hz, $J_{9,9a}$ = 8.5 Hz, H-9), 3.75 (t, 1 H, $J_{9,9a}$ = $J_{9a,5a}$ = 8.5 Hz, H-9a), 3.85 (m, 1 H, H-2), 3.93 (dd, 1 H, $J_{9a,5a}$ = 8.5 Hz, $J_{5a,6}$ = 10 Hz, H-5a), 4.18 (m, 1 H, H-4), 4.59 (s, 1 H, H-10a), 4.67 (dd, 1 H, $J_{6,7}$ = 4.5 Hz, $J_{7,8}$ = 6 Hz, H-7); MS *m/e* 385 (M − CH_3), 382 (M − H_2O).

Spin decoupling: irradiation at δ 2.82 (H-6) caused the d of d at δ 3.93 (H-5a) to collapse to a doublet (J = 8.5 Hz) and the d of d centered at δ 4.67 (H-7) to collapse to a doublet (J = 6 Hz); irradiation at δ 4.67 (H-7) caused the collapse of the d of d at δ 2.82 (H-6) and 3.47 (H-8) to doublets (J = 10 and 8 Hz, respectively).

(2*R*)-2α,4β,4aβ,5aβ,6β,7β,8β,9α,9aα,10aβ-Decahydro-2-methyl-6,8-bis(methylamino)-2*H*-pyrano[2,3-*b*][1,4]benzodioxin-4,4a,7,9-tetrol 4,4a-Acetonide 6,7-Cyclic Carbamate (18b). The hydrogenolysis of the 6,7-cyclic carbamate **18a** (30 mg, 0.056 mmol) in 2-propanol (20 mL) containing 5% Pd/C (30 mg) was carried out as described for **17a** to afford 20 mg of **18b** as an oil: IR (KBr) 3330, 1765 cm^{-1}; NMR ($CDCl_3$–D_2O) δ 1.26 (d, 3 H, C-2 CH_3), 1.46 [s, 6 H, $C(CH_3)_2$], 1.50–2.10 (m, 2 H, H-3), 2.51 (s, 3 H, C-8 N–CH_3), 2.59 (dd, 1 H, $J_{7,8}$ = 4.5 Hz, $J_{8,9}$ = 9.5 Hz, H-8), 3.00 (s, 3 H, C-6 N–CH_3), 3.50 (t, 1 H, $J_{8,9}$ = 9.5 Hz, $J_{9,9a}$ = 10 Hz, H-9), 3.52 (dd, 1 H, $J_{5a,6}$ = 8 Hz, $J_{6,7}$ = 6.5 Hz, H-6), 3.70 (t, 1 H, $J_{9a,5a}$ = $J_{9,9a}$ = 10 Hz, H-9a), 3.80 (m, 1 H, H-2), 4.02 (dd, 1 H, $J_{5a,6}$ = 8 Hz, $J_{5a,9a}$ = 10 Hz, H-5a), 4.12 (m, 1 H, H-4), 4.60 (s, 1 H, H-10a), 4.75 (dd, 1 H, $J_{6,7}$ = 6.5 Hz, $J_{7,8}$ = 4.5 Hz, H-7); MS *m/e* 400 (M^+), 385 (M − CH_3).

Spin decoupling: irradiation at δ 2.59 (H-8) collapsed the t at δ 3.50 (H-9) to a doublet (J = 10 Hz) and collapsed the d of d at δ 4.75 (H-7) to a doublet (J = 6.5 Hz); irradiation at δ 4.75 (H-7) caused the collapse of the d of d at δ 2.59 (H-8) and 3.52 (H-6) to give doublets (J = 9.5 and 8 Hz, respectively).

Hydrolysis and Regeneration of 17a. A methanol solution (1 mL) of the 7,8-cyclic carbamate **17a** (18.5 mg, 0.0346 mmol) containing 1 N HCl solution (1 mL) was heated to reflux on a steam bath for 25 min. Concentration of the total reaction solution followed by purification by preparative TLC using *n*-hexane–EtOAc (3:7) gave 17.1 mg (100%) of pure **19:** IR (KBr) 3400, 1784, 1695 cm^{-1}; MS *m/e* 366 (M − 128).[3]

A dry DMF solution (1 mL) of **19** (13.3 mg, 0.027 mmol) was allowed to react with 2,2-dimethoxypropane (1.5 mL) and *p*-toluenesulfonic acid (1 mg) for 24 h. Removal of the low boiling solvents in vacuo and treatment of the residue with methanol (10 mL) containing AG 1-X8 (OH^-) afforded, after filtration and concentration of the filtrate, 14.2 mg (99%) of **17a.**

Hydrolysis and Regeneration of 18a. Hydrolysis of the 6,7-cyclic carbamate **18a** (22 mg, 0.041 mmol) as described for **17a** above yielded 18 mg (90%) of pure **20:** IR (KBr) 3440, 1750, 1694 cm^{-1}; MS *m/e* 366 (M − 128).[3]

Reintroduction of the isopropylidene group as described for **19** above afforded 10 mg (100%) of **18a** from 93 mg of the triol **20.**

(2*R*)-2α,4β,4aβ,5aα,6α,7α,8α,9β,9aβ,10aβ-Decahydro-2-methyl-8-[*N*-(benzyloxycarbonyl)-*N*-methylamino]-6-methylamino-2*H*-pyrano[2,3-*b*][1,4]benzodioxin-4,4a,7,9-tetrol 4,4a-Acetonide 6,7-Cyclic Carbamate (21a) and (2*R*)-2α,4β,4aβ,5aα,6α,7α,8α,9β,9aβ,10aβ-Decahydro-2-methyl-6-[*N*-(benzyloxycarbonyl)-*N*-methylamino]-8-methylamino-2*H*-pyrano[2,3-*b*][1,4]benzodioxin-4,4a,7,9-tetrol 4,4a-Acetonide 7,8-Cyclic Carbamate (22a). A mixture of the diastereomeric acetonide **11** (130 mg, 0.202 mmol) in dry DMF (3 mL) containing K_2CO_3 (60 mg) was heated at 95 °C for 4 h. After cooling to room temperature, the solids were filtered off and washed with toluene and the combined filtrates were concentrated in vacuo to leave 110 mg of an oil.

Preparative TLC on silica gel developed with *n*-hexane–EtOAc (3:7) afforded 51 mg of the 6,7-cyclic carbamate **21a** as a glass: R_f 0.46; IR (KBr) 3450, 1768, 1699 cm^{-1}; NMR ($CDCl_3$–D_2O) δ 1.28 (d, 3 H, C-2 CH_3), 1.51 [s, 6 H, $C(CH_3)_2$], 1.90–2.10 (m, 2 H, H-3), 3.02 and 3.04 (2s, 6 H, N–CH_3), 3.50–4.30 (m, 5 H), 4.41 (m, 1 H, H-4), 4.47 (dd, 1 H, $J_{7,8}$ = 4.5 Hz, $J_{8,9}$ = 8 Hz, H-8), 4.71 (dd, 1 H, $J_{6,7}$ = 6 Hz, $J_{7,8}$ = 4.5 Hz, H-7), 4.81 (s, 1 H, H-10a), 5.13 (s, 2 H, CH_2Ph), 7.32 (s, 5 H, arom); MS *m/e* 534 (M^+), 519 (M − CH_3), 427 (M − OCH_2Ph), 399 (M − $OCOCH_2Ph$).

Anal. Calcd for $C_{26}H_{34}N_2O_{10}$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.20; H, 6.51; N, 5.21.

The 7,8-cyclic carbamate **22a,** 54 mg, was obtained as a glass: R_f 0.25; IR (KBr) 3440, 1765, 1700 cm^{-1}; NMR ($CDCl_3$–D_2O) δ 1.27 (d, 3 H, C-2 CH_3), 1.41 and 1.48 [2s, 6 H, $C(CH_3)_2$], 1.90–2.10 (m, 2 H, H-3), 3.04 (s, 6 H, N–CH_3), 3.34–4.20 (m, 5 H), 4.41 (m, 1 H, H-4), 4.56 (dd, 1 H, $J_{5a,6}$ = 10.5 Hz, $J_{6,7}$ = 4 Hz, H-6), 4.70 (dd, 1 H, $J_{6,7}$ = 4 Hz, $J_{7,8}$ = 6 Hz, H-7), 4.86 (s, 1 H, H-10a), 5.14 (s, 2 H, CH_2Ph), 7.32 (s, 5 H, arom); MS *m/e* 534 (M^+), 519 (M − CH_3), 427 (M − OCH_2Ph), 399 (M − $OCOCH_2Ph$).

Anal. Calcd for $C_{26}H_{34}N_2O_{10}$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.32; H, 6.21; N, 5.30.

(2*R*)-2α,4β,4aβ,5aα,6α,7α,8α,9β,9aβ,10aβ-Decahydro-2-methyl-6,8-bis(methylamino)-9-benzoyloxy-2*H*-pyrano[2,3-*b*][1,4]benzodioxin-4,4a,7-triol 4,4a-Acetonide 6,7-Cyclic Carbamate (21b). A solution of the 6,7-cyclic carbamate **21a** (53 mg, 0.0991 mmol) in pyridine (2 mL) containing benzoyl chloride (0.042 mL, 52 mg, 0.3 mmol) was stirred at room temperature for 24 h. The reaction solution was concentrated, and the residue was dissolved in $CHCl_3$, washed once with H_2O, dried, and concentrated. The crude product was purified by preparative TLC on silica gel using *n*-hexane–EtOAc (3:7) to yield 56 mg (89%) of (2*R*)-2α,4β,4aβ,5aα,6α,7α,8α,-9β,9aβ,10aβ-decahydro-2-methyl-8-[*N*-(benzyloxycarbonyl)-*N*-methylamino]-6-methylamino-9-benzoyloxy-2*H*-pyrano[2,3-*b*]-[1,4]benzodioxin-4,4a,7-triol 4,4a-acetonide 6,7-cyclic carbamate as a foam: IR (KBr) 1773, 1730, 1694 cm^{-1}; NMR ($CDCl_3$) (two rotamers) δ 1.18 (d, 3 H, C-2 CH_3), 1.49 [broad s, 6 H, $C(CH_3)_2$], 1.95–2.20 (m, 2 H, H-3), 2.84, 2.90, and 3.03 (3s, 6 H, N–CH_3), 3.50–3.80 (m, 3 H), 4.02 (m, 1 H, H-2), 4.46 (broad t, 1 H, J = 3 Hz, H-4), 4.66 (s, 1 H, H-10a), 4.70–5.00 (m, 2 H), 5.07 (s, 2 H, CH_2Ph), 5.66 (dd, 1 H, $J_{8,9}$ = 10 Hz, $J_{9,9a}$ = 8 Hz, H-9), 7.34 (s, 5 H, arom), 7.20–7.60 (m, 3 H, O_2CPh), 7.97 (m, 2 H, O_2CPh); MS *m/e* 638 (M^+), 623 (M − CH_3), 516 (M − $PhCO_2H$).

Hydrogenolysis of the above benzoate (54 mg, 0.0845 mmol) in 2-propanol (30 mL) containing 5% Pd/C (40 mg), as described for **17b,** gave 30 mg (70%) of **21b** as a glass: IR (KBr) 1768, 1727 cm^{-1}; NMR ($CDCl_3$–D_2O) δ 1.21 (d, 3 H, C-2 CH_3), 1.51 and 1.52 [2s, 6 H, $C(CH_3)_2$], 1.95–2.40 (m, 2 H, H-3), 2.53 (s, 3 H, C-8 N–CH_3), 3.04 (s, 3 H, C-6 N–CH_3), 3.06 (dd, 1 H, $J_{7,8}$ = 4 Hz, $J_{8,9}$ = 6 Hz, H-8), 3.65 (dd, 1 H, $J_{5a,9a}$ = 10.5 Hz, $J_{9,9a}$ = 7.5 Hz, H-9a), 3.74 (t, 1 H, $J_{5a,6}$ = 8 Hz, $J_{6,7}$ = 7.5 Hz, H-6), 4.03 (m, 1 H, H-2), 4.20 (dd, 1 H, $J_{5a,6}$ = 8 Hz, $J_{5a,9a}$ = 10.5 Hz, H-5a), 4.50 (broad t, 1 H, J = ~3 Hz, H-4), 4.72 (s, 1 H, H-10a), 4.85 (dd, 1 H, $J_{6,7}$ = 7.5 Hz, $J_{7,8}$ = 4 Hz, H-7), 5.34 (dd, 1 H, $J_{8,9}$ = 6 Hz, $J_{9,9a}$ = 7.5 Hz, H-9), 7.30–7.60 (m, 3 H, arom), 8.02 (m, 2 H, arom); MS *m/e* 489 (M − CH_3), 382 (M − $PhCO_2H$).

Spin decoupling: irradiation at δ 5.34 (H-9) caused the collapse of the d of d centered at δ 3.06 (H-8) to a doublet (J = 4 Hz) and the d of d at δ 3.65 (H-9a) to a doublet (J = 10.5 Hz).

(2*R*)-2α,4β,4aβ,5aα,6α,7α,8α,9β,9aβ,10aβ-Decahydro-2-methyl-6-[*N*-(benzyloxycarbonyl)-*N*-methylamino]-8-methylamino-9-benzoyloxy-2*H*-pyrano[2,3-*b*][1,4]benzodioxin-4,4a,7-triol 4,4a-Acetonide 7,8-Cyclic Carbamate (22b). The 7,8-cyclic carbamate **22a** (54 mg, 0.101 mmol) in dry pyridine (1.5 mL) was treated with benzoyl chloride (0.042 mL, 52 mg, 0.3 mmol), and this solution was stirred at room temperature for 20 h. The reaction mixture was concentrated and the residue was dissolved in $CHCl_3$ and washed once with H_2O. Drying and concentration of the $CHCl_3$ solution left 63 mg (98%) of pure **22b** as a foam: IR (KBr) 1773, 1733, 1703 cm^{-1}; NMR ($CDCl_3$) δ 1.18 (d, 3 H, C-2 CH_3), 1.44 [broad s, 6 H, $C(CH_3)_2$], 1.80–2.40 (m, 2 H, H-3), 2.82 and 3.07 (2s, 6 H, N–CH_3), 3.70 (t, 1 H, $J_{9,9a}$ = $J_{9a,5a}$ = 10 Hz, H-9a), 3.87 (dd, 1 H, $J_{7,8}$ = 6 Hz, $J_{8,9}$ = 8 Hz, H-8), 4.00 (t, 1 H, $J_{5a,6}$ = 9 Hz, $J_{5a,9a}$ = 10 Hz, H-5a), 4.47 (broad t, 1 H, J = ~3 Hz, H-4), 4.65 (dd, 1 H, $J_{6,7}$ = 4 Hz, $J_{5a,6}$ = 9 Hz, H-6), 4.69 (s, 1 H, H-10a), 4.82 (dd, 1 H, $J_{6,7}$ = 4 Hz, $J_{7,8}$ = 6 Hz, H-7), 5.18 (s, 2 H, CH_2Ph), 5.48 (dd, 1 H, $J_{8,9}$ = 8 Hz, $J_{9,9a}$ = 10 Hz, H-9), 7.34 (s, 5 H, arom), 7.51 (m, 3 H, O_2CPh), 8.04 (m, 2 H, O_2CPh); MS *m/e* 638 (M^+), 623 (M − CH_3), 593 (M − $PhCO_2H$).

Spin decoupling: irradiation at δ 5.48 (H-9) caused the collapse of the t centered at δ 3.70 (H-9a) to a doublet (J = 10 Hz), and the d of d at δ 3.87 (H-8) collapsed to a doublet (J = 6 Hz).

Anal. Calcd for $C_{33}H_{38}N_2O_{11}$: C, 62.06; H, 6.00; N, 4.39. Found: C, 62.23; H, 6.22; N, 4.30.

Rearrangement of the 6,7-Cyclic Carbamate 21a into the 7,8-Cyclic Carbamate 17a. The 6,7-cyclic carbamate **21a** (5 mg, 0.009 mmol) was dissolved in 0.5 mL of MeOH, 1 N HCl solution (0.5 mL) was added, and this solution was heated to reflux on a steam bath for 20 min. The total reaction solution was concentrated, and the residue was redissolved in MeOH–toluene (1:1) and reconcentrated. The crude product was then dissolved in a mixture of dry DMF (0.5 mL), 2,2-dimethoxypropane (1 mL), and *p*-toluenesulfonic acid (0.1 mg) and stirred overnight at room temperature. After concentration of the reaction solution in vacuo, the residue was dissolved in MeOH (10 mL) and stirred for 10 min with AG 1-X8 (OH^-) (1 mL). The resin was filtered off, the filtrate concentrated, and the product purified by preparative TLC using *n*-hexane–EtOAc (3:7) to yield 5 mg of pure product identical with **17a** by TLC, IR, and MS.

Rearrangement of the 7,8-Cyclic Carbamate 22a into the 6,7-Cyclic Carbamate 18a. Treatment of the 7,8-cyclic carbamate **22a** (5 mg, 0.009 mmol) as described for **21a** above afforded 5 mg of a foam, whose TLC, IR, and MS data were identical with those of **18a.**

Acknowledgment. We wish to thank David Greeley and

Gino Sasso of the NMR Laboratory (under the direction of Dr. T. Williams) for their assistance in obtaining 100-MHz NMR spectra and carrying out numerous decoupling experiments. The skilled assistance of Mr. Jack Lin in preparing compound i[5] and isolating some of the initial quantities of 11 is gratefully acknowledged. We also thank Dr. J. F. Blount for the X-ray analysis confirming the structure of compound i.

Registry No.—**1a**, 1695-77-8; **6**, 56782-21-9; **7**, 58515-30-3; **8**, 67421-50-5; **9**, 67421-51-6; **10**, 67421-52-7; **11**, 67462-78-6; **11** 7-*O*-acetyl derivative, 67421-53-8; **14**, 67462-79-7; **15**, 67462-80-0; **17a**, 67421-54-9; **17b**, 67421-55-0; **18a**, 67421-56-1; **18b**, 67421-57-2; **19**, 67421-58-3; **20**, 67421-59-4; **21a**, 67462-81-1; **21b** 9-benzoate, 67421-62-9; **21b**, 67421-60-7; **22a**, 67462-82-2; **22b**, 67421-61-8; 2,2-dimethoxypropane, 77-76-9.

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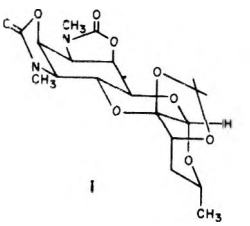
(5) An X-ray analysis carried out on the bis(carbamate) i, prepared in a series of steps from the acetonide **7**, confirmed its structure as well as that of **7** (J. Lin, unpublished results).



i

(6) For recent discussions of the "anomeric effect" see, Romers, C.; Altona, C.; Buys, H. R.; Havinga, E. *Top. Stereochem.* **1969**, *4*, 73–7. David, S.; Einstein, O.; Hehre, W. J.; Salem, L.; Hoffmann, R. *J. Am. Chem. Soc.*, **1973**, *95* 3806–7. Bailey, W. F.; Eliel, E. L. *ibid.* **1974**, *96*, 1798–1806.
(7) The numbering system used in this paper is that of the 2*H*-pyrano[2,3-*b*][1,4]benzodioxin ring system. This numbering system also corresponds to the one used for spectinomycin.
(8) Details of the spin decoupling experiments may be found in the Experimental Section.
(9) The narrow line width of the triplet, $J = 2.5–3$ Hz, observed for H-4 indicates that the actinospectose ring exists in the boat conformation. Examination of Dreiding models reveals that the chair conformation would result in considerable steric interaction between the C-2 methyl group and the oxygen atom of the 1,4-benzodioxin ring.
(10) The unlikely possibility that the keto alcohol **13** represents the most stable form of this molecule may be discounted since the 4(*S*)-dihydrospectinomycin **1c** or its derivatives do not rearrange under conditions used for preparing the acetonides or on treatment with mild base (unpublished results).
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Malyngamides D and E, Two *trans*-7-Methoxy-9-methylhexadec-4-enamides from a Deep Water Variety of the Marine Cyanophyte *Lyngbya majuscula*

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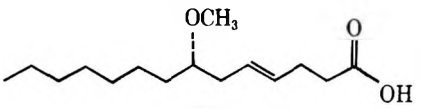
Received May 12, 1978

Malyngamides D and E are two *trans*-7-methoxy-9-methylhexadec-4-enamides that have been isolated from the lipid extract of a deep water variety of the marine blue-green alga *Lyngbya majuscula*. Detailed spectral analysis, mostly NMR, and chemical degradation show that malyngamides D and E have the gross structures **2** and **3**, respectively. Malyngamides D and E produce the same diacetate on acetylation. The ring stereochemistry of **2** and **3** has been defined from NMR and chemical reactivity data.

Malyngamides A, B, and C are chlorine-containing *trans*-7(*S*)-methoxytetradec-4-enamides that are present in shallow-water varieties of the marine blue-green alga *Lyngbya majuscula*.[1,2] Free *trans*-7(*S*)-methoxytetradec-4-enoic acid (**1**) is also a lipophilic constituent of the shallow-water strains.[1]

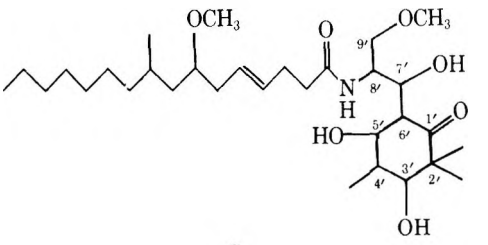


1

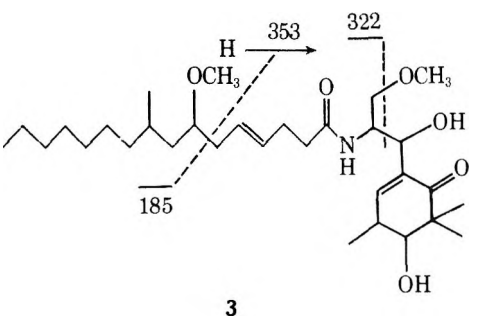
Neither **1** nor amides of **1** have been found in a toxic, deep-water variety of *L. majuscula* from Enewetak.[3,4] Instead two closely related *trans*-7-methoxy-9-methylhexadec-4-enamides, malyngamides D (**2**) and E (**3**),[5] are present in this alga. This paper describes the gross structure elucidations of malyngamides D and E.

Structure Determination

Mass spectral analysis showed that amides **2**, $[\alpha]_D$ −33.0° in $CHCl_3$, and **3**, $[\alpha]_D$ +24.2° in $CHCl_3$, differed in molecular composition by the elements of H_2O. Except for a small M^+ ion at *m/e* 555 for **2**, the mass spectra of **2** and **3** were essentially identical, with compound **3** showing a M^+ ion at *m/e* 537.40235 for $C_{31}H_{55}NO_6$ (calcd 537.40295). The



2



3

molecular formula of **2** was therefore $C_{31}H_{57}NO_7$ and this agreed with the formula determined from ^{13}C NMR (5 CH_3 bonded to carbon, 2

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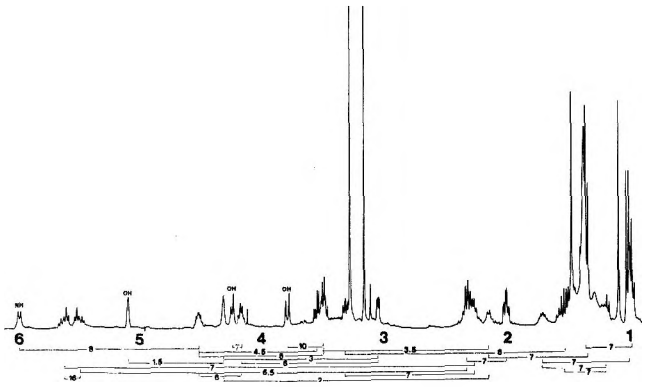


Figure 1. The 360-MHz ^1H NMR spectrum of malyngamide D (**2**) in benzene-d_6 at 54 °C. The chemical shift scale is in δ (ppm) units. Connecting lines denote coupled (in Hz) proton signals that have been determined by homonuclear decoupling and deuterium exchange (addition of D_2O) experiments. The sample contains a small amount of malyngamide E (**3**).

OCH_3, 11 CH_2, 10 CH, 1 C bonded to carbon only, 2 C=O) and ^1H NMR (3 OH, 1 NH) spectral data.

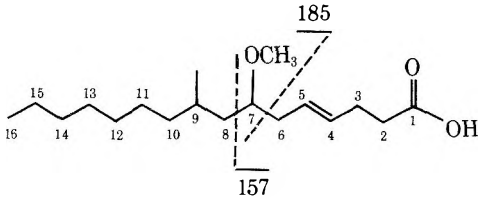
The ^{13}C NMR spectrum of **2** (Table I) exhibited only four unsaturated carbon signals, i.e., δ 217.04 (ketone C=O), 172.48 (amide C=O), and 131.00 and 127.2 (-CH=CH-) in benzene-d_6; **2** was therefore monocyclic. The ^{13}C NMR spectrum also indicated that, in addition to two methoxyl carbons (δ 58.64, 56.00), five other carbon atoms were singly bonded to oxygen, one methylene (δ 70.57) and four methines (δ 84.76, 79.37, 79.02, 72.53). In the ^1H NMR spectrum of **2** in benzene-d_6 (Figure 1), three hydroxyl signals appeared as doublets at δ 5.11 (partially resolved, J = 1.5 Hz), 4.26 (J = 7 Hz), and 3.81 (J = 10 Hz) and an amide NH signal was observed as a doublet at δ 6.00 (J = 8 Hz); on addition of D_2O all four of these signals disappeared. The IR spectrum of **2** supported the presence of ketone (1700 cm^{-1}) and amide (1660 cm^{-1}) functionalities and furthermore indicated that the disubstituted double bond was trans (975 cm^{-1}). All seven oxygens and the single nitrogen could therefore be accounted for by a ketone, a secondary amide, two methoxyl (one attached to CH_2 and the other to CH), and three secondary alcohol functionalities.

The ^{13}C NMR spectrum of **3** (Table I) differed from the ^{13}C NMR spectrum of **2** in two ways. First it had absorptions at δ 136.08 (singlet) and 145.68 (doublet) in $CDCl_3$ for an additional double bond which was trisubstituted and conjugated with the ketone carbonyl as shown in a. The UV spectrum, λ_{max} 235 nm (ϵ 6400), was consistent with this interpretation.

a b

Second it lacked two saturated methine absorptions, one for a methine attached to carbon only and the other for a methine bonded to an oxygen and to a carbon, and this suggested that **2** was the corresponding β-hydroxy ketone of partial structure b.

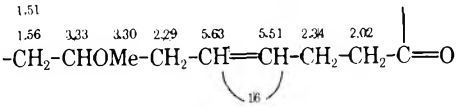
Acid hydrolysis of **3** yielded *trans*-7-methoxy-9-methylhexadec-4-enoic acid (**4**). The ^1H NMR spectrum of **4** showed signals for the



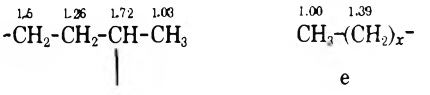
4

C-2, C-3, C-4, C-5, and C-6 protons that were superimposable on those of **1**;[1] the C-7 methine signal, however, was at slightly lower field (in $CDCl_3$ δ 3.25 compared with δ 3.15 for **1**). The mass spectrum of **4** showed fragmentation that was compatible with the molecular formula $C_{18}H_{34}O_3$ and the placement of the methoxyl substituent on C-7. The ^1H NMR spectrum also indicated that **4** contained a secondary methyl group (broad doublet at δ 0.88, J = 7 Hz).

The presence of the *trans*-7-methoxy-9-methylhexadec-4-enoyl unit in **2** and **3** was demonstrated by high-frequency ^1H-NMR experiments. Successive homonuclear decoupling experiments on **2** (Figure 1) and **3** established partial structures c, d, and e. Since the

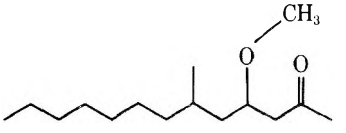


c



d e

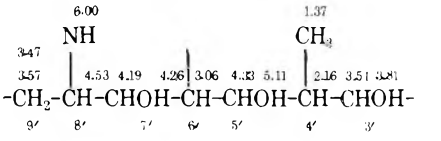
nonequivalent C-8 methylene proton signals (δ 1.51 and 1.57 for **2**) were sharp, we felt that the methyl group had to be attached to either C-9 or C-10. The proton decoupling studies favored the C-9 position since the C-8 absorptions appeared to be doublets (J_{gem} = −12 to −14 Hz) of triplets (J = 6–7 Hz) which collapsed to doublets of doublets on irradiation of the C-7 methine (δ 3.33). Since another methylene (C-11) resonated at δ 1.5 (broad signal), however, we were not able to make a definite decision. The ^{13}C NMR data of **2** and **3**, however, were only consistent with the placement of the methyl substituent on C-9 (Table I). Calculated carbon-13 chemical shifts agreed with the observed values when the methyl group was on C-9 and not on C-10. The assignment was confirmed by a lanthanide induced shift (LIS) study of **5** (from ozonolysis of **2** and **3**) which clearly showed that a single methylene separated the methoxyl and methyl bearing methines. In the presence of 6.25 equiv of $Eu(fod)_3$ in $CDCl_3$ the C-4 methylene signal of **5** was observed as a well-defined triplet at δ 4.37 which col-



5

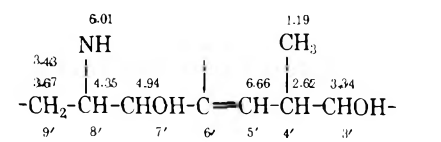
lapsed to a doublet when the quintet for the C-3 methine was irradiated (δ 9.1).

Additional proton spin–spin decoupling experiments on **2** (Figure 1) established the sequence f in **2**. Addition of D_2O led to changes in



f

the signals at δ 4.53, 4.19, 4.33, and 3.51, in agreement with the decoupling results. Since **4** was furnished on hydrolysis the fatty acyl group had to be attached to the NH. The ketone carbonyl therefore was connected to C-6′, since only this position had an OH β to the C=O as in b. The other OCH_3 (δ 3.18) group had to be on C-9′ from NMR evidence. The remaining *gem*-dimethyl carbon [^{13}C δ 52.59; ^1H δ 1.10 (3 H, s) and 1.49 (3 H, s)] was then placed between the ketone carbonyl and C-3′ to form a cyclohexanone ring. In support of these structural conclusions, proton spin–spin decoupling studies of **3** led to the related partial structure g. Unlike the ^1H NMR spectrum of **2**, however, the C-3′ and C-7′ proton signals of **3** did not show coupling to hydroxyl protons and the two OH signals could not be observed. The attachment of OH groups at C-3′ and C-7′ in **3** was verified by acetylation (see below).



g

Stereochemistry

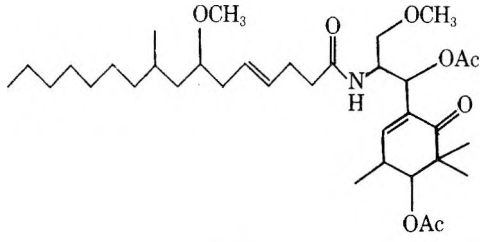
Malyngamide D was recovered unchanged when treated with acetic anhydride and pyridine at room temperature;

Table I. Carbon-13 NMR Data for Malyngamides D (2) and E (3)

Chemical shift[a]				
2		3		
$CDCl_3$	C_6D_6	$CDCl_3$	C_6D_6	Assignment[b]
216.75	217.04 (s)	202.21 (s)	202.5	1′
172.27	172.48 (s)	173.07 (s)	173.09	1
		145.68 (d)	145.97	5′
		136.08 (s)	136.90	6′
130.35	131.00 (d)	130.62 (d)	131.17	4
127.27	127.2 (d)	127.18 (d)	127.2	5
84.56	84.76 (d)	79.63 (d)	79.74	3′[c]
79.63	79.37 (d)			5′[c]
78.66	79.02 (d)	78.84 (d)	79.21	7[c] (75.5)
72.32	72.53 (d)	69.06 (d)	69.00	7′[c,d]
70.03	70.57 (t)	71.70 (t)	71.99	9′
58.85	58.64 (q)	58.93 (q)	58.96	OCH_3 on 9′
56.07	56.00 (q)	56.20 (q)	56.32	OCH_3 on 7
52.24	52.59 (d)			6′[c]
51.45	52.59 (s)	48.10 (s)	48.48	2′
49.86	50.01 (d)	53.21 (d)	54.03	8′[c,d]
41.06	41.54 (t)	41.14 (t)	41.70	8[c] (40.9)
36.83	37.36 (t)	36.83 (t)	37.47	10[c] (37.2)
36.21	36.80 (t)	36.39 (t)	36.94	6[c]
36.21	36.15 (t)	36.2 (t)	36.41	2[c]
34.45	34.84 (d)	32.95 (d)	33.42 (d)	4′[c,d]
31.81	32.26 (t)	31.81	32.36 (t)	14 (32.4)
29.74	30.33 (t)	30.0	30.43 (t)	12 (30.2)
29.34	29.87 (d)	29.43	29.90 (d)	9[c] (29.5)
29.34	29.74 (t)	29.43 (t)	29.90	13 (29.7)
28.46	28.84 (t)	28.37 (t)	28.84	3
26.79	27.33 (t)	26.79 (t)	27.43	11 (27.3)
25.47	25.49 (q)	23.27 (q)	23.56	CH_3 on 4′[e]
22.56	23.03 (t)	22.65 (t)	23.21	15 (22.7)
20.63	21.32 (q)	21.24	21.80 (q)	eq CH_3 on 2′[c]
20.10	20.46 (q)	20.10 (q)	20.56	CH_3 on 9[c] (20.1)
14.20	14.72 (q)	16.84 (q)	17.22	ax CH_3 on 2′[e]
14.02	14.28 (q)	14.11 (q)	14.57	16[c] (13.9)

[a] Reported in δ units relative to the solvent peak, i.e., benzene-d_6 (δ 128.0) or chloroform-*d* (δ 76.9), as an internal standard. [b] Numbers in parentheses are calculated chemical shifts [G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, 1972, pp 41 and 47]. [c] Based on proton single frequency off-resonance decoupling (sford) experiments on **2** in C_6D_6 at 90 MHz. [d] Based on proton sford experiments on **3** in $CDCl_3$. [e] Tentative assignments; removal of OH from C-5′ should result in an upfield shift of the Me on C-4′ and the removal of axial proton from C-6′ should shift the signal for the axial Me on C-2′ downfield.

however, **2** did react slowly at 55 °C to form a diacetate which was spectrally and optically identical with malyngamide E diacetate (**6**), obtained by a similar acetylation of **3** at 55 °C.

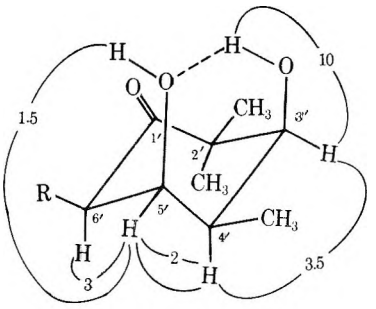


6

The ^1H NMR spectrum of **6** in $CDCl_3$ exhibited sharp singlets at δ 1.98 and 2.04 for the two acetoxyl groups. As expected the C-3′ and C-7′ protons of **6** resonated at much lower field, δ 5.16 and 5.62, than the C-3′ and C-7′ protons of **3**, δ 3.53 and 4.71, respectively.

The resistance of **2** to acetylation suggested that the hydroxyl groups on C-3′ and C-5′ are axially disposed. Furthermore the facile β elimination of the C-5′ hydroxyl during the acetylation of **2** suggested that the C-6′ proton is axial and therefore trans to the C-5′ hydroxyl group. The small proton–proton coupling constants for $J_{3',4'}$, $J_{4',5'}$, and $J_{5',6'}$ agree with these stereochemical conclusions.

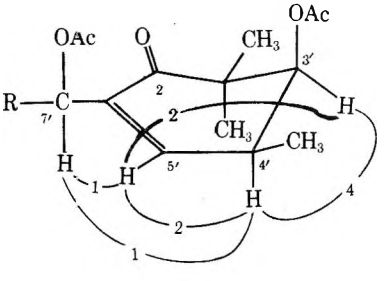
In the ^1H NMR spectrum of **2** in benzene-d_6 at 54 °C the signals for the three hydroxyl protons appear as well-resolved doublets, reflecting coupling to the adjacent methine protons. In the ^1H NMR spectrum of **3** in benzene-d_6 at 54 °C, however, the signals for the two hydroxyl protons cannot be seen. Moreover, the C-3′ and C-7′ proton signals of **3** do not show any coupling to OH protons. Obviously the proton exchange rate is much slower in **2** than it is in **3**. When the C-3′ and C-5′ OH groups are axial, intramolecular hydrogen bonding is allowed, not only between the C-3′ and C-5′ OH groups, but also between the C-5′ and C-7′ OH groups of **2**. Since the C-5′ OH is missing in **3**, intramolecular hydrogen bonding is not possible between the C-3′ and C-7′ OH groups. In **2** the magnitudes of J_{CHOH} for the OH signals at δ 3.81 (10 Hz) and 5.11 (1.5 Hz) indicate dihedral angles of approximately 180 and 60°, respectively.[6] At C-3′ the OH proton must therefore be trans to the C-3′ methine proton and at C-5′ the OH proton must be gauche to the C-5′ methine proton as shown in h. The



h

stereochemistry at C-7′, however, as well as at the other chiral centers in the side chain, cannot be deduced from the NMR data.

In the ^1H NMR spectra of **3** and **6**, W coupling (2 Hz) is observed between the C-3′ and C-5′ protons, requiring that the C-3′ proton in **3** and **6** be equatorial as it is in **2**. The methyl group on C-4′ must therefore be in an equatorial position. If the C-3′ and C-4′ substituents of **3** and **6** were trans, it would be impossible to have both groups axial in the preferred conformer. The C-4′ methyl group in **2** is then also equatorially oriented. Small (1 Hz) but significant homoallylic coupling can be detected between the C-4′ and C-7′ protons of **3** and **6**. From Dreiding models of **3** and **6** the dihedral angle between the C-4′ and C-5′ protons appears to be close to 90° which is consistent with the observed homoallylic coupling.[7] The proposed stereochemistry of the ring in **6** (absolute configuration not implied) is depicted in i.



i

Experimental Section

^{1}H- and ^{13}C-NMR spectra were obtained on a Varian XL-100 spectrometer equipped with a Digilab Fourier transform system. High-frequency ^{1}H- and ^{13}C-NMR studies were performed on the HXS-360 instrument at the Stanford Magnetic Resonance Laboratory. Proton chemical shifts are reported in δ units relative to the benzene-d_5 peak (δ 7.24) when benzene-d_6 was used as the solvent or to $(CH_3)_4Si$ (δ 0) as an internal standard when chloroform-d was used as the solvent; J values are given in hertz. Electron impact mass spectra were determined at 70 eV on a Varian MAT 311 high-resolution mass spectrometer. Optical rotations were measured on a ETL-NPL (Ericsson Telephone Unlimited) automatic polarimeter. Elemental analyses were performed by the Chemical Analytical Services, University of California, Berkeley.

Isolation. Wet *Lyngbya majuscula*[3] (3 kg), collected from Reefer 8 pinnacle (80–100 ft), Enewetak lagoon in September, 1975, was extracted with chloroform–methanol (1:2). Water was added to the extract and the chloroform layer was evaporated to give 22 g of a dark brown oil. Chromatography on a column of Florisil (40 cm × 4.7 cm) gave a toxic fraction[4] which was eluted with chloroform–methanol (9:1). Gel filtration of the toxic oil (1.9 g) on a column (1.15 m × 1.5 cm) of Sephadex LH-20 with chloroform–methanol (1:1) gave 580 mg of a fraction which was then rechromatographed on a column (1 cm × 24 cm) of silica gel PF254 with ethyl acetate. The resulting mixture of malyngamides (341 mg) was finally separated by preparative TLC on plates of silica gel PF254 with two developments of chloroform–methanol (19:1) into 71 mg of malyngamide D and 190 mg of malyngamide E.

Malyngamide D (**2**) had the following properties: $[\alpha]^{25}_D$ −33.0° ($CHCl_3$, c 0.53); IR (CCl_4) ν_{max} 1700 (s), 1660 (s), 975 cm^{-1} (s); ^{1}H NMR (benzene-d_6, 54°, 360 MHz) δ 6.00 (br d, J = 8, amide NH), 5.63 (dt, $J_{5,4}$ = 16, $J_{5,6}$ = 7, C-5 –CH=), 5.51 (dt, $J_{4,5}$ = 16 and $J_{4,3}$ = 6.5, C-4 =CH–), 5.11 (br d, $J_{OH,5'}$ = 1.5, OH on C-5′), 4.53 (br dq, $J_{8',NH}$ = 8, $J_{8',9'}$ = 4.5 and 6, $J_{8',7'}$ = 6, C-8′ H), 4.33 (br m, $J_{5',OH}$ = 1.5, $J_{5',6'}$ = 3, $J_{5',4'}$ = 2, C-5′ H), 4.26 (d, $J_{OH,7'}$ = 7, OH on C-7′), 4.19 (quartet, $J_{7',OH}$ = 7, $J_{7',8'}$ = $J_{7',6'}$ = 6, C-7′ H), 3.81 (d, $J_{OH,3'}$ = 10, OH on C-3′ H), 3.57 (dd, J_{gem} = −10, $J_{9',8'}$ = 4.5, C-9′ proton), 3.51 (m, obscured by dd at 3.47 ppm, C-3′ H), 3.47 (dd, C-9′ proton), 3.33 (quintet, $J_{7,8}$ = 6, $J_{7,6}$ = 7, C-7 H), 3.30 (s, OMe on C-7), 3.18 (s, OMe on C-9′), 3.06 (dd, $J_{6',5'}$ = 3, $J_{6',7'}$ = 6, C-6′ H), 2.34 (quartet, $J_{3,4}$ = 6.5, $J_{3,2}$ = 7, C-3 methylene), 2.29 (m, C-6 methylene), 2.16 (m, C-4′), 2.02 (m, J_{gem} = −14, C-2 methylene), 1.72 (br m, C-9), 1.57 (dt, C-8 proton), 1.51 (dt, C-8 proton), 1.5 (br m under dt at 1.51, C-11 methylene), 1.49 (s, Me on C-2′), 1.39 (br m, C-12, C-13, C-14, C-15 methylenes), 1.37 (d, J = 7, Me on 4′), 1.26 (m, C-10 methylene), 1.10 (s, Me on C-2′), 1.03 (d, J = 7, Me on C-9), 1.00 (br t, J = 7, C-16 methyl); MS m/e (rel intensity) 555 (0.1, M$^+$), 537 (1, M − H_2O), 522 (1), 519 (2), 505 (1), 460 (3), 442 (2), 354 (28), 353 (25), 335 (22), 323 (22), 322 (64), 299 (13), 281 (35), 267 (12), 199 (15), 185 (91), 139 (51), 116 (68), 111 (49), 97 (100), 85 (67), 83 (100).

Malyngamide E (**3**) had the following properties: $[\alpha]^{24}_D$ + 24.2° ($CHCl_3$, c 0.6); UV (MeOH) λ_{max} 235 nm (ϵ 6400); IR (CCl_4) ν_{max} 1675 (s, broad), 985 cm^{-1} (m); ^{1}H NMR (benzene-d_6, 54°, 360 MHz) δ 6.66 (br, $J_{5',4'} \sim J_{5',3'} \sim J_{5',7'} \sim 1$, C-5′), 6.01 (br d, $J_{NH,8'}$ = 8, amide NH), 5.63 (dt, $J_{5,4}$ = 16, $J_{5,6}$ = 6.5, C-5 –CH=), 5.54 (dt, $J_{4,5}$ = 16, $J_{4,3}$ = 6.5, C-4 =CH–), 4.94 (br d, $J_{7',8'}$ = 6, $J_{7',4'} \sim 2$, $J_{7',5'} \sim 1$, C-7′), 4.35 (br m, $J_{8',NH}$ = 8, $J_{8',7'}$ = 6, $J_{8',9'}$ = 3 and 5, C-8′ H), 3.67 (dd, J_{gem} = −10, $J_{9',8'}$ = 3, C-9′ proton), 3.43 (dd, J_{gem} = −10, $J_{9',8'}$ = 5, C-9′ proton), 3.34 (m, C-7 H), 3.34 (m, C-3′ H), 3.29 (s, OMe on C-7), 3.12 (s, OMe on C-9′), 2.62 (m, C-4′ H), 2.40 (quartet, $J_{3,4}$ = 6.5, $J_{3,2}$ = 7, C-3 methylene), 2.29 (br m, C-6 methylene), 2.13 (dt, J_{gem} = −14.5, $J_{2,3}$ = 7, C-2 proton), 2.06 (dt, J_{gem} = −14.5, $J_{2,3}$ = 7, C-2 proton), 1.72 (br m, C-9 H), 1.55 (m, C-8 proton), 1.50 (m, C-8 proton), 1.5 (br m, C-11 methylene), 1.42 (s, Me on C-2′), 1.39 (br, C-12, C-13, C-14, C-15 methylenes), 1.24 (m, C-10 methylene), 1.19 (d, J = 7, Me on C-4′), 1.03 (d, J = 7, Me on C-9), 1.01 (s, Me on C-2′), 1.01 (br t, J = 7, C-16 methyl); ^{1}H NMR ($CDCl_3$, 360 MHz), δ 6.58 (br, C-5′ H → t, J = 2 on irr at 4.71), 6.14 (br d, J = 8, NH), 5.48 (m, C-5 H), 5.44 (m, C-4 H), 4.71 (br d, J = 6, C-7′ H → dd, J = 6 and 2 on irr at 6.58), 4.16 (m, C-8′ H), 3.60 (dd, J = −11 and 3.5, C-9′ proton), 3.53 (t, J = 2, C-3′ H), 3.42 (dd, J = −11 and 5.5, C-9′ proton), 3.29 (s, OMe), 3.27 (s, OMe), 3.22 (quintet, C-7 H), 2.93 (m, C-4′ H), 2.27 (m, CH_2), 2.20 (m, CH_2), 2.10 (m, CH_2), 1.47 (m, C-9 H), 1.24 (d, J = 7, Me on C-4′), 1.23 (br m, C-8, C-10, C-11, C-12, C-13, C-14, C-15 methylenes), 1.19 (s, Me on C-2′), 1.07 (s, Me on C-2′), 0.85 (br t, C-16 methyl), 0.83 (d, J = 7, Me on C-9); MS m/e (rel intensity) 537 (3, M$^+$), 522 (2, M − CH_3), 519 (2.5, M − H_2O), 505 (5, M − CH_3OH), 460 (5), 354 (44), 353 (40), 335 (33), 323 (34), 322 (64), 299 (12), 281 (26), 199 (12), 185 (89), 139 (32), 113 (51), 111 (78), 97 (100), 85 (90), 83 (94); high resolution MS m/e 537.40235 (calcd for $C_{31}H_{55}NO_6$, 537.40295), 353.22585 (calcd for $C_{19}H_{31}NO_5$, 353.22023), 322.27208 (calcd for $C_{20}H_{36}NO_2$, 322.27461), 185.19049 (calcd for $C_{12}H_{25}O$, 185.19055).

Anal. Calcd for $C_{31}H_{55}NO_6 \cdot H_2O$: C, 67.0; H, 10.3; N, 2.5. Found: C, 66.7; H, 9.9; N, 2.6.

Acid Hydrolysis of Malyngamide E. A solution of 9.8 mg of **3** in 5 mL of aqueous 2NHCl and 5 mL of methanol was heated at 50 °C for 19 h. The mixture was diluted with water and extracted with chloroform. Gel filtration of the extract on a 1.4 m × 1.5 cm column of Sephadex LH-20 with chloroform–methanol (1:1) gave three fractions, A (108–125 mL, 3.5 mg), B (125–138 mL, 3.5 mg), and C (138–159 mL, 1.7 mg). Fraction A was unreacted **3**. Fraction B was *trans*-7-methoxy-9-methylhexadec-4-enoic acid (**4**): ^{1}H NMR ($CDCl_3$) δ 5.51 (br m, 2 H, C-4 and C-5 methines), 3.33 (s, OCH_3 on C-7), 3.25 (m, 1 H, C-7 methine), 2.40 (br s, 4 H, C-2 and C-3 methylenes), 2.14 (br m, 2 H, C-6 methylene), 1.26 (br s with low field sh, 15 H), 0.89 (br t, J = 7, 3 H), 0.88 (br d, J = 7, 3 H), chemical shift of CO_2H proton not determined; MS m/e (rel intensity) 213 (3), 185 (50), 157 (6), 111 (26), 97 (100), 85 (49), 83 (63), 71 (76), 69 (48); high resolution MS m/e 185.19103 (calcd for $C_{12}H_{25}O$, 185.19055), 157.08658 (calcd for $C_8H_{13}O_3$, 157.08647). Fraction C was methyl *trans*-7-methoxy-9-methylhexadec-4-enoate: ^{1}H NMR ($CDCl_3$) δ 5.49 (br m, 2 H, C-4 and C-5 methines), 3.68 (s, ester OCH_3), 3.32 (s, OCH_3 on C-7), 3.24 (m, 1 H, C-7 methine), 2.38 (br s, 4 H, C-2 and C-3 methylenes), 2.18 (m, 2 H, C-6 methylene), 1.27 (br s with low field sh, 15 H), 0.90 (br t, J = 7, 3 H), 0.88 (br d, J = 7 Hz, 3 H); MS m/e (rel intensity) 312 (0.2, M$^+$), 281 (0.7, M − OCH_3), 185 (100), 171 (3), 111 (19), 97 (73), 85 (44), 83 (43), 71 (43), 69 (26); high resolution MS m/e 185.19121 (calcd for $C_{12}H_{25}O$, 185.19055), 111.11853 (calcd for C_8H_{15}, 111.11738).

Ozonolysis of Malyngamides D and E. A solution of 27 mg of **3** in 5 mL of methanol was cooled to −77 °C and treated with excess ozone. When TLC analysis indicated that **3** had been consumed, the excess ozone was removed in a stream of nitrogen and 1 mL of dimethyl sulfide was added. The mixture was allowed to warm to room temperature and then evaporated in vacuo. Gel filtration on a 117 × 1.75 cm column of Sephadex LH-20 with chloroform–methanol (1:1) gave a fraction (119.0–122.5 mL) that contained an almost quantitative yield of crude 3-methoxy-5-methyldodecanal (**5**): ^{1}H NMR ($CDCl_3$) δ 9.83 (t, J = 2, C-1), 3.76 (quintet, J = 6, C-3 methine), 3.34 (s, OMe on C-3), 2.55 (dd, J = 6 and 2, C-2 methylene), 1.4 (m), 1.25 (br m), 0.89 (d, J = 7, Me on C-5), 0.87 (br, t, J = 7, C-12 methyl); ^{1}H NMR ($CDCl_3$ + 6.25 equiv of Eu(fod)$_3$) δ 9.1 (m, C-3 H), 4.37 (t, J = 6-7, C-4 methylene); MS m/e (rel intensity) 185 (7), 149 (6), 111 (16), 97 (27), 87 (54), 85 (34), 71 (53), 69 (34), 59 (84), 57 (67), 55 (50), 43 (100).

3-Methoxy-5-methyldodecanal was also produced by a similar ozonolysis of **2**.

Jones oxidation of **5** gave 3-methoxy-5-methyldodecanoic acid: ^{1}H NMR ($CDCl_3$) 3.73 (quintet, J = 6, C-3 H), 3.42 (s, OMe), 2.56 (d, J = 6, C-2 CH_2), 1.80–1.20 (br multiplets), 0.93 (d, J = 7, Me on C-5), 0.90 (br t, J = 7, C-12 Me); MS m/e (rel intensity) 244 (0.1, M$^+$), 243 (0.5), 229 (4), 212 (4), 185 (8), 174 (11), 128 (18, loss of OH and $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$ from M$^+$), 103 (100), 97 (23), 85 (20), 83 (20), 71 (28), 69 (26), 61 (77); high resolution MS m/e 212.17922 (calcd for $C_{13}H_{24}O_2$, 212.17764), 185.19049 (calcd for $C_{12}H_{25}O$, 185.19055), 128.08432 (calcd for $C_7H_{12}O_2$, 128.08373), 103. 03972 (calcd for $C_4H_7O_3$, 103.03952).

Acetylation of Malyngamides D and E. A solution of 10 mg of **2** in 1 mL of pyridine and 0.5 mL of acetic anhydride was heated (55 °C) under nitrogen for 1.5 h. The mixture was evaporated in vacuo and the residual oil was subjected to LC on a 3/8 in. × 4 ft column of Porasil A (37–75 μm) using CH_3CN–$CHCl_3$ (1:9) to give 1.1 mg of malyngamide E diacetate (**6**): $[\alpha]^{25}_D$ +37.5° ($CHCl_3$, 0.12); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.46 (br t, $J_{5',4'} = J_{5',3'}$ = 2.5, $J_{5',7'} \sim 1$, C-5′ H), 6.04 (d, $J_{NH,8'}$ = 9, amide NH), 5.62 (dt, $J_{7',8'}$ = 9, $J_{7',5'} \sim J_{7',4'} \sim 1$, C-7′ H), 5.46 (dt, $J_{5,4}$ = 15, $J_{5,6}$ = 6, C-5 H), 5.43 (dt, $J_{4,5}$ = 15, $J_{4,3}$ = 6, C-4 H), 5.16 (dd, $J_{3',4'}$ = 5, $J_{3',5'}$ = 2.5, C-3′ H), 4.31 (tt, $J_{8',NH}$ = $J_{8',7'}$ = 9, $J_{8',9'}$ = 3, C-8′ H), 3.49 (dd, J_{gem} = −10, $J_{9',8'}$ = 3, C-9′ proton), 3.38 (dd, J_{gem} = −10, $J_{9',8'}$ = 3, C-9′ proton), 3.29 (s, OMe), 3.28 (s, OMe), 3.20 (quintet, $J_{7,6}$ = $J_{7,8}$ = 6, C-7 H), 2.94 (br m, C-4′ H), 2.25 and 2.13 (2 H and 4 H multiplets, C-2, C-3, C-6 methylenes), 2.04 (s, OCOMe), 1.98 (s, OCOMe), 1.48 (m, C-9 H), 1.3–1.2 (br m, C-8, C-10, C-11, C-12, C-13, C-14, C-15 methylenes), 1.15 (s, Me on C-2′), 1.06 (d, J = 7, Me on C-4′), 1.04 (s, Me on C-2′), 0.84 (br t, J = 7, C-16 methyl), 0.83 (d, J = 7, Me on C-9).

Acetylation of **3** (6.5 mg) using the procedure above gave 2.5 mg of malyngamide E, $[\alpha]^{25}_D$ +38.4° ($CHCl_3$, c 0.13); ^{1}H NMR spectrum identical to that of **6** obtained from acetylation of **2**.

Malyngamide D was recovered unchanged when a solution of 3 mg of **2** in 0.25 mL of acetic anhydride and 0.25 mL of pyridine was allowed to stand at room temperature for 3.5 h.

Acknowledgments. Financial support by the National Science Foundation (CHE76-82517) is gratefully acknowledged. The authors thank Dennis Russell, Department of Botany, University of Hawaii for identifying the algal specimens; the algal collection at Enewetak was supported by ERDA contract AT(26-1)628. High-frequency NMR studies at the Stanford Magnetic Resonance Laboratory were made possible by NSF Grant No. GP-23633 and NIH Grant No RR00711.

Registry No.—**2**, 67488-04-4; **3**, 67488-05-5; **4**, 67488-06-6; **4** methyl ester, 67488-07-7; **5**, 67488-08-08; **6**, 67488-09-9; 3-methoxy-5-methyldodecanoic acid, 67488-10-2.

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Notes

Cationic π Cyclizations.[1] Alkenes vs. Alkynes as the π Participant

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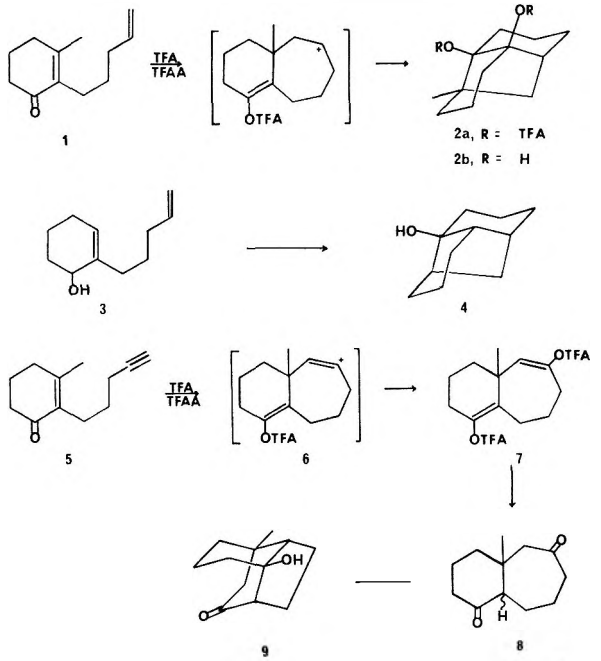
Received April 25, 1978

Terminal alkynes have been used as the π participant in a variety of cationic π cyclizations.[2] In those cases previously studied, the basic course of the cyclization has been the same as that observed with terminal alkenes. We now report a cyclization in which the change of π participant significantly affects the type of products observed. As part of our continuing studies on the synthetic utility of cationic π cyclizations of α,β-unsaturated enones[1,3] we investigated the cyclization of the enone **1**. Not surprisingly, treatment of enone **1**



with trifluoroacetic acid in trifluoroacetic anhydride[1,3b] led, in 71% yield, to a tricyclic diol assigned structure **2** in analogy with the known cyclization of alcohol **3** to tricyclic alcohol **4**.[4,5] Our interest in obtaining bicyclic products from this type of cyclization led us to examine the acetylenic enone **5**. Molecular models suggested that the geometry of the bicyclic vinyl cation **6** generated from cyclization of **5** would not favor further cyclization to a tricyclic product. In fact, the only product observed from TFA/TFAA cyclization of enone **5** was the bis(trifluoroacetate) **7**. Mild hydrolysis gave, in 85% yield, the diketone **8** as a mixture of cis and trans isomers. Based on the chemical shift of the angular methyl,[6] the major isomer is assumed to be the cis isomer. Mild base treatment of diketone **8** led to a tricyclic keto alcohol which is assigned the tricyclo[5.4.0.0^{4,8}]undecane structure **9**.[7]

These cyclization studies show that, in this system, use of the alkyne bond as the π participant allows isolation of bicyclic products rather than the tricyclic product obtained using an alkene bond as the π participant.[9] Application of this methodology to the synthesis of natural terpenoid systems is in progress.

Experimental Section

The ^{1}H NMR spectra were obtained on a Varian Associates HA-100 or T-60 spectrometer. The ^{13}C NMR spectra were obtained in the Fourier transform mode on a JEOL PFT-100 spectrometer system operating at 25.034 MHz (proton resonance frequency 99.539 MHz) and equipped with a Nicolet 1085 data system. High-resolution mass spectra were obtained on a CEC Model 21-110 spectrometer under the supervision of Dr. R. Grigsby.

The vapor phase chromatographic (VPC) analyses were performed using a 1/8 in. × 6 ft 10% Carbowax on Chromosorb W column or a 1/8 in. × 6 ft 1.5% OV-101 on Chromosorb G column. All percent-composition values are reported as relative peak areas without correction for relative detector response. Preparative VPC separations for MS analyses were performed using a 1/4 in. × 6 ft 10% SE-30 on Chromosorb A column.

All distillations were conducted as bulb-to-bulb (Kugelrohr) short-path distillations. The temperatures cited for these distillations are the maximum temperature of the oven during the distillation. "Brine" refers to a saturated aqueous solution of sodium chloride. Anhydrous ether was stored over sodium. *tert*-Butyl alcohol was distilled from calcium hydride.

2-(4-Pentenyl)-3-methyl-2-cyclohexen-1-one (1). Sodium hydride (176 mg, 7.4 mmol) was added to 80 mL of *tert*-butyl alcohol to generate sodium *tert*-butoxide. To this stirred solution was added 1.32 g (7.4 mmol) of 4-carbethoxy-3-methyl-2-cyclohexen-1-one (Hagemann's ester) in 10 mL of *tert*-butyl alcohol over a period of 20 min. Then 5-bromo-1-pentene (1 g, 6.7 mmol) in 10 mL of *tert*-butyl alcohol was added dropwise followed by 2 g of anhydrous powdered

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KI in one portion. The mixture was stirred for 22 h at room temperature and then at reflux for 2 h. The cooled solution was poured into 200 mL of 10% HCl overlaid with 200 mL of ether. The aqueous layer was separated and washed with ether. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to give 1.41 g of material. This material consisted of starting Hagemann's ester, the desired α-alkylated product, and some γ-alkylated material as shown by ^1H NMR. The mixture was stirred with 20 mL of 15% KOH in 95% ethanol for 12 h at 0 °C. The reaction was poured into 50 mL of water overlaid with 50 mL of ether. The separated aqueous layer was extracted twice with ether to remove unhydrolyzed material (primarily the γ-alkylated ester). The aqueous layer was acidified and extracted with ether until no color remained. The combined ether extracts were washed with brine, dried (Na_2SO_4), concentrated, and evaporatively distilled (130 °C (6.2 mm)) to give 710 mg (59% yield) of ketone **1**: IR (film) 1670 (C=O), 3100, 1625, 990, and 925 cm^{-1} (C=C); ^1H NMR (100 MHz, $CDCl_3$) δ 1.95 (bs, 3 H, CH_3) and 4.8–6.05 (m, 3 H, $CH=CH_2$); ^{13}C NMR ($CDCl_3$) δ 21.1 (C-3 methyl), 22.4, 24.8, 28.3 (C-2′), 32.9, 33.9 (C-3′), 37.9, 114.3 (C-4′), 135.6 (C-2), 138.7 (C-5′), 154.9 (C-3), and 198.3 (C-1). The ^{13}C spectrum and VPC analysis (OV-101, 130 °C) indicated a purity >95%. MS *m/e* calcd for $C_{12}H_{18}O$, 178.135760; found, 178.135076.

Cyclization of Enone 1. To 380 mg (2.1 mmol) of enone **1** was added 10 mL of trifluoroacetic acid and 5 mL of trifluoroacetic anhydride. The mixture was stirred for 2 h at room temperature. The TFA and TFAA were removed by concentration and the residue was distilled (115 °C (0.2 mm)) to give 650 mg of product: IR (film) 1780 cm^{-1} (trifluoroacetate C=O); ^1H NMR (60 MHz, CCl_4) δ 1.2 (angular methyl). This material was treated at room temperature with 20 mL of 10% KOH in methanol. After 20 min, the methanol was removed by concentration. Methylene chloride was added and salts were removed by filtration. The solution was dried (Na_2SO_4), concentrated, and distilled (125 °C (0.15 mm)) to give 310 mg (75% yield) of crystalline diol **2b** which was recrystallized from hexane: mp 133–135 °C; IR (KBr) 3400 and 1050 cm^{-1} (OH); ^1H NMR (100 MHz, $CDCl_3$) δ 0.94 (s, angular methyl); ^{13}C NMR (benzene-d_6) δ 18.6, 19.4, 20.5 (CH_3), 25.8, 30.3, 33.9, 34.0, 34.3, 39.6 (>C-H), 40.7 (>C<), 78.4 (>C-O–), and 78.8 (>C-O–); MS *m/e* calcd for $C_{12}H_{20}O_2$, 196.146320; found, 196.145711.

2-(4-Pentynyl)-3-methyl-2-cyclohexen-1-one (5). This material was prepared in a manner similar to that of enone **1** using 3.7 g (20 mmol) of Hagemann's ester and 3 g (20 mmol) of 5-bromo-1-pentyne.[11] In this case the crude alkylation product (3 g) was chromatographed on a silica gel column using methylene chloride to obtain 900 mg of starting ester and 2.0 g (52% yield based on recovered starting material) of pure α-alkylated product. Hydrolysis gave 1.3 g (91% yield) of enone **5**: IR (film) 3300 and 2150 (C≡CH), 1650 and 1630 cm^{-1} (C=CC=O); ^1H NMR (100 MHz, $CDCl_3$) δ 1.94 (s, 3 H, CH_3), 1.92 (t, J = 2 Hz, C≡CH); ^{13}C NMR ($CDCl_3$) δ 18.4 (C-3′), 21.2 (C-3 methyl), 22.3, 24.4, 27.9 (C-2′), 32.9, 37.8, 68.4 (C-5′), 84.5 (C-4′), 134.8 (C-2), 155.8 (C-3), and 198.4 (C-1). Analysis by VPC (OV-101, 130 °C) showed only one peak. MS *m/e* calcd for $C_{12}H_{16}O$, 176.120110; found, 176.119792.

Cyclization of Enone 5. A mixture of 10 mL of trifluoroacetic acid and 5 mL of trifluoroacetic anhydride was added to 650 mg (3.7 mmol) of enone **5**. The mixture was stirred at room temperature for 2.5 h. The TFAA and TFA were removed by concentration and the residue was distilled (115 °C (0.1 mm)) to give 1.23 g (86% yield) of bis(enoltrifluoroacetate) **7**: IR (film) 1785 (trifluoroacetate C=O) and 1680 (C=C); ^1H NMR (100 MHz, CCl_4) δ 1.29 (s, angular methyl), 5.24 (bs, C=CH). This ester was treated with 25 mL of saturated sodium bicarbonate in methanol for 20 min at room temperature. The methanol was removed by concentration and methylene chloride and $MgSO_4$ were added. The solution obtained after filtration was concentrated and distilled (125 °C (0.15 mm)) to give 600 mg (85% overall yield) of diketone **8** as a 6:1 mixture of cis and trans isomers: IR (film) 1725 cm^{-1} (C=O); ^1H NMR (100 MHz, $CDCl_3$) δ 1.07 (s, cis angular methyl) and 0.78 (s, trans angular methyl); ^{13}C NMR ($CDCl_3$) (major isomer) δ 20.9, 21.3, 26.6, 27.4 (C-1 methyl), 37.6, 39.0 (C-1), 39.5, 43.3, 53.3 (C-2), 60.4 (C-7), 212.0 (C-3 or C-8), 212.6 (C-3 or C-8). Analysis by VPC (Carbowax, 200 °C) showed one major peak with a shoulder for the trans isomer. MS *m/e* calcd for $C_{12}H_{18}O_2$, 194.130670; found, 194.130136.

Hydrolysis of bis(enoltrifluoroacetate) **7** under more vigorous conditions or treatment of diketone **8** with methanolic hydroxide led to a tricyclic aldol product. A 220-mg sample of diketone **8** was treated with 10 mL of 15% KOH in methanol at room temperature for 1 h. The mixture was poured into water and extracted with ether. The combined ether extracts were washed with brine, dried (Na_2SO_4), concentrated, and distilled (130 °C (0.2 mm)) to give 200 mg (90% yield) of a solid keto alcohol assigned structure **9**: mp 146–148 °C (from hexane); IR (CCl_4) 1715 (C=O) and 3450 cm^{-1} (OH); ^1H NMR (100 MHz, $CDCl_3$) δ 1.00 (s, angular methyl); ^{13}C NMR ($CDCl_3$) δ 19.9 (C-10), 22.7, 27.2 (C-1 methyl), 27.4, 34.5, 37.0 (C-1), 39.6, 46.2 (C-2), 52.4 (C-7), 60.9 (C-4), 81.1 (C-8), and 214.2 (C-3).[11]

Acknowledgment. We thank the Robert A. Welch Foundation for support of this research. Acknowledgment is also made to the National Science Foundation for purchase of the JEOL PFT-100 NMR used in this work. This work constitutes a portion of the Ph.D. requirements of J.L.C. and P.M.P.

Registry No.—**1**, 67425-72-3; **2a**, 67425-73-4; **2b**, 67425-74-5; **5**, 67425-75-6; **7**, 67425-76-7; *cis*-**8**, 67425-77-8; *trans*-**8**, 67425-78-9; **9**, 67463-82-5; Hagemann's ester, 487-51-4; 5-bromo-1-pentene, 1119-51-3; trifluoroacetic acid, 76-05-1; 5-bromo-1-pentyne, 28077-72-7.

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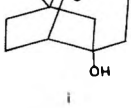

i

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(9) It should be noted that the differences observed are a result of the different allowable geometries for the bicyclic cationic intermediates in these two cyclizations and are not necessarily applicable to all alkyne cyclizations. In particular, tricyclic products have been observed in cases involving an internal alkyne as the π participant.[5b,5c]
(10) Prepared from 4-pentyn-1-ol using PBr_3 in pyridine.
(11) This ^{13}C NMR spectrum correlates well with the spectrum of an isomeric tricyclic alcohol, 8-methyltricyclo[5.4.0.0^{4,8}]undecan-3-on-1-ol: K. E. Harding and J. L. Cooper, unpublished results.

Carbon–Carbon Bond Formation. 6.[1] Alkyl Halide Coupling from an Electrochemically Generated Iron Promoter

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Received May 1, 1978

The use of transition metal complexes to promote organic reactions has been well-established. However, the nature of

Table I

	A[a]	B	C
base electrolyte	TEAB	TEAB	TEAB
working electrode	Al	Al	Al
counter electrode	Al	Al	Al
E_{ref}, V, vs. Cd(Hg)	−0.90	−0.90	−0.90
$C_{16}H_{34}$, %	59.0[b]	48.8	none
C_8H_{18}, %	23.8	27.0	<0.04 mmol
C_8H_{16}, %	10.9	8.4	<0.06 mmol
reaction, %	57.5	37.0	

[a] There is no organic product formed in this type of experiment in the absence of $Fe(acac)_3$. [b] Percent yields were based on the amount of 1-bromooctane used.

the actual metallic promoters[3] and the methods of their generation are not as well-established. In this note, we wish to provide evidence for the heterogeneous character of an iron promoter which has been generated by the electrochemical reduction of *iron acetylacetonate*, $Fe(acac)_3$.

In 1973, Lehmkuhl reported[4] that transition metal promoters could be generated in nonaqueous solvents by the electrochemical reduction of metal acetylacetonates. These promoters were characterized as "naked" homogeneous catalysts[5] which could be either trapped as an organometallic complex or used to promote organic reactions from the organic components in situ. The released ligand, acetylacetonate, is complexed by aluminum ions generated from the sacrificial anode. In a previous article, we reported[1] our preliminary findings[6] on the use of promoters generated from nickel acetylacetonate to couple benzylic or aryl halides, and $Fe(acac)_3$ to couple alkyl halides. More details of the latter reaction which is shown below are now presented.

$$n\mathrm{RCH_2CH_2Br} + \mathrm{Fe(acac)_3} \xrightarrow[\substack{\text{DMF}\\ \text{Al electrodes}\\ \text{controlled potential}\\ \text{at } -0.90 \text{ V vs. Cd(Hg)}}]{e^-} (\mathrm{RCH_2CH_2})_2 + \mathrm{RCH_2CH_3} + \mathrm{RCH{=}CH_2}$$

Experiment A of Table I is an example of the results obtained from a standard, controlled potential, cathodic reduction of $Fe(acac)_3$ in the presence of the substrate 1-bromooctane[7] at aluminum electrodes. The yield of coupled product is surprisingly high in light of the fact that other iron-promoted coupling reactions such as the Kharasch reaction give poor yields of the symmetrically coupled alkane product. Particularly low yields of the symmetrically coupled product are obtained in the Kharasch reaction if a proton exists on the β carbon of the alkyl halide.[8] Presumably, the presence of this proton facilitates the well-known elimination of metal hydride and alkene formation. Kochi[9] and Ohbe[10] have circumvented this problem by introducing the labile alkyl group into the Kharasch reaction as the Grignard component. As a result they have achieved 50–83% yields of cross-coupled product.[9a] Thus, it is apparent that the iron promoter in our electrolytic reaction is somewhat different from those previously reported. Inspection of our reaction electrodes revealed the aluminum cathode to be coated with a black material which was subsequently shown to contain iron[11] and promote coupling of alkyl halides (experiment B).

The results of experiments B and C show that the mechanism for coupled and disproportionated product formation must have a heterogeneous iron component. These two experiments were conducted in the following manner. An electrochemical cell was charged with all the components mentioned for experiment A except for 1-bromooctane. Controlled potential electrolysis was conducted for 24 h[12] at a potential of −0.9 V vs. Cd(Hg). The black deposit on the cathode formed as usual. This electrode assembly was subsequently removed from the original solution and placed into a new cell containing all the components including 1-bromooctane, but no $Fe(acac)_3$ was added. Experiment B was started by electrolyzing this last solution at −0.9 V vs. Cd(Hg). The current rose immediately to an instrument limited current of 200 mA followed shortly by an exponential decay to 5 mA. The products obtained therefrom were the same as those obtained in a standard reaction represented as experiment A.

The original solution, from which the electrodes for experiment B were removed, was charged with 1-bromooctane and equipped with a set of new aluminum electrodes. Continued electrolysis of this solution, experiment C, failed to generate a significant yield of products.[13]

The results of experiments A, B, and C clearly demonstrate that the iron-containing material deposited on the cathode is directly involved in the reactions noted above for alkyl halides.

These results are significant in two ways. First, they demonstrate that an iron promoter may be prepared and reacted with alkyl halides resulting in carbon–carbon bond formation *even in the presence of protons on the β carbon.* Second, they demonstrate that a metallic component is first *deposited on the aluminum cathode* followed by reaction with the alkyl halide. This is in contrast to Lehmkuhl's report in which the metal is reduced to a *homogeneous* "naked" metallic state which subsequently interacts with the organic substrate. Thus, our work suggests that in some cases the soluble organometallic compound alluded to by Lehmkuhl may be formed by interaction of the organic substrate with a deposited metal. At least, in the case of $Fe(acac)_3$ reduction in DMF at −0.9 V vs. Cd(Hg) using an aluminum cathode, a totally homogeneous reaction cannot be assumed.

Details of the reaction pathway are not fully understood at this time, but there are indications that free-radical intermediates may account for the product distribution. For example, Kochi[14] reported in 1970 that the relative rate ratio (k_d/k_c) of disproportionated to dimeric or combined products was 0.12–0.15 for primary radicals. The same ratios for experiments A and B are 0.18 and 0.17, respectively.[15]

Experimental Section

Preparation of TEAB and $Fe(acac)_3$ has been reported previously.[1]

Dimethylformamide (DMF). "Baker Analyzed" reagent grade DMF was distilled under atmospheric conditions. The fraction boiling at 144 °C was collected and stored in an amber colored bottle over Linde 4A molecular sieves. The solvent was used within 14 days after distillation.

1-Bromooctane. This reagent was used as it was received from Aldrich Chemical Co. as was the *n*-decane (Gold Label) which was used for the internal standard in quantitating the organic reaction products.

Electrolysis Cell. The cell was compsoed of a rubber stoppered beaker[1] containing two 6061-T6 aluminum electrodes (45 × 45 × 0.9 mm) separated by 6–8 mm, 60 mL of DMF, 4.4 g (12.46 mmol) of $Fe(acac)_3$, 1.5 g (5.66 mmol) of Ph_3P, 0.802 g (3.81 mmol) of Et_4NBr, and 8.6 mL (49.78 mmol) of 1-bromooctane. The Cd(Hg) reference electrode[6] was positioned on the opposite side of the working electrode from the counter electrode.

Isolation and Analysis of Organic Products. Octane and octene were removed from the original reaction mixture by vacuum distillation and analyzed by GC using *n*-decane as a standard. The remaining reaction mixture was treated with 100 mL of H_2O containing 2 mL of concentrated HCl. Extraction of this solution with ether, drying, and concentration followed by alumina chromatography resulted in the isolation of hexadecane and unused 1-bromooctane. These products were also analyzed by GC using *n*-decane as a standard. The GC column was 8 ft × ⅛ in. copper tubing packed with 20% Carbowax 20 M on 80–100 mesh Chromosorb W.

Acknowledgment. We thank Montana State University for support of this research.

Registry No.—$Fe(acac)_3$, 14024-18-1; 1-bromooctane, 111-83-1; hexadecane, 544-76-3; octane, 111-65-9; octene, 111-66-0.

References and Notes

(1) For previous work see: *J. Org. Chem.*, **41**, 719 (1976).
(2) Abstracted in part from the Ph.D. Thesis of J.L.H., Montana State University, 1976.
(3) The term promoter is used here to refer to a positive catalyst which enhances the rate of a given reaction. An inhibitor would be referred to as a negative catalyst.
(4) A review by H. Lehmkuhl, *Synthesis*, 377 (1973).
(5) The term "nachtem Nichel" is used extensively by G. Wilke [*Justus Liebigs Ann. Chem.*, **727**, 183 (1969)] to describe the metallic species generated by Et_2AlOEt reduction of $Ni(acac)_2$. Lehmkuhl proposes that the same species can be generated electrochemically (p 379 of ref 4).
(6) In this earlier work electrochemical reactions were conducted under conditions of constant applied potential. The present work uses potentiostatic control of the working electrode with a Cd (Hg) reference electrode. See J. L. Hall and P. W. Jennings, *Anal. Chem.*, **48**, 2026 (1976), for details of the reference electrode.
(7) The electrochemical cell components consisted of two 6061-T6 aluminum electrodes (45 × 45 × 0.9 mm) separated by 6–8 mm, 60 mL of dried DMF, 4.4 g (12.46 mmol) of $Fe(acac)_3$, 1.5 g (5.66 mmol) of Ph_3P, 0.802 g (3.81 mmol) of Et_4NBr, and 8.6 mL (49.78 mmol) of 1-bromooctane. The reference electrode was placed on the opposite side of the working electrode from the counter electrode. The same experiment conducted at a potential of −0.90 V vs. Cd(Hg) in the absence of $Fe(acac)_3$ for three times the length of time does not yield any of the organic products shown in the table. This is not surprising since the reduction potential of 1-bromooctane is 900 mV more cathodic of the controlled potential.
(8) (a) M. S. Kharasch, J. K. Hambling, and T. P. Rudy, *J. Org. Chem.*, **24**, 303 (1959). This particular paper dealt with cobalt rather than iron but is analogous as shown later by Kochi (see ref 8b). (b) M. Tamura and J. Kochi, *J. Organometal. Chem.*, **31**, 289 (1971); (c) M. Tamura and J. K. Kochi, *Bull. Chem. Soc. Jpn.*, **44**, 3063 (1971).
(9) (a) The other component to which the alkyl group couples is a vinyl or allyl halide; (b) M. Tamura and J. Kochi, *J. Am. Chem. Soc.*, **93**, 1487 (1971); (c) S. M. Neumann and J. K. Kochi, *J. Org. Chem.*, **40**, 599 (1975); (d) R. S. Smith and J. K. Kochi, *J. Org. Chem.*, **41**, 502 (1976); (e) C. L. Kwan and J. K. Kochi, *J. Am. Chem. Soc.*, **98**, 4903 (1976).
(10) Y. Ohbe and T. Matsuda, *Tetrahedron*, **29**, 2989 (1973).
(11) X-ray fluorescence investigations have shown that there are two different types of iron material coated on the aluminum electrode. More detail on this aspect of the problem will be reported later.
(12) By 24 h the current had decreased from 200 mA to less than 5 mA.
(13) The trace of products formed could be due to the small amount of cathode deposit which flakes off and remains suspended in the solution.
(14) Sheldon and J. K. Kochi, *J. Am. Chem. Soc.*, **92**, 4395 (1970).
(15) Kochi determined the k_d/k_c rate ratios from product yields assuming that alkene formed only by disproportionation.

New Synthetic Design for Formation of Carbon–Carbon Triple Bonds

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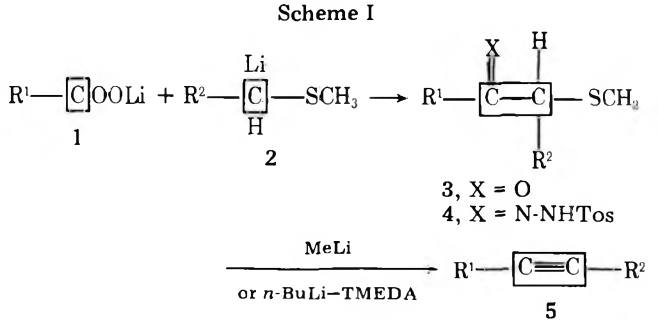
Received April 3, 1978

Alkynes serve as key starting materials of versatile intermediates in organic synthesis, providing access to a wide va-

Scheme I



a, $R^1 = R^2 = C_6H_5$
b, $R^1 = 3,4\text{-}(CH_3O)_2C_6H_3$; $R^2 = H$
c, $R^1 = C_6H_5CH_2CH_2$; $R^2 = H$
d, $R^1 = CH_3(CH_2)_7$; $R^2 = H$
e, $R^1 = CH_3(CH_2)_8$; $R^2 = H$
f, $R^1 = C_6H_{11}$; $R^2 = H$

Table I. Preparation of Alkynes from Lithium Carboxylates through α-Sulfenylated Ketones (3) and *p*-Toluenesulfonylhydrazones (4)

run no.	lithium carboxylate (1) compd no.	registry no.	α-sulfenylated ketone (3) compd no.	registry no.	yield, %	m/e (M⁺)	¹H NMR (CCl₄), ppm SCH₃	¹H NMR (CCl₄), ppm COCHS	*p*-toluenesulfonylhydrazone (4)[15] compd no.	registry no.	yield, %	mp, °C	alkyne (5) compd no.	registry no.	yield, %
1	**1a**, C_6H_5COOLi	553-54-8	**3a**	32368-19-7	70	242	1.93	5.35	**4a**	67489-14-9	85	157–160	**5a**[6]	501-65-5	65
2	**1b**, $3,4\text{-}(CH_3O)_2C_6H_3COOLi$	67489-09-2	**3b**	67489-10-5	95	226	2.05	3.58	**4b**	67489-15-0	90	169–172	**5b**[10]	4302-52-7	93
3	**1c**, $C_6H_5CH_2CH_2COOLi$	15082-45-8	**3c**	67489-11-6	90	194	1.90	2.97	**4c**	67489-16-1	85	125–128	**5c**[11]	16520-62-0	73
4	**1d**, $CH_3(CH_2)_7COOLi$	63710-31-6	**3d**	67489-12-7	95	202	2.02	3.03	**4d**	67489-17-2	95	81–83	**5d**[11]	764-93-2	70
5	**1e**, $CH_3(CH_2)_8COOLi$	20336-95-2	**3e**	67489-13-8	95	216	2.02	3.02	**4e**	67489-18-3	95	91–93	**5e**[12]	2243-98-3	66
6	**1f**, $C_6H_{11}COOLi$	16090-10-1	**3f**	39195-70-5	90	172	2.03	3.10	**4f**	67489-19-4	90	105–108	**5f**[13]	931-48-6	77

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riety of functional groups.[1] Alkynes are most often prepared by dehydrogenation of *vic*- and *gem*-dihalogeno compounds and halogeno vinyl derivatives with strong base.[1] The decomposition of *p*-toluenesulfonylhydrazones of carbonyl compounds possessing a leaving group such as mesyloxy, acetoxyl, halogene,[2] and epoxy group[3] at the α position have been used for preparation of alkynes. Pyrolysis of 5-chloromethyl-1*H*-tetrazole[4] was also treated as a unique method for synthesis of alkynes. We have investigated a new synthetic design for formation of carbon–carbon triple bond by the use of carboxylic acid and (methylthio)methyllithium derivatives as two carbon units of the triple bond as outlined in Scheme I. We describe the results of the study in this paper.

Reaction of benzoic acid with 2.5 equiv of (methylthio)benzyllithium[5] (**2**: $R^2 = C_6H_5$) afforded phenyl (methylthio)benzyl ketone **3a**, whose *p*-toluenesulfonylhydrazone **4a** was treated with methyllithium in dry Et_2O to give diphenylacetylene **5a**[6] in 65% yield.[7] Treatment of lithium 3,4-dimethoxybenzoate **1b**[8] with (methylthio)methyllithium[9] (**2**, R^2 = H) in dry THF gave 3,4-dimethoxyphenyl (methylthio)methyl ketone **3b** in 93% yield. *p*-Toluenesulfonylhydrazone **4b**, derived from **3b**, was treated with methyllithium in dry Et_2O with stirring to afford 3,4-dimethoxyphenylacetylene **5b**[10] in 95% yield. In this way, lithium phenylpropionate **1c**, lithium *n*-nonanoate **1d**, lithium *n*-decanoate **1e** and lithium cyclohexylcarboxylate **1f** were converted to 4-phenyl-1-butyne **5c**,[11] 1-decyne **5d**,[11] 1-undecyne **5e**,[12] and cyclohexylacetylene **5f**.[13] Furthermore, *n*-butyllithium was also found to be useful for synthesis of alkynes from *p*-toluenesulfonylhydrazone of α-methylsulfenylated ketones. *p*-Toluenesulfonylhydrazone **4e** was treated with *n*-butyllithium in dry THF in the presence of TMEDA to give 1-undecyne in 80% yield.[14]

This new method for preparation of alkynes starting from carboxylic acid should be applicable for formation of a variety of alkynes.

Experimental Section

All reactions were carried out under a nitrogen atmosphere unless otherwise stated. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried and distilled from $LiAlH_4$ before use. Nuclear magnetic resonance spectra were recorded on a Varian T-60 instrument and mass spectra were determined on a Hitachi RMU-7L instrument.

General Procedure for Preparation of α-Methylsulfenylated Ketones (3) from Lithium Carboxylate (1). To a suspension of lithium carboxylate **1** (13.7 mmol), prepared from the carboxylic acid and an equimolar amount of *n*-BuLi in THF at 0 °C, was added a solution of (methylthio)methyllithium[9] (20.5 mmol) in THF at 0 °C. After stirring at 0 °C for 0.5 h and then at room temperature for 14 h, the mixture was poured into water and extracted with benzene. The extract was washed with water, dried over Na_2SO_4, and evaporated to leave **3** in 90–95% yield. For the preparation of **3a**, benzoic acid was treated with (methylthio)benzyllithium (2.5 equiv) in THF at −78 °C under stirring. The mixture was maintained at the same temperature for 0.5 h and then at room temperature for 14 h. The mixture was worked up as above to give **3a** in 70% yield. The crude ketones thus obtained were used for preparation of *p*-toluenesulfonylhydrazones **4** without purification.

General Procedure for Preparation of *p*-Toluenesulfonylhydrazones (4). A mixture of **3**, an equimolar amount of *p*-toluenesulfonylhydrazide, and EtOH was refluxed for 3 h except in the case of **3a** and **3b**. For the preparation of **4a** and **4b**, the mixture was heated for 30 h under reflux. Evaporation of the solvent gave **4** as colorless needles in 85–95% yield.[15]

General Procedure for Preparation of Alkynes (5). (a) To a stirred suspension of **4** (6 mmol) in Et_2O (40 mL) was added an ethereal solution of MeLi (36 mmol) at 0 °C. After 0.5 h at 0 °C and then 30 h at room temperature with stirring, the mixture was poured into water and extracted with Et_2O. The extract was washed with water, dried over Na_2SO_4, and evaporated to leave **5**. (b) To a stirred suspension of **4** (6.5 mmol) in THF (40 mL) containing TMEDA (19.5 mmol) was added *n*-BuLi (hexane solution, 19.5 mmol) at −78 °C. After stirring had been continued at 0 °C for 0.5 h and then at room temperature for 24 h, the mixture was worked up as above to give **5**. By this method 1-undecyne (**5e**) was obtained in 80% yield.

Registry No.—*p*-Toluenesulfonyl hydrazide, 1576-35-8.

References and Notes

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(4) H. Behlinger and M. Matner, *Tetrahedron Lett.*, 1663 (1966).
(5) Benzyl methyl sulfide and an equimolar amount of LDA in THF at −78 °C for 0.5 h provided the lithium salt.
(6) G. H. Coleman and R. D. Maxwell, *J. Am. Chem. Soc.*, **56**, 132 (1934).
(7) Yields were based in analytically pure materials.
(8) Lithium carboxylates were prepared from carboxylic acids by treatment with *n*-BuLi (hexane solution, 1 equiv) in THF at 0 °C.
(9) D. J. Peterson, *J. Org. Chem.*, **32**, 1717 (1967).
(10) J. D. Fulton and R. Robinson, *J. Chem. Soc.*, 1463 (1933).
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(14) The reaction of lithium *n*-decanoate with (phenylthio)methyllithium was also examined. Although the corresponding α-phenyl thioketone was obtained in 60% yield, the decomposition of *p*-toluenesulfonylhydrazone with *n*-BuLi–TMEDA gave 1-undecyne in much lower yield (20%).
(15) All *p*-toluenesulfonylhydrazones gave satisfactory analyses.

Conversion of Aromatic and α,β-Unsaturated Aldehydes to Dichlorides by Thionyl Chloride and Dimethylformamide[1]

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Received May 2, 1978

In an attempt to convert the bisulfite addition product of benzaldehyde **1** to the corresponding dichloro compound, **2**, by treatment with thionyl chloride in the presence of dimethylformamide (DMF)[3] we found that benzal chloride, **3**, was formed in high yield. This reaction was studied because it was hoped to be of value in converting substituted benz[*a*]-anthracenes into corresponding dichlorides.

$C_6H_5CHOHSO_6Na$ (**1**) $C_6H_5CHClSO_2Cl$ (**2**) $C_6H_5CHCl_2$ (**3**)

Further study revealed that treatment of benzaldehyde with thionyl chloride in the presence of a catalytic amount of DMF yielded **3** almost quantitatively at room temperature. Without DMF no reaction occurred.[4,5] The generality of this reaction with aromatic and α,β-unsaturated aldehydes was demonstrated with 1-naphthaldehyde **6** (91% yield), cinnamaldehyde **7** (90%), and α-methylcinnamaldehyde **8** (85% only about 75% of which was (*E*)-1,1-dichloro-2-methyl-3-phenyl-2-propene). Slightly smaller yields were obtained with the corresponding bisulfite addition compounds of **6**, **7**, and **8**. However, since aldehydes are often isolated and/or purified by means of their bisulfite addition compounds, the conversion of the latter to the dichloro compounds could save a step without overall loss of yield. In the case of *n*-octanal, cyclohexanone, and acetophenone, such mixtures of products were obtained that this reaction was of no utility.

When equal moles of DMF and $SOCl_2$ are mixed in the cold in CH_2Cl_2 and the solvent is removed under vacuum a colorless solid, **4**, remains for which the ionic structures **4a** and **4b** have been advanced[6–8] largely because of the slight solubility in nonpolar solvents. If this complex is heated SO_2 is lost and **5** is formed. Heating of DMF with PCl_5, $COCl_2$, oxalyl chlo-

0022-3263/78/1943-4367$01.00/0

Table I. Reactions of C_6H_5CHO and $C_6H_5CHOHSO_3Na$ with $SOCl_2$

time, min	% reaction[a] C_6H_5CHO 4a[b]	C_6H_5CHO 5[c]	$C_6H_5CHOHSO_3Na$[d]
15	76	26	16
30	85	57	31
60	88	81	58
120[e]	95	90	86

[a] The percent reaction was estimated by integration of the singlet (^1H NMR) at δ 6.60 ($C_6H_5CHCl_2$) compared to the singlet at 9.95 (C_6H_5CHO) assuming a direct relationship between the integrated values and concentration of the species involved. [b] Reaction involving 4 (we assume structure **4a**). [c] Reaction involving **5**. [d] Reaction involving bisulfite addition compound and 4. [e] After longer reaction times both benzaldehyde and the bisulfite addition compound gave about 90% isolated yields of **3** which showed no carbonyl hydrogen peak by ^1H NMR.

ride, and other compounds also leads to **5**,[3,9] frequently called the Vilsmeier reagent.

$[(CH_3)_2N{=}CHOSOCl]^+Cl^-$ **4a** $[(CH_3)_2N{=}CHCl]^+SO_2Cl^-$ **4b**

$[(CH_3)_2N{=}CHCl]^+Cl^-$ **5**

We prefer **4a** as the structure for **4** because the rate of reaction of benzaldehyde with the DMF·$SOCl_2$ complex which has not lost SO_2, **4**, is greater than the rate of reaction of benzaldehyde with **5** (see Table I).

Since only catalytic amounts of DMF complexes were used in experiments b and c in Table I only the rate involved in the first 15-min interval relates to comparative rates because complex **5** on reaction produces DMF. The latter then reacts with thionyl chloride to produce a complex of type **4**. Hence the reactions occurring at the later times are all with type **4** complexes.

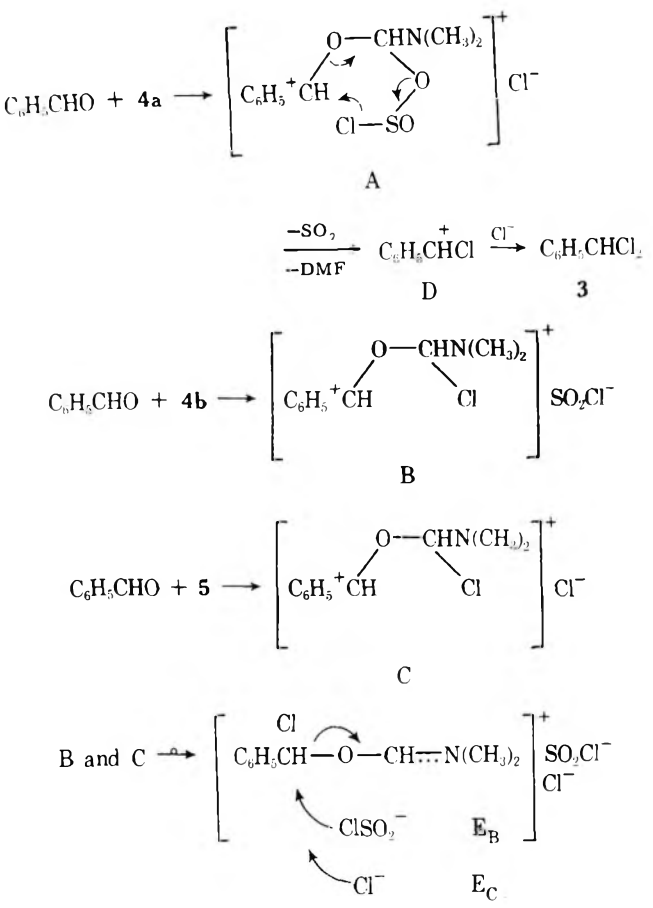
The effectiveness of DMF as a catalyst for the reaction of $SOCl_2$ with a variety of organic compounds has been discussed in terms of three intermediates, **4a, 4b,** and **5,** which may be formed by reaction of DMF with $SOCl_2$.[6] When these reagents are mixed in the cold (−10 to 0 °C) **4a** and/or **4b** are produced.[6] On warming SO_2 is lost and **5** results. The ionic form for each is preferred over a covalent form because of physical properties (e.g., insolubility in nonpolar solvents).

In most reactions involving the use of DMF and $SOCl_2$ it is not clear whether **4ab** and/or **5** was the active reagent because mixtures of DMF, $SOCl_2$, and the compound in question were heated and no measurements of the temperatures involved in the beginning were recorded. We are studying by X-ray crystallographic analysis the structure of the solid complex, **4a** or **4b.** In solution the two may be in equilibrium.

When benzaldehyde reacts with **4a, 4b,** and **5** we assume that the first step involves attack of the carbonyl oxygen at the cationic carbon to yield intermediates A, B, and C, respectively, as shown in Scheme I. Intermediate A can react by a cyclic six-atom path to yield carbonium ion D, SO_2, and DMF, followed by combination of D with a chloride ion to yield benzal chloride, **3.** Intermediates B and C, *which differ only in the nature of the negative counterion,* can undergo a chlorine shift to give intermediates E_B and E_C, respectively, which also differ only in the nature of the counterion. The reaction is then completed by attack of SO_2Cl^- or Cl^- on the benzylic carbon of E_B or E_C to yield **3** and DMF as shown.

We favor the route involving A. We see no reason why there should be an appreciable rate difference for the attack of benzaldehyde on **4b** or **5** because the intermediates, B and C,

Scheme I

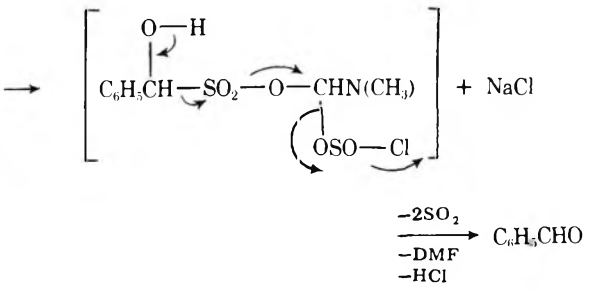


formed differ only by the negative counterion. Furthermore, there should be little difference in the rate at which B and C change to E_B and E_C prior to attack by SO_2Cl^- or Cl^- to yield **3** and DMF. Hence, if **4b** were involved we believe the rate of reaction of benzaldehyde with **4b** and **5** would be practically identical. The fact is, however, that benzaldehyde reacts much more rapidly with **4** than **5.** Because of this we believe that **4a** is involved and that the intervention of the cyclic path shown in Scheme I for A is responsible for the greater rate.

The generation of benzaldehyde from its bisulfite addition compound on reaction with the DMF–$SOCl_2$ complex (for example, **4a**) is undoubtedly initiated (at least in part) by attack of the bisulfite anion on the cationic carbon of **4a** followed by decomposition of the resulting complex as shown below.

$C_6H_5CHSO_2O^-Na^+ + [(CH_3)_2N{=}CHOSOCl]^+Cl^-$

4a



With regard to diaryl ketones benzophenone has been reported to react at reflux with $SOCl_2$[10] as have xanthone and thiazanthone.[11] We believe thionyl chloride which contained a catalytically active impurity must have been used[4] since we found no reaction at reflux with any of these ketones with pure thionyl chloride. However, benzophenone does yield dichlo-

rodiphenylmethane on long heating at reflux with $SOCl_2$ and DMF.

Experimental Section[12]

Reactions with $SOCl_2$–DMF. In typical preparative experiments 10.0 g of bisulfite addition compound, or 7.0 g of aldehyde, was added in portions to a stirred mixture of 35 mL of $SOCl_2$ (pure,[13] freshly distilled) and 0.5–1.0 mL of DMF held at −10 to −5 °C at all times during preparation. The temperature was allowed to rise slowly and the mixture was stirred for 4 h at room temperature then poured on ice and the products were collected by ether extraction in the cold. The ether layer was washed with saturated salt solution and dried over $MgSO_4$. The products (percent yield) were isolated by vacuum distillation. Benzal chloride, **3**, bp 89–90 °C (9.5 mm) (89 or 87% when an equivalent of the bisulfite addition compound was used), was characterized by its NMR spectrum.[14] Dichloro-1-naphthylmethane (91 or 86% from addition compound), bp 106–108 °C (0.5 mm) (lit.[15] bp 146–147 °C (2 mm)), was obtained from **6** and (*E*)-1,1-dichloro-3-phenyl-2-propene, mp 58.0–58.5 °C (lit[16] mp 57.5–58.5 °C), was obtained from **7**. From **8** a complex mixture of dichlorides was produced in which about 70–75% was estimated to be (*E*)-1,1-dichloro-2-methyl-3-phenyl-2-propene by integration of the NMR peak at δ 5.45 (s, 1) assigned to the $CHCl_2$ assuming the integration value as $^1/_5$ of the five ArH (m, 5, δ 7.0–7.5). Both *E* and *Z* forms were present. Because of difficulty in attempted separation and instability of the mixture no C,H analyses were attempted. However, the mass spectra of all fractions had peaks (M + 1) at 186, 188, and 190[12] indicating that two chlorine atoms were present.

Kinetic Experiments, Table I. In experiments similar to the above but on a smaller scale with benzaldehyde only the reaction mixture was poured on ice and the entire crude product, isolated as described above, was analyzed by NMR (see Table I). Reagent **5** was prepared by heating 70 mL of $SOCl_2$ and 0.5 mL of DMF at reflux for $^1/_2$ h. After cooling to −10 °C 14 g of benzaldehyde was added and aliquots were taken for analysis by the usual method described above. Similar experiments were done on the bisulfite addition compounds.

Dichlorodiphenylmethane. A solution of 4.0 g of benzophenone in 20 mL of $SOCl_2$ and 0.5 mL of DMF was held at reflux for 16 h. Vacuum distillation yielded 4.4 g (85%) of dichlorodiphenylmethane, bp 98–100 °C (0.5 mm), characterized by its IR spectrum.[14] None of this product was obtained when DMF was omitted. Xanthone and thiazanthone were recovered largely unchanged when DMF was present or absent even on heating at reflux.

Registry No.—**1**, 100-52-7; **3**, 98-87-3; **6**, 66-77-3; **7**, 104-55-2; **8**, 101-39-3; thionyl chloride, 7719-09-7; dimethylformamide, 68-12-2; (*E*)-1,1-dichloro-2-methyl-3-phenyl-2-propene, 67488-96-4; octanal, 124-13-0; cyclohexanone, 108-94-1; acetophenone, 98-86-2; $C_6H_5CHOHSO_3Na$, 4657-12-9; dichloro-1-naphthylmethane, 17180-26-6; (*E*)-1,1-dichloro-3-phenyl-2-propene, 51157-80-3; (*Z*)-1,1-dichloro-2-methyl-3-phenyl-1-propene, 67488-97-5; benzophenone, 119-61-9; dichlorodiphenylmethane 2051-90-3.

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Use of Dipolar Aprotic Solvents to Alter the Chemoselectivity of Lithium Dimethylcuprate[1]

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Received June 16, 1978

Although the presence of good donor solvents such as THF or HMP [$(Me_2N)_3PO$] increases the rate of the displacement reaction at alkyl halides with lithium diorganocuprate reagents,[2,3] such donor solvents either retard or inhibit the conjugate addition of cuprate reagents to unsaturated carbonyl compounds.[4] Since the displacement reaction at an alkyl halide and the conjugate addition reaction exhibit opposite responses to added donor solvents, it seemed possible to effect either type of reaction selectively with a cuprate reagent by merely selecting the appropriate reaction solvent. To explore this idea, the bromo enone **5** was prepared by the sequence indicated in Scheme I.

Reaction of this bromo enone **5** with Me_2CuLi in Et_2O–Me_2S solution formed the typical conjugate adduct, bromo ketone **6**, in high yield. This result is not unexpected because conjugate addition reactions of cuprate reagents are typically much faster than displacement reactions at alkyl halides. Since our earlier studies[4] had indicated that stable solutions of Me_2CuLi could be formed in Et_2O–DMF and that these solutions failed to react with enones having reduction potentials more negative than 2.0 V (vs. SCE), we first examined the reaction of Me_2CuLi with the bromo enone **5** in an Et_2O–DMF mixture. Although the conjugate addition reaction was completely inhibited, the alternative displacement reaction was very slow. After 20 h at 25 °C only 22% of the displacement product **7** was isolated and 75% of the unchanged bromo enone **5** was recovered. Since it was also possible to prepare stable solutions of Me_2CuLi in mixtures of Me_2S, Et_2O, and *carefully purified* HMP, we also examined the reaction of the bromo enone **5** with Me_2CuLi in this solvent mixture. In this solvent system, the desired conversion of the bromo enone **5** to the methylated enone **7** was complete after 7–8 h at 25 °C and we found no evidence for the presence of any byproduct from conjugate addition. Thus, we conclude that by appropriate choice of reaction medium, it is possible to select only one of the two common synthetic applications of Me_2CuLi, either coupling with a halide or conjugate addition. This same solvent effect is presumably also applicable to other cuprate reagents provided that the cuprate reagents have sufficient thermal stability to allow their use in the relatively slow coupling reaction with an alkyl halide.

Experimental Section[5]

Preparation of the Dibromo Ketone 4 and the Bromo Enone 5. Previously described procedures[6] were employed to prepare the imine **1** and convert it successively to the unsaturated aldehyde **2** and the dienone **3**, bp 38 °C (22 mm), $n^{25}D$ 1.4617 [lit.[6] bp 44 °C (25 mm), $n^{25}D$ 1.4617]. Following a general procedure described earlier,[7] a solution of 500 mg (2.4 mmol) of the dienone **3** in 250 mL of pentane was flushed with N_2 and then a stream of anhydrous HBr was passed through the solution for 5 min while the solution was irradiated with the light from a 450-W medium-pressure Hg lamp. The pentane solution was again flushed with N_2 and then washed with aqueous $Na_2S_2O_3$, dried, and concentrated. The residual colorless liquid (850 mg) was chromatographed on silica gel with an Et_2O–hexane eluent (1:9 v/v) to separate 377 mg (44%) of the crude dibromide **4** as a white solid, mp 35–37 °C. Recrystallization from hexane separated 339 mg (40%) of the pure dibromide **4** as white needles: mp 46–47 °C; IR (CCl_4) 1710 cm^{-1} (C=O); NMR (CCl_4) δ 4.55 (1 H, d of d, J = 2 and 10 Hz, CH–Br), 3.0–3.5 (3 H, m, $BrCH_2$ and CHCO), 2.65 (1 H, d of d, J = 10 and 17 Hz, CHCO), 1.4–2.2 (4 H, m, CH_2), 1.18 (9 H, s, *t*-Bu), and 1.08 (6 H, s, CH_3); mass spectrum, *m/e* (rel intensity) 299 (9), 219

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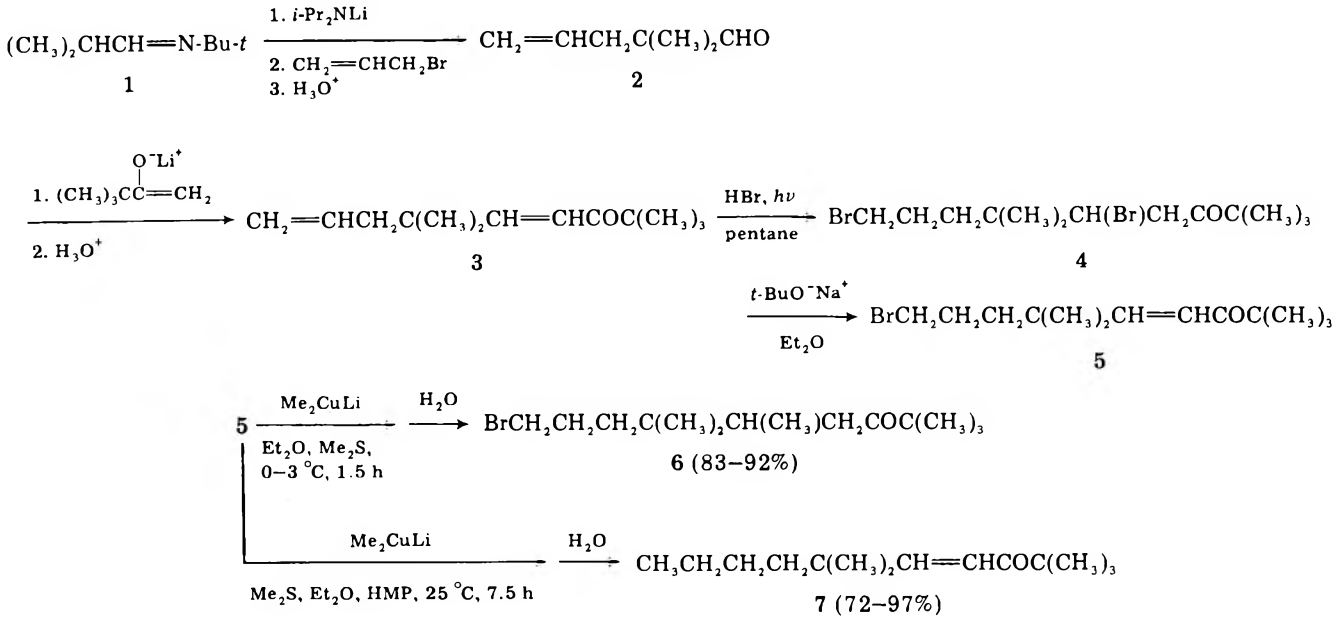
Scheme I



(100), 217 (100), 191 (10), 189 (10), 125 (10), 110 (14), 69 (17), 56 (72), and 41 (29).

Anal. Calcd for $C_{13}H_{24}Br_2O$: C, 43.84; H, 6.79; Br, 44.87. Found: C, 43.77; H, 6.82; Br, 44.86.

In a comparable experiment the crude product from 500 mg (2.4 mmol) of the dienone **3** was distilled under reduced pressure (with accompanying dehydrobromination) to yield 432 mg (65%) of the bromo enone **5** as a colorless liquid: bp 48–52 °C (1 mm), n^{25}_D 1.4775; IR (CCl_4) 1685 (C=O), 1618 (C=C), and 995 cm^{-1} (trans CH=CH); UV max (95% EtOH) 229 nm (ϵ 20 500); NMR (CCl_4) δ 6.81 (1 H, d, J = 16 Hz, vinyl CH), 6.35 (1 H, d, J = 16 Hz, vinyl CH), 3.2–3.6 (2 H, m, CH_2Br), 1.2–2.2 (4 H, m, CH_2), 1.13 (9 H, s, t-Bu), and 1.10 (6 H, s, CH_3); mass spectrum, m/e (rel intensity) 276 (M^+, 1), 274 (M^+, 1), 219 (100), 217 (100), 108 (16), 69 (16), and 57 (17).

Anal. Calcd for $C_{13}H_{23}BrO$: C, 56.73; H, 8.42; Br, 29.03. Found: C, 56.82; H, 8.46; Br, 28.93.

In a more satisfactory dehydrobromination procedure, a suspension of 2.41 g (25 mmol) of t-BuONa in 75 mL of Et_2O was treated with a solution of 5.4 g (15 mmol) of the dibromide **4** in 25 mL of Et_2O and the resulting suspension was stirred at 25 °C for 15 h. After the resulting mixture had been diluted with Et_2O, filtered, and concentrated, the residual crude bromo enone (4.53 g of yellow liquid) was chromatographed on silica gel with an Et_2O–hexane eluent (1:39 v/v) to separate 2.8 g (70%) of the bromo enone **5** as a colorless liquid, n^{25}_D 1.4771, that was identified with the previously described sample by comparison of NMR spectra.

Reaction of the Bromo Enone 5 with Me_2CuLi. A. In Et_2O. To a cold (0 °C) solution of Me_2CuLi, from 365 mg (1.78 mmol) of Me_2SCuBr, 3.56 mmol of MeLi (halide free), 8 mL of Et_2O, and 5 mL of Me_2S, was added a solution of 295 mg (1.07 mmol) of the bromo enone **5** in 5 mL of Et_2O. The resulting mixture, from which an orange precipitate separated, was stirred at 0–3 °C for 1.5 h and then siphoned into a cold aqueous solution (pH 8) of NH_3 and NH_4Cl. The ethereal extract of this mixture was dried and concentrated and the residual crude product (0.35 g of yellow liquid) was chromatographed on silica gel with an Et_2O–hexane eluent (1:39 v/v). The bromo ketone **6** was collected as 0.28 g (92%) of colorless liquid: n^{25}_D 1.4687; IR (CCl_4) 1710 cm^{-1} (C=O); ^1H NMR (CCl_4) δ 3.2–3.5 (2 H, m, CH_2Br), 2.2–2.4 (2 H, m, CH_2CO), 1.3–2.1 (5 H, m, aliphatic CH), 1.12 (9 H, s, t-Bu), and 0.7–1.0 (9 H, m, CH_3 including a CH_3 singlet at 0.85); mass spectrum, m/e (rel intensity) 292 (M^+, 4), 290 (M^+, 4), 276 (16), 274 (16), 234 (100), 232 (100), 127 (16), 83 (18), 69 (33), 57 (57), 55 (22), 43 (20), and 41 (29); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling) δ 213.7 (s), 44.0 (s), 38.8 (t), 38.5 (t), 35.2 (t), 34.5 (s), 27.2 (t), 26.2 (q, 5 C atoms), 24.4 (d), and 14.7 (q).

Anal. Calcd for $C_{14}H_{27}BrO$: C, 57.73; H, 9.34; Br, 27.43. Found: C, 57.97; H, 9.39; Br, 27.21.

From a comparable reaction in Et_2O at 0–5 °C for 2 h, the yield of the bromo ketone **6** was 83%.

B. In Et_2O–HMP. Before use commercial hexamethylphosphoramide (HMP, Fisher Scientific Co.) was refluxed under reduced pressure (60 °C at 0.5 mm) over BaO for 1 h and then distilled from BaO under reduced pressure [bp 55–60 °C (0.4–0.5 mm)]. During this distillation a substantial forerun (ca. 30 mL) was discarded and especial care was taken to avoid exposure of the purified solvent to either H_2O or O_2. To a solution of Me_2CuLi, from 365 mg (1.78 mmol) of Me_2SCuBr, 3.56 mmol of MeLi (halide free), 6 mL of Me_2S, and 8 mL of ether, was added 15 mL of freshly purified HMP. To the resulting colorless solution was added, dropwise and with stirring, a solution of 295 mg (1.07 mmol) of the bromo enone **5** in 5 mL of Et_2O. The resulting solution was stirred at 25 °C for 7.5 h during which time the solution slowly turned dark yellow in color but no precipitate separated. The reaction mixture was siphoned into a cold aqueous solution (pH 8) of NH_3 and NH_4Cl and extracted with Et_2O. The ethereal extract was washed with H_2O, dried, and concentrated to leave a yellow liquid (a mixture of product and HMP). Chromatography on silica gel with an EtOAc–hexane eluent (1:65 v/v) separated 0.22 g (97%) of the enone **7** as a colorless liquid: n^{25}_D 1.4536; IR (CCl_4) 1690 (conj C=O) and 1620 cm^{-1} (C=C); UV max (95% EtOH) 229 nm (ϵ 8600); ^1H NMR (CCl_4) δ 6.80 (1 H, d, J = 14 Hz, vinyl CH), 6.33 (1 H, d, J = 14 Hz, vinyl CH), and 0.7–1.5 (24 H, m, aliphatic CH including a t-Bu singlet at 1.16 and a CH_3 singlet at 1.07); mass spectrum, m/e (rel intensity) 210 (M^+, 2), 153 (100), 69 (58), 57 (53), 55 (29), 41 (45), and 39 (52); ^{13}C NMR ($CDCl_3$, multiplicity in off-resonance decoupling), 202.8 (s), 155.6 (d), 119.6 (d), 42.7 (s), 42.0 (t), 36.5 (s), 26.7 (t), 26.5 (q, 2 C atoms), 26.2 (q, 3 C atoms), 23.3 (t), and 14.0 (q).

Anal. Calcd for $C_{14}H_{26}O$: C, 79.93; H, 12.46. Found: C, 79.78; H, 12.42.

In three comparable experiments employing a mixture of Et_2O, Me_2S, and HMP as the reaction solvent with reaction times of 8–20 h at 22–25 °C, the isolated yields of enone **7** were 72, 78, and 80%. In a similar experiment, a solution of 1.09 mmol of Me_2CuLi and 0.72 mmol of the bromo enone **5** in 6 mL of Me_2S, 9.4 mL of Et_2O, and 15 mL of DMF [freshly distilled, bp 43 °C (16 mm)] was stirred at 23 °C for 20 h and subjected to the usual isolation procedure. By use of preparative TLC (silica gel coating with an Et_2O–hexane eluent, 1:4 v/v), 34 mg (22%) of the enone **7** (R_f 0.78) and 151 mg (75%) of the starting bromo enone **5** (R_f 0.70) were isolated.

Registry No.—**3**, 67489-20-7; **4**, 67489-21-8; **5**, 67489-22-9; **6**, 67489-23-0; **7**, 67489-24-1; lithium dimethylcuprate, 15681-48-8.

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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otherwise stated $MgSO_4$ was employed as a drying agent. The IR spectra were determined with a Perkin-Elmer, Model 257, infrared recording spectrophotometer fitted with a grating. The UV spectra were determined with a Cary, Model 14, or a Perkin-Elmer, Model 202, recording spectrophotometer. The proton NMR spectra were determined at 60 mHz with a Varian, Model A-60 or Model T-60-A, NMR spectrometer and the ^{13}C NMR spectra were determined at 25 mHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in δ values (ppm) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi Perkin-Elmer, Model RMU-7, mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

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Structural Studies on Juncusol. A Novel Cytotoxic 9,10-Dihydrophenanthrene Derivative from the Marsh Plant *Juncus roemerianus*[1]

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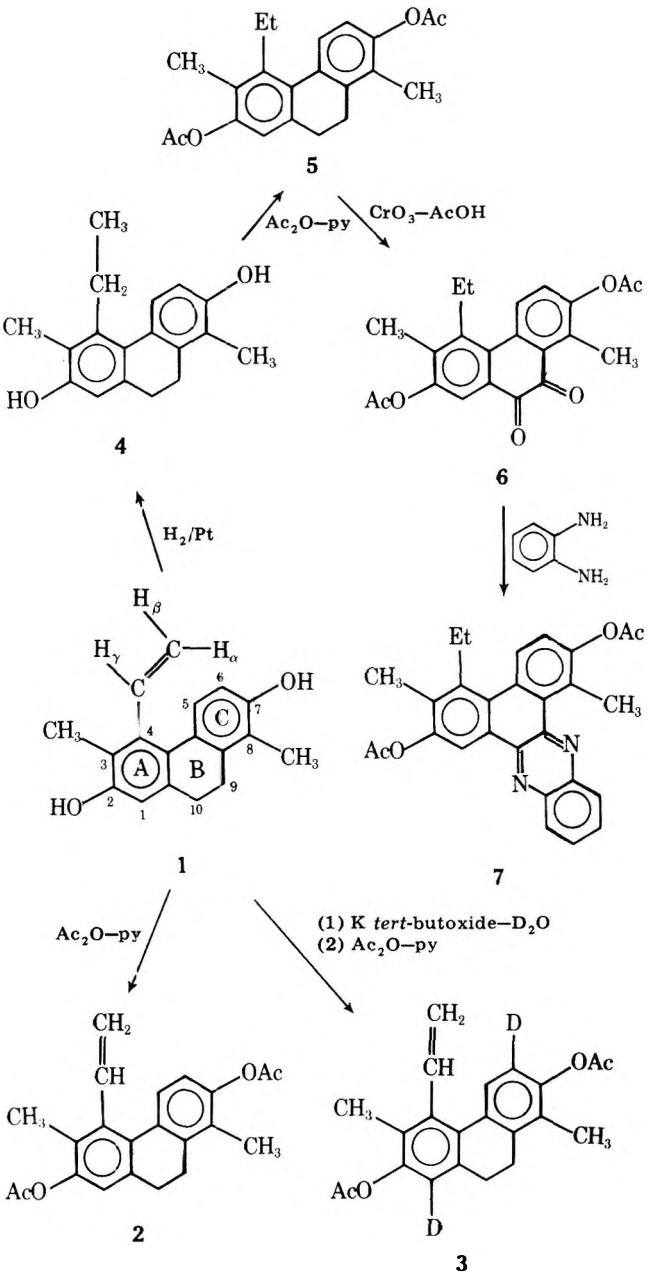
Received April 3, 1978

Juncus roemerianus (NO Juncaceae) is the most dominant among a group of plants, commonly known as "marsh grass", which grow abundantly on and near the coastal areas of the southeastern United States. An earlier report[3] indicated that 95% of the organic matter produced in the marsh is not attacked by the marsh herbivores, but on death and decomposition the plants enter the detritus food chain. A 95% ethanolic extract of the tops of *J. roemerianus* showed activity against P 388 lymphocytic leukemia in BDF_1 mice.[4] A preliminary study on the volatile constituents of *J. roemerianus* was reported earlier from our laboratory.[5] To our knowledge no detailed chemical investigation of *J. roemerianus* or any other marsh grass had been reported in the literature prior to our work. The $CHCl_3$ extract of the tops of this plant, upon chromatography over silica gel, yielded, inter alia, the cytotoxic[6] compound juncusol, $C_{18}H_{18}O_2$, mp 175–176 °C. Recently we reported[7] the structure of juncusol diacetate based on an X-ray crystallographic study. We now wish to report an extensive chemical and spectral study of juncusol and its derivatives in support of the structure of juncusol as 1 (Scheme I). Although about 20 of the relatively rare 9,10-dihydrophenanthrene derivatives are known from nature,[8] juncusol is unique in possessing an alkenyl substituent in the ring system in addition to rarely encountered alkyl groups. Juncusol, like all other members of its class, is a phenol, but unlike others it does not contain a methoxyl substituent.

Results and Discussion

The finely ground plant tops (above ground) of *J. roemerianus* were extracted with chloroform. The concentrated chloroform extract was triturated with chloroform–benzene (1:1). Chromatography of the soluble portion on silica gel followed by crystallization from benzene yielded (0.01% dry weight) juncusol, $C_{18}H_{18}O_2$ (M^+ at m/e 266), mp 175–176 °C. The IR spectrum of juncusol (1) in KBr exhibits peaks at 3350 (OH), 1603 (aromatic), 930 (vinyl), and 870 and 830 (two adjacent Ar–H) cm^{-1}. The UV spectrum in ethanol shows λ_{max} at 247 sh, 266 sh, 284 sh (log ϵ 4.12), and 318 sh nm, characteristic of the 9,10-dihydrophenanthrenes. A typical 4 H singlet at δ 2.50 in the ^1H NMR spectrum of juncusol confirms[9,10]

Scheme I



its 9,10-dihydrophenanthrene skeleton. The 100 MHz NMR spectrum of juncusol in $CDCl_3$ (with a few drops of acetone-d_6) also shows sharp singlets at δ 2.26 (3 H, Ar–CH_3) and 2.31 (3 H, Ar–CH_3), ABX type of signals for a vinyl group consisting of three sets of "quartets" at δ 5.20 (1 H, J_{AX} = 18 Hz and J_{AB} = 2 Hz), 5.46 (1 H, J_{BX} = 11 Hz and J_{AB} = 2 Hz), and 6.78 (1 H, J_{AX} = 18 Hz and J_{BX} = 11 Hz), two ortho aromatic proton doublets at δ 6.66 (J = 8 Hz) and 7.50 (J = 8 Hz), and an aromatic proton singlet at δ 6.70. The relative low field shift of one of the aromatic proton doublets at δ 7.50 indicates it to be at C-5 (or C-4) of the 9,10-dihydrophenanthrene ring system. Therefore, the ortho aromatic protons must be present at C-5 and C-6 and the remaining proton must be in ring A in juncusol. In the ^1H NMR spectrum of juncusol in pyridine-d_5, the CH_3 groups shift to δ 2.51 ($\delta_{pyridine} - \delta_{chloroform}$ = 0.25 ppm) and 2.62 ($\delta_{pyridine} - \delta_{chloroform}$ = 0.31 ppm), the C-6 aromatic proton shifts to δ 7.07 ($\delta_{pyridine} - \delta_{chloroform}$ = 0.41 ppm), and the ring A aromatic proton singlet shifts to δ 7.10 ($\delta_{pyridine} - \delta_{chloroform}$ = 0.40 ppm). These significantly large pyridine-induced solvent shifts to lower fields can only be attributed to the orientations of the CH_3 groups and the aromatic protons in question being ortho to the OH groups.[11]

0022-3263/78/1943-4371$01.00/0

Juncusol is soluble in dilute NaOH solution, and it gives a deep blue color with $FeCl_3$ solution. The reactions of juncusol are shown in Scheme I. Upon treatment with acetic anhydride in pyridine, juncusol yields a diacetate (**2**), $C_{22}H_{22}O_4$ (M^+ at *m/e* 350), mp 110 °C, showing the presence of both the oxygen atoms as phenolic functions. The aromatic protons in the diacetate (**2**) appear, as expected, at lower fields as doublets at δ 7.66 (H-5) and 7.30 (H-6) and as a singlet at δ 6.88 (ring A proton) in the NMR spectrum. Upon deuteration with D_2O in the presence of K *tert*-butoxide followed by acetylation, juncusol gives a dideuterated (demonstrated by mass spectrum) diacetate (**3**) which shows only the aromatic proton at C-5 as a singlet at δ 7.66 in the NMR spectrum. The disappearance of the proton at C-6 and the one in ring A upon deuteration confirms[9] that the former must be ortho and the latter either ortho or para to the hydroxyl groups. Therefore, one of the hydroxyl groups must be present at C-7, and consequently one of the CH_3 groups should be present at C-8 (ortho to OH group). Also, the aromatic proton in ring A, if para to a hydroxyl group, would not be expected to experience a pyridine-induced solvent shift of 0.40 ppm. Moreover, juncusol gives a negative Gibbs test, indicating that there is no proton para to a hydroxyl group in it. Therefore, the ring A proton must be ortho to a hydroxyl group.

Catalytic hydrogenation of juncusol produces a dihydro derivative (**4**), $C_{18}H_{20}O_2$ (M^+ at *m/e* 268), mp 167–168 °C. The absence of the ABX signals and the appearance of a quartet at δ 2.74 (2 H, J = 7 Hz, Ar–C**H**$_2$–CH_3) and a triplet at δ 1.22 (3 H, J = 7 Hz, Ar–CH_2–C**H**$_3$) in the NMR spectrum of the dihydro derivative confirm the presence of a vinyl group in juncusol.

Dihydrojuncusol on treatment with acetic anhydride in pyridine affords a dihydro diacetate (**5**), $C_{22}H_{24}O_4$ (M^+ at *m/e* 352), mp 138 °C. The latter, when oxidized with CrO_3 in acetic acid, gives an orange-yellow quinone (**6**), $C_{22}H_{20}O_6$ (M^+ at *m/e* 380), mp 213–214 °C. The quinone gives a condensation product (**7**) with *o*-phenylenediamine, confirming that it is a 9,10-phenanthrenequinone. The ring A aromatic proton singlet shifts considerably to a lower field at δ 7.55 in the NMR spectrum of the quinone (**6**). This large low field shift can be explained if the ring A aromatic proton is peri to the carbonyl group in the quinone and therefore at C-1 in juncusol. Consequently, the second hydroxyl group must be present at C-2 (ortho to the C-1 proton), and the second CH_3 group is at C-3 (ortho to the C-2 OH). The vinyl group must therefore be present at C-4. The vinyl group at C-4 has a restricted rotation, and consequently the methylene proton (designated by α in **1**) which is trans to the Ar–C–H proton (designated by γ) is expected to be somewhat shielded by the ring current of ring C in orientations where the vinyl group is at right angles to the plain of the 9,10-dihydrophenanthrene ring system. Therefore, the α proton appears at higher field than the methylene proton (designated by β in **1**) which is cis to the Ar–C–H (γ) proton in the NMR spectrum of juncusol. Exactly the reverse is the case of the vinyl protons in styrene, where the vinyl group has free rotation.

As previously reported[7] the structure of juncusol (**1**) was confirmed by a single crystal X-ray diffraction experiment on the diacetate derivative (**2**). Recently, we also reported[12] the carbon-13 NMR analysis of juncusol and its derivatives.

Experimental Section

Nuclear magnetic resonance spectra were obtained using a Jeolco Minimar spectrometer equipped with a spin decoupler and a Varian HA-100 spectrometer. Tetramethylsilane was used as an internal standard, and chloroform-*d* (99.8%) and acetone-d_6 were used as solvents. The hydrogenation was carried out in a Parr pressure reaction apparatus. Mass spectral data were obtained using a Perkin-Elmer Model 270 or a Hewlett-Packard Model 5930 mass spectrometer. Mass spectra were obtained at 70 eV. Infrared spectra were obtained using a Perkin-Elmer Model 137G spectrophotometer. The spectra of solids were obtained by incorporating the sample into a pellet of potassium bromide. The band at 11.035 μm in a polystyrene film (0.05 mm) was used as a reference peak. Column chromatography (wet and dry column chromatography) was performed in glass columns with sintered glass using silica gel, 40–140 mesh, Baker Analyzed Reagent. Thin-layer chromatography (TLC) was performed using E. Merck (Darmstadt) silica gel G and GF-254, Applied Science Laboratories, Inc., coated (20 × 20 cm and 5 × 20 cm) glass plates. Chromatoplates were prepared by using a Desaga spreader with a thickness of 0.25 mm. The plates were activated at 110 °C for 1 h. The solvent system was $CHCl_3$–acetone–diethylamine (5:4:1) or $CHCl_3$–MeOH (95:5) unless otherwise stated. Phosphomolybdic acid reagent (Applied Science) and ultraviolet light were used as detecting agents. Melting points were obtained on a Fisher-Jones apparatus and are uncorrected. Elemental microanalyses were done by Galbraith Laboratories Inc., Knoxville, Tenn. Biological activities were performed by the Cancer Chemotherapy National Service Center, Bethesda, Md.

Isolation of Juncusol (1). The dry ground aerial parts of *Juncus roemerianus* (7000 g), collected from Bay St. Louis, Miss., during the summer of 1972–1973, were extracted with $CHCl_3$ for 24 h in a Soxhlet apparatus. The combined $CHCl_3$ extracts were evaporated in vacuo, the residue was dissolved in a minimum volume of benzene–$CHCl_3$ (1:1), and the undissolved material was collected by filtration. The filtrate was placed in a column (9.5-cm diameter) of silica gel (1000 g). The column was eluted consecutively with benzene–hexane (1:1), benzene–hexane (4:1), benzene, benzene–chloroform (4:1), and benzene–chloroform (1:1). The fractions of 500 mL each were collected and monitored by TLC. Fractions eluted with benzene (25 L) on evaporation gave a dark greenish mass (30.0 g) which was rechromatographed on a column (2.5-cm diameter) of silica gel (185 g), eluting the fractions successively with the same sequence of solvent mixtures used in the previous chromatography. Fractions eluted with benzene–hexane (6 L) and benzene (5 L) were combined and evaporated. The residue was recrystallized several times from benzene–chloroform mixtures. Final recrystallization from benzene gave 1.0 g of juncusol (**1**) as stout colorless needles, mp 175–176 °C. Spectral properties of **1** were the following: UV (EtOH) λ_{max} (log ϵ) 247 sh, 266 sh, 284 sh (4.12), 318 sh nm; IR ν_{max} (KBr) 3550, 1603, 930, 870, 830 cm^{-1}; ^1H NMR ($CDCl_3$–acetone-d_6) δ 2.26 (3 H, s, Ar–CH_3), 2.31 (3 H, s, Ar–CH_3), 2.50 (s, 4 H), 5.20 (1 H, J_{AX} = 18 Hz, J_{AB} = 2 Hz), 5.46 (1 H, J_{BX} = 11 Hz, J_{AB} = 2 Hz), 6.66 (1 H, d, J = 8 Hz), 6.70 (1 H, s), 6.78 (1 H, J_{AX} = 18 Hz, J_{BX} = 11 Hz), 7.50 (1 H, d, J = 8 Hz). The mass spectrum gave a parent ion peak at *m/e* 266 (M^+) and important peaks at *m/e* 41, 43, 55, 77, 79, 81, 104, 149, 165, 236, 251, and 266 (relative % 70, 63, 54, 40, 50, 47, 44, 48. 90, 56, 100, and 98).

Anal. Calcd for $C_{18}H_{18}O_2$ (mol wt 266): C, 81.20; H, 6.76. Found: C, 81.02; H, 6.92.

Juncusol Diacetate (2). Juncusol (0.1 g) was dissolved in dry pyridine (1 mL), acetic anhydride (0.5 mL) was added to it, and the mixture was stirred at room temperature for 4 h in a round-bottom flask with a drying tube. The resulting mass was freed from excess pyridine in vacuo and poured onto cold water (20 mL). Extraction with chloroform followed by washing of the chloroform layer successively with dilute HCl, H_2O, Na_2CO_3, and H_2O, drying over anhydrous Na_2SO_4, and evaporation of $CHCl_3$ gave a solid product which upon crystallization from benzene gave juncusol diacetate (**2**), mp 110 °C, as white needles (0.1 g). The spectral properties of **2** were the following: IR ν_{max} (KBr) 1750, 1603, 940, 900, 870, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.18 (3 H, s), 2.20 (3 H, s), 2.36 (6 H, s), 2.72 (4 H, s), 5.3 (1 H, d), 5.44 (1 H, d), 6.7 (1 H, d), 6.88 (1 H, s), 7.30 (1 H, d), 7.66 (1 H, d). The mass spectrum gave a parent ion peak at *m/e* 350 (M^+) and fragmentation at *m/e* 236, 251, 266, 280, and 350.

Anal. Calcd for $C_{22}H_{22}O_4$ (mol wt 350): C, 75.42; H, 6.28. Found: C, 75.66; H, 6.30.

Deuteration of Juncusol. A mixture of juncusol (0.06 g), potassium *tert*-butoxide (0.5 mol equiv), and deuterium oxide (0.5 mL) was heated in a sealed nitrogen-filled tube at 100 °C for 3 days. The solvent was evaporated, and the product was acetylated (acetic anhydride–pyridine at room temperature for 24 h) and purified on TLC plates in the usual way to give the deuterated acetate (**3**) in high yield. The NMR spectrum showed that two aromatic protons exchanged with deuterium. The mass spectrum gave a parent peak at *m/e* 352 (M^+) (calcd for $C_{22}H_{20}D_2O_4$, mol wt 352).

Dihydrojuncusol (4). Juncusol (600 mg) was hydrogenated in methanol solution (25 mL) with 10% Pd/C (10 mg) as a catalyst in the presence of hydrogen gas at 50 psi for 2 h at room temperature. The solution was then filtered. The residue, after evaporation, was dissolved in benzene and filtered again. The mother liquor (15 mL) on

standing yielded transparent crystals, mp 167–168 °C, in quantitative yield. Spectral properties of **4** were the following: IR ν_{max} (KBr) 3550, 1603, 920, 870, 830, 815 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.22 (3 H, t, J = 7 Hz, Ar–CH_2–CH_3), 2.25 (6 H, s), 2.6 (4 H, s), 2.74 (2 H, q, J = 7 Hz, Ar–CH_2–CH_3), 6.85 (1 H, s), 7.05 (1 H, d), 7.45 (1 H, d), 9.4 (2 H, s); mass spectrum, m/e 268 (M^+), and fragmentation at m/e 115, 119, 151, 164, 181, 195, 238, 268.

Dihydrojuncusol Diacetate (5). Acetylation of dihydrojuncusol (**4**) was carried out in pyridine and acetic anhydride in the usual way and the product was crystallized from benzene, mp 138 °C. Compound **5** gave the following spectral data: IR ν_{max} (KBr) 1750, 1603, 920, 870, 830, 815 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.3 (3 H, t), 2.4 (6 H, s), 2.5 (6 H, s), 2.8 (4 H, s), 2.9 (2 H, q), 6.9 (1 H, s), 7.4 (1 H, t), 9.4 (1 H, s). The mass spectrum gave fragmentation at m/e 238, 253, 268, and 310 and a parent peak at m/e 352 (M^+).

Anal. Calcd for $C_{22}H_{24}O_4$ (mol wt 352): C, 75.00; H, 6.81. Found: C, 75.16; H, 6.69.

CrO_3 Oxidation of Dihydrojuncusol Diacetate. Compound **5** (400 mg) was dissolved in glacial acetic acid (10 mL) and gradually added to a solution of CrO_3 (800 mg) in 80% aqueous acetic acid (5 mL), keeping the temperature below 5 °C. After the addition, the mixture was stirred at room temperature for 4 h. The resulting mixture was then poured onto ice water (100 mL), extracted thoroughly with $CHCl_3$, dried over anhydrous Na_2SO_4, and evaporated. The quinone **6** was crystallized from benzene as yellow needles (0.15 g): mp 210–215 °C dec; IR ν_{max} (KBr) 1750, 1650, 1603, 925, 915, 875, 180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (3 H, t, J = 7 Hz), 2.25 (3 H, s), 2.3 (6 H, s), 2.4 (3 H, s), 2.85 (2 H, q, J = 7 Hz), 7.26 (1 H, d, J = 5 Hz), 7.55 (1 H, s), 7.46 (1 H, d, J = 5 Hz). The mass spectrum gave a parent ion peak at m/e 380 (M^+) and fragmentation at m/e 181, 253, 268, 305, 337, 352, and 380.

Anal. Calcd for $C_{22}H_{20}O_6$ (mol wt 380): C, 69.47; H, 5.26. Found: C, 69.64; H, 5.20.

Reaction of Quinone 6 with *o*-Phenylenediamine. Compound **6** (0.04 g) was refluxed in glacial acetic acid (3 mL) with *o*-phenylenediamine (0.02 g) for 2.5 h. The reaction product was cooled and poured onto ice-cold water, at which time a yellow precipitate separated. The latter was extracted with chloroform, and the chloroform layer was washed with water, dried with anhydrous Na_2SO_4, and evaporated. The dark yellow mass was recrystallized from benzene to give short, fine yellow needles. Compound **7** shrinks at 250–255 °C and finally decomposes at 270 °C. The IR spectrum showed the disappearance of the carbonyl band of the quinone **6** at 1650 cm^{-1}.

Acknowledgment. This work was supported by a grant from the National Cancer Institute (3-ROI-CA-13268), National Institute, Bethesda, Md. 20014. We thank Dr. Sidney McDaniel and Dr. Armanda de la Cruz for collection of the plant material.

Registry No.—**1**, 62023-90-9; **2**, 62023-91-0; **3**, 67489-25-2; **4**, 64052-93-3; **5**, 64052-94-4; **6**, 67489-26-3; **7**, 67489-27-4; *o*-phenylenediamine, 95-54-5.

References and Notes

(1) (a) Contribution 4 in the series of antineoplastic agents. For part 3, refer to ref 7. (b) Part 7 in the series "Constituents of Marsh Grass."
(2) (a) Department of Chemistry, Mississippi State University. (b) The Institute for Natural Products Research and the Department of Chemistry, University of Georgia. (c) Partly taken from the Ph.D. Thesis of N. V. Mody, Mississippi State University. (d) Boll Weevil Research Laboratory, U.S. Department of Agriculture, Mississippi State, Miss.
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Convenient Synthesis of *N*-Noratropine[1]

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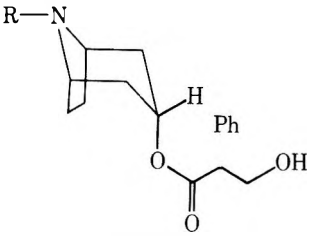
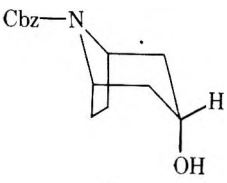
Received May 19, 1978

Due to their pronounced biological activities, compounds containing the tropane structure have been of interest for a number of decades.[2-4] Recently, derivatives of *N*-alkylnoratropine, especially the bronchodilator *N*-isopropyl-*N*-methylnoratropinium bromide[5-7] (Ipratropium bromide, Sch 1000), have commanded particular attention.

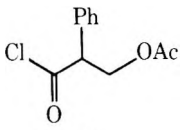
N-Noratropine (**1**) itself, long known as a constituent of various solanaceous plants,[8] was first synthesized by Nádor et al.[9,10] who reacted *N*-carbobenzyloxynortropine (**2**) with *O*-acetyltropic acid chloride (**3**) in the presence of pyridine,



1, R = H
4, R = Cbz
7, R = Me



2



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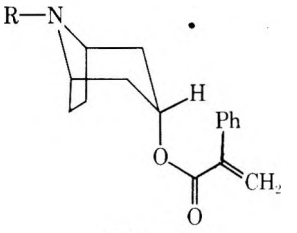
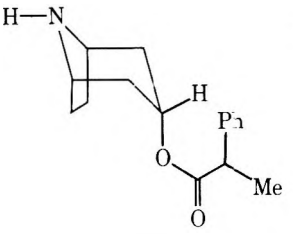
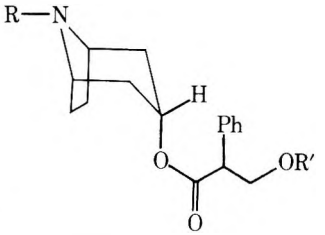


5, R = Cbz
10, R = H



6



8, R = Cl_3CCH_2OCO; R′ = H
9, R = R′ = Cl_3CCH_2OCO

followed by acid-catalyzed hydrolysis of the *O*-acetyl group. The resulting *N*-carbobenzyloxynoratropine (**4**) was subjected to hydrogenolytic cleavage to afford noratropine (**1**). However, Bertholdt et al.[11] claimed that under the acylation conditions mentioned above, the acrylate **5** was formed by elimination of AcOH. They conclusively proved that after hydrogenolysis, the phenyl propionate **6** was the final product. The same elimination reaction has also been observed by other workers[12] in a closely related series of compounds. Both groups of investigators pointed out that the desired tropate esters could be obtained in fair yields if the acylation step was carried out in the absence of basic catalysts. Nevertheless, it seemed worthwhile to examine the possibility of N-demethylating commercially available atropine (**7**), which would constitute a much simpler method of synthesizing noratropine.

It has already been shown that the simple bases tropine and tropinone can be demethylated with ethyl chloroformate,[13] but the strongly acidic conditions required for the hydrolysis of the resulting carbamate intermediates were deemed to be

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incompatible with the sensitive β-hydroxy ester functionality present in atropine. Demethylation with trichloroethyl chloroformate[14] seemed potentially more useful, since trichloroethyl carbamates can be cleaved under mild conditions with Zn in AcOH.

In a trial experiment, treatment of atropine with Cl_3CCH_2OCOCl under conditions similar to those employed for the PhOCOCl demethylation of morphine[15] resulted in the quantitative formation of two nonbasic, oily compounds (ratio ~9:1), which were separated by column chromatography and assigned structures **8** and **9** on the basis of NMR and IR spectroscopy. When treated with Zn dust in AcOH, both **8** and **9** were converted into the same polar product, presumed to be noratropine.

On a preparative scale, the reaction mixture consisting of **8** and **9** was directly treated with Zn dust in AcOH to produce crystalline noratropine (**1**) in 90.5% yield. Care had to be exercised during the workup, since concentration of the filtered AcOH solution containing noratropine on a rotary evaporator at 60 °C gave primarily the dehydration product **10** (oxalate mp 268–269 °C, NMR (Me_2SO-d_6) δ 6.32 [d, J = 28 Hz]), again demonstrating the sensitivity of this system. Therefore, the basification–extraction scheme described below was adopted.

Experimental Section

A mixture of 5.0 g (17.3 mmol) of atropine (**7**), 12 mL (87 mmol) of Cl_3CCH_2OCOCl, 17.28 g (173 mmol) of $KHCO_3$, and 250 mL of $CHCl_3$ was refluxed for 4 h. The cooled mixture was filtered, the solvent removed on a rotary evaporator, and the residue freed from excess Cl_3CCH_2OCOCl (kugelrohr setup, oil pump, 80 °C). The remaining mixture of carbamates was stirred with 10 g of activated Zn dust[16] in 100 mL of AcOH at 15 °C for 16 h. Inorganic matter was filtered off and the filter cake was washed with AcOH (50 mL). The filtrate was diluted with 150 mL of H_2O and cooled in an ice bath. Aqueous NH_3 (58%) was added dropwise (T < 10 °C) with stirring to pH ~6, at which point the mixture was extracted with ether to remove a small amount of neutral material. Addition of NH_3 to the aqueous phase was continued to pH ~10. Extraction with four 150-mL portions of $CHCl_3$, washing the combined extracts with brine, drying over anhydrous K_2CO_3, and evaporating afforded 4.3 g (90.5%) noratropine (**1**) as colorless crystals, mp 114 °C (lit. mp 114 °C),[11] homogeneous on TLC (silica gel, 50 CH_2Cl_2/50 MeOH/1 Et_3N).

Acknowledgment. The author would like to thank Dr. John G. Moffatt for helpful discussions.

Registry No.—**1**, 16839-98-8; **7**, 51-55-8; **8**, 67393-86-6; **9**, 67393-87-7; Cl_3CH_2OCOCl, 17341-93-4.

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Side-Chain Extension of 17-Keto Steroids to 17α,22-Aldehydes

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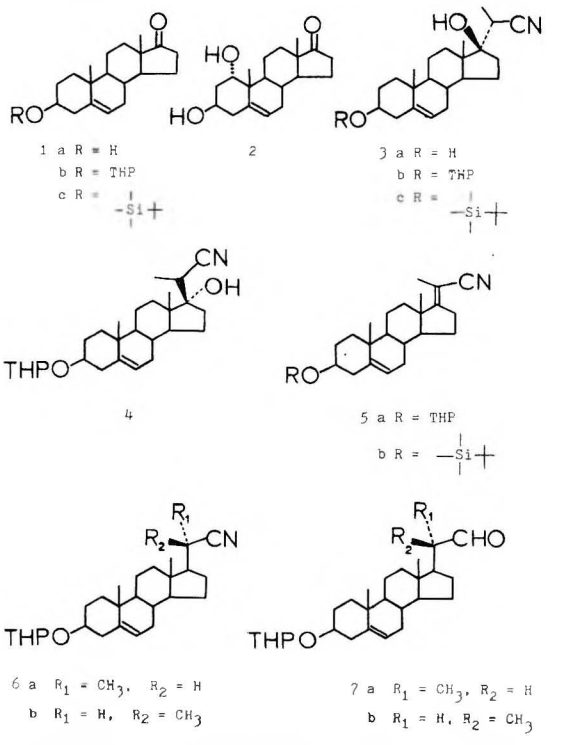
Received May 3, 1978

We wished to develop a method for side-chain extension of 17-keto steroids which could be applied to 1α,3β-dihydroxyandrost-5-en-17-one, readily available from 3β-hydroxyandrost-5-en-17-one by microbiological methods.[2] Thus an alternative route to the steroidal precursors of the clinically important 1α,25-dihydroxyvitamin D_3[3,4] and its analogues might become available. We now report a simple method of converting such 17-keto steroids into the 17α*H*-23,24-bisnorchol-5-en-22-al derivatives and related compounds.

3β-Hydroxyandrost-5-en-17-one (**1a**) was converted to the THP ether **1b**,[5] which upon treatment with excess propionitrile and lithium diisopropylamide (LDA)[6] at −78 °C for 90 min, followed by addition of the cold solution to water, gave a single product **3b** (88%). The 17β orientation of the hydroxyl in **3b** is assigned from mechanistic considerations and from the observed downfield shift of the C-18 methyl NMR signal (δ 0.88 in **1b**) to δ 0.95. The product was formed as a mixture of epimers at C-20, which was not resolvable by recrystallization or thin-layer chromatography. In the presence of Eu(fod)$_3$ (ca. 1 equiv), the originally sharp C-18 methyl singlet became shifted substantially downfield, and appeared as two singlets of nearly equal intensity at δ 1.18 and 1.21.[7]

When the propionitrile addition reaction was conducted by stirring the reactants at −78 °C for 20 min followed by stirring at 25 °C for 20 h before workup, a mixture of **3b** and an isomeric product assigned the structure **4** (ratio of **3b**–**4**, ca. 1:2) was obtained in very low yield, accompanied by recovered starting material (80%). After recrystallization of the **3b** + **4** mixture, the pure **4** was obtained. Product **4** closely



resembled **3b** in its IR and ^{1}H NMR spectra. The latter were practically superimposable in the region δ 3.0–6.0, and differed mainly in the chemical shifts of the C-20–H (**3b**, δ 2.74; **4**, δ 2.85), C-21 methyl (**3b**, 1.47; **4**, δ 1.42), and C-18 methyl (**3b**,

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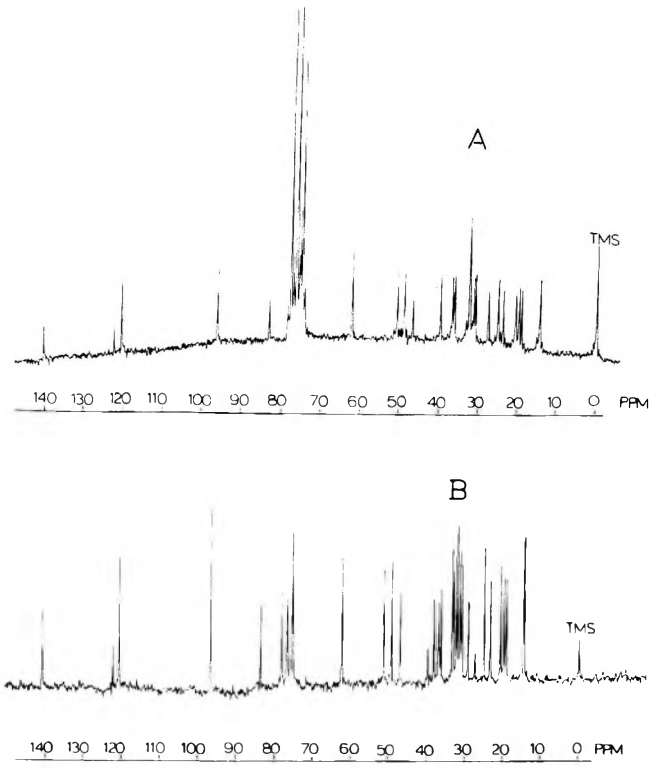

Figure 1: ^{13}C NMR spectra: A, compound **4**, 0.03 M in $CDCl_3$; B, compound **3b**, 0.16M in $CDCl_3$.

δ 0.95; **4**, δ 0.90). Furthermore the ^{13}C NMR (Figure 1) were nearly superimposable in all regions of the spectra except for slight differences in the δ 20–40 region. In the presence of Eu(fod)$_3$, again the ^1H signal for the C-18 methyl group was shifted downfield, appearing as two singlets at δ 1.25 and 1.28[8] of approximately equal intensities. Since both products **3b** and **4** were thereby demonstrated to consist of an epimeric mixture (presumably at C-20), it follows that if **3b** is to be formulated as the 17β-OH isomer, then **4** must be the 17α-OH isomer. The higher field C-18 methyl signal of **4** supports its formulation as the 17α-OH isomer. Both **3b** and **4** on treatment with lithium diisopropylamide (without propionitrile) at −78 °C slowly underwent fragmentation to their precursor, **1b**. Thus, it appears that addition of propionitrile anion to the 17-keto group is reversible. Under the low-temperature conditions, the kinetically controlled product **3b** is formed exclusively, whereas at higher temperature, a moderate amount of the more stable **4** is generated. However, at this temperature, reversion to starting material becomes predominant, and a very low yield of the addition products is obtained.

Following the method used for the production of **3b**, the *tert*-butyl dimethylsilyl ether **1c** and the unprotected **1a** gave with propionitrile and LDA (−78 °C, 90 min) in good yields the addition products **3c** and **3a**, respectively. Upon treatment with thionyl chloride in benzene–pyridine, **3b** and **3c** underwent nearly quantitative dehydration to **5a** and **5b**, respectively. The products were, presumably, $E + Z$ mixtures as indicated by the broadened vinyl methyl signal (δ 1.83), although both were chromatographically homogeneous and had sharp melting points. We did not separate the $E + Z$ mixtures of **5a** or **5b**. The sequence **1b** or **1c** → **5a** or **5b** provides a simple, high-yield alternative to the Wittig reaction approach recently reported by Watt et al.[9] for the interconversion of **1b** to **5a**, which in turn can be converted into progesterone.[9] Attempted selective dehydration of **3a** gave unsatisfactory results.

Reduction of **5a** to the 17αH saturated nitrile **6** was carried out with magnesium in methanol, essentially as previously described,[9] except that the THP ether was not hydrolyzed before workup. The product consisted of an inseparable 2:1 mixture of the 20*S* isomer **6a** (major) and 20*R* isomer **6b** as shown by the relative intensities of doublets in the NMR spectrum at δ 1.33 (major) and δ 1.29 (minor). The structural assignment is based on the conversion of the mixture into a corresponding mixture of aldehydes **7** which can be identified. Attempts to carry out a similar reduction of the *tert*-butyl dimethylsilyl ether **5b** were foiled by its extreme insolubility in methanol.

Further treatment of **6** with diisobutylaluminum hydride[10] gave a mixture of aldehydes **7a** and **7b** (87%) in a ca. 2:1 ratio, as shown by the signals for the C-18 methyl group at δ 0.68 (**7b**, minor) and δ 0.72 (**7a**).[11] After recrystallization of the mixture, the pure isomer **7a** was isolated, albeit in rather low yield (20%). Thus the sequence **1a** → **7** provides a partially satisfactory solution to the problem of side-chain assembly[12] and should be applicable to other 17-keto steroids such as **2**.[13]

Experimental Section

Melting points were taken on a hot-stage apparatus and are corrected. Specific rotations were measured on a Rudolph Model 80 polarimeter. Tetrahydrofuran (THF) was dried by distillation from $LiAlH_4$. Benzene was dried by shaking with concentrated H_2SO_4, followed by distillation. Diisopropylamine and pyridine were dried by distillation from barium oxide. Silica gel HF 254 + 366 (E. Merck) was used for thin-layer chromatography (TLC) in the solvents noted. IR spectra were determined in $CHCl_3$ solution on a Perkin-Elmer Model 237 or 337 spectrometer. ^1H NMR spectra were obtained in $CDCl_3$ solutions on Varian A-60, EM-360, or HA-100 instruments, with tetramethylsilane as internal reference. ^{13}C NMR spectra were obtained in $CDCl_3$ solutions on a Bruker SXP 22/100 spectrometer operating at 22.63 MHz. Peak positions are expressed in ppm (δ) downfield from Me_4Si. Mass spectra were determined on a Nuclide 12-90-G mass spectrometer equipped with a Nuclide DA/CSI.2 data acquisition system. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz.

3β-*tert*-Butyldimethylsilyloxyandrost-5-en-17-one (1c). 3β-Hydroxyandrost-5-en-17-one (1 g, 3.47 mmol) was stirred with *tert*-butyldimethylchlorosilane (630 mg, 4.2 mmol) and imidazole (585 mg, 8.6 mmol) in DMF (8 mL) at room temperature for 19 h. Then water (50 mL) and ether (50 mL) were added, and the ether extract was washed with dilute HCl, water, and saturated NaCl, dried (Na_2SO_4), and evaporated. Crystallization from methanol gave **1c**: 1.0 g, blades; mp 145–147 °C; IR ν 2950, 1740 cm^{-1}; NMR δ 0.05 (s, 6), 0.90 (12 H, s), 1.04 (s, 3, 19-CH_3), 3.50 (br m, 1, $W_{1/2}$ = 20 Hz, 3α H), 5.37 (br d, 1, J = 5 Hz, vinyl H).

Anal. Calcd for $C_{25}H_{42}O_2Si$: C, 74.55; H, 10.52. Found: C, 74.67; H, 10.60.

22-Cyano-17β-hydroxy-3β-tetrahydropyran-2′-yloxy-17α-pregn-5-ene (3b). To a solution of dry diisopropylamine (6 g, 59.4 mmol) in dry THF (150 mL) at −78 °C under N_2 was added a solution of *n*-butyllithium in hexane (59.4 mL, 1.0 M) followed immediately by propionitrile (3.0 g, 54.5 mmol) in dry THF (10 mL). The mixture was stirred 10 min at −78 °C, then **1b** (7.5 g, 20.2 mmol) in dry THF (12 mL) was added dropwise over 5 min. Stirring was continued for 90 min. The cold mixture was diluted with ether and water, and the ether solution washed with dilute HCl, 10% $NaHCO_3$, water, and saturated NaCl, dried (Na_2SO_4), and evaporated. The product was crystallized from ethanol–ether, giving 7.5 g of **3b**: needles; mp 175–177 °C; $[\alpha]^{23}_D$ −77° (c 1.6, $CHCl_3$); IR ν 3850, 2240 cm^{-1}; NMR δ 0.95 (s, 3, 18-CH_3), 1.03 (s, 3, 19-CH_3), 1.47 (d, 3, J = 7 Hz, 21-CH_3), 2.74 (q, 1, J = 7 Hz, 20-H), 3.5 (m, 2), 3.85 (m, 1), 4.73 (br s, 1, $W_{1/2}$ = 6 Hz, 2′-H), 5.34 (br d, 1, J = 4 Hz, vinyl H).

Anal. Calcd for $C_{27}H_{41}NO_3$: C, 75.84; H, 9.66; N, 3.28. Found: C, 76.16; H, 9.84; N, 3.39.

In a similar manner, **1c** (2.0 g, 5 mmole) was converted to **3β-*tert*-butyldimethylsilyloxy-22-cyano-17β-hydroxy-17α-pregn-5-ene (3c)** (1.94 g, 85%): blades from ethanol–ether; mp 210–212 °C; IR ν 3580, 2235 cm^{-1}; NMR δ 0.06 (s, 6), 0.90 (s, 9), 0.97 (s, 3, 18-CH_3), 1.02 (s, 3, 19-CH_3), 1.48 (d, 3, J = 7 Hz, 21-CH_3), 2.77 (q, 1, J = 7 Hz, 20-H), 3.5 (br s, 1, $W_{1/2}$ = 20 Hz, 3α-H), 5.34 (br d, 1, J = 5 Hz).

Anal. Calcd for $C_{28}H_{47}NO_2Si$: C, 73.45; H, 10.36; N, 3.06. Found: C, 73.76; H, 10.34; N, 2.91.

Similarly, **1a** (1.0 g, 3.47 mmol) was converted to **22-cyano-3β,17β-dihydroxy-17α-pregn-5-ene (3a)** (0.98 g, 84%): prisms from $CHCl_3$; mp 214–217 °C; IR ν 3600, 2225 cm^{-1}; NMR δ 0.94 (s, 3, 18-CH_3), 1.03 (s, 3, 19-CH_3), 1.44 (d, 3, J = 7 Hz, 21-CH_3), 3.77 (q, 1, J = 7 Hz, 20-H), 3.55 (br s, 1, $W_{1/2}$ = 20 Hz, 3α-H), 5.38 (br s, 1, $W_{1/2}$ = 10 Hz, vinyl H); mass spectrum, m/e 343 (M^+, 58, $C_{22}H_{33}NO_2$ requires 343), 325 (61), 310 (39), 270 (26), 246 (44), 228 (54), 213 (100), 145 (70), 107 (54).

22-Cyano-17α-hydroxy-3β-tetrahydropyran-2′-yloxypregn-5-ene (4). To a solution of diisopropylamine (315 mg, 3.1 mmole) in dry THF (15 mL) containing triphenylmethane (10 mg) at −78 °C under N_2 was added n-butyllithium in hexane (3.1 mL, 1 M) followed by propionitrile (170 mg, 3.1 mmol), and the solution was stirred 10 min at −78 °C. Then **1b** (936 mg, 2.52 mmol) in dry THF (15 mL) was added dropwise over 15 min, and then the solution was stirred at room temperature for 20 h. The mixture was then diluted with ether and the solution washed with dilute HCl, water, dilute $NaHCO_3$, and saturated NaCl, dried (Na_2SO_4), and evaporated. TLC (10% ethyl acetate–hexane) indicated the presence of mainly (ca 80%) starting material plus one major product band which was isolated by preparative TLC to give 110 mg of a mixture of **3b** (18-Me, δ 0.95) and **4** (18-Me, δ 0.90) (ratio **3b**–**4**, ca. 1:2). Recrystallization from ethanol–ether gave pure **4:** 35 mg; needles; mp 158–160 °C; IR ν 3640, 2240 cm^{-1}; NMR δ 0.90 (s, 3, 18-CH_3), 1.05 (s, 3, 19-CH_3), 1.42 (d, 3, 21-CH_3), 1.1–2.5 (complex m), 2.85 (q, 1, J = 7 Hz, 20-H), 3.5 (m, 2), 3.85 (m, 1), 4.76 (br s, 1, $W_{1/2}$ = 5 Hz, 2′-H), 5.37 (br d, 1, vinyl H); mass spectrum m/e 409 (M − H_2O, 2), 343 (30), 326 (71), 325 (100), 310 (32), 271 (31), 270 (32), 228 (37), 214 (50), 159 (26), 145 (38), 121 (32), 85 (96).

Anal. Calcd for $C_{27}H_{41}NO_3$: C, 75.84: H, 9.66. Found: C, 75.73; H, 9.69.

20-Cyano-3β-tetrahydropyran-2′-yloxypregna-5,17(20)-diene (5a). To a solution of **3b** (2.2 g, 5.91 mmol) in dry benzene (44 mL) and dry pyridine (44 mL) cooled in cold water (5–10 °C) was added thionyl chloride (2.2 g, 18.5 mmol) in dry benzene (44 mL). The solution was slowly heated to reflux (over 30 min) and refluxed for 1 h. After cooling, the solution was added to cold water and extracted with ether. The extract was washed with dilute HCl, 5% $NaHCO_3$, water, and saturated NaCl, dried (Na_2SO_4), and evaporated to yield pure **5a:** 1.98 g (95%); needles from ethanol–ether; mp 160–161 °C (lit.[9] mp 185–194 °C);[14] $[\alpha]^{25}_D$ −9° (c 1.64, $CHCl_3$); IR ν 2200, 1640 cm^{-1}; NMR δ 0.93 (s, 3, 18-CH_3), 1.03 (s, 3, 19-CH_3), 1.83 (slightly br s, 3, 21-CH_3), 3.2–4.2 (br m, 3), 4.73 (br s, 1, $W_{1/2}$ = 7 Hz, 2′-H), 5.36 (br d, 1, J = 4 Hz, vinyl H).

Anal. Calcd for $C_{27}H_{39}NO_2$: C, 79.17; H, 9.60; N, 3.42. Found: C, 78.89; H, 9.61; N, 3.44.

In a similar manner, **3c** (1.0 g, 2.28 mmol) was converted to **3β-*tert*-butyldimethylsilyloxy-20-cyanopregna-5,17(20)-diene (5b)** (890 mg, 93%): blades from ethanol–ether; mp 192–194 °C; IR ν 2200, 1092, 887, 870, 835 cm^{-1}; NMR δ 0.05 (s, 6), 0.90 (s, 9), 0.92 (s, 3, 18-CH_3), 1.02 (s, 3, 19-CH_3), 1.83 (br s, 3, 20-CH_3), 1.1–2.9 (complex m), 3.6 (br m, 1, 3α-H), 5.35 (br d, 1, J = 4 Hz, vinyl H).

Anal. Calcd for $C_{28}H_{45}NOSi$: C, 76.46; H, 10.32; N, 3.19. Found: C, 77.15; H, 10.22; N, 3.02.

20-Cyano-3β-tetrahydropyran-2′-yloxypregn-5-ene (6). Unsaturated nitrile **5a** (5.27 g, 12.8 mmol) was treated with magnesium turnings (25.5 g, 1.05 g-atom) in methanol (260 mL) with stirring at room temperature for 2 h, maintaining the reaction mixture at ca. 25 °C with cooling as required. The progress of the reaction was monitored by taking IR spectra of aliquots extracted with ether and following the change in nitrile absorption (**5a,** ν 2200 cm^{-1}; **6,** ν 2235 cm^{-1}). Additional magnesium (6.4 g, 0.26 g-atom) and methanol (150 mL) were added, and stirring was continued at room temperature for 24 h. Ether was added, and the mixture acidified with cold 6 N HCl, keeping the mixture at ca. 25 °C. Additional ether was added and the extract was washed with saturated $NaHCO_3$, water, and saturated NaCl, dried (Na_2SO_4), and evaporated to yield **6:** 4.77 g (90%); needles from ethanol; mp 148–151 °C; $[\alpha]^{23}_D$ +20° (c 1.08, $CHCl_3$); IR ν 2235, 1209, 1028, 1021 cm^{-1}; NMR δ 0.74 (s, 3, 18-CH_3), 1.02 (s, 3, 19-CH_3), 1.29 (d, J = 7 Hz, 20R-CH_3), 1.33 (d, J = 7 Hz, 20S-CH_3) (ratio of δ 1.29–δ 1.33 ca. 1:2), 1.0–2.4 (complex m), 2.63 (d qu, 1, J_1 = 7 Hz, J_2 = 7 Hz, 20-H), 3.5 (m, 2), 3.9 (m, 1), 4.74 (br s, 1, $W_{1/2}$ = 7 Hz, 2′-H), 5.35 (br d, 1, J = 4 Hz, vinyl H).

Anal. Calcd for $C_{27}H_{41}NO_2$: C, 78.78; H, 10.04; N, 3.40. Found: C, 78.86; H, 10.26; N, 3.53.

3β-Tetrahydropyran-2′-yloxy-23,24-bisnorchol-5-en-22-al (7a). A solution of **6** (400 mg, 0.96 mmol) in dry benzene (8 mL) and heptane (5 mL) at 0 °C under N_2 was treated with a solution of diisobutylaluminum hydride (4 mL, 0.81 M, 3.24 mmol) for 3 h, with spontaneous warming to room temperature. The solution was then poured into ice-cold saturated NH_4Cl and acidified with dilute H_2SO_4. The mixture was extracted with ether, and the extract was washed with saturated $NaHCO_3$ and saturated NaCl, dried (Na_2SO_4), and evaporated to yield a mixture from which **7**, 350 mg (mixture of **7a** + **7b**), was isolated by preparative TLC (30% ethyl acetate–hexane); NMR included singlets at δ 0.68 and 0.72 (ratio ca. 1:2). A portion (25%) of the mixture was recrystallized three times from absolute ethanol giving **7a:** 18 mg; needles; mp 127–129 °C; $[\alpha]^{25}_D$ −39° (c 0.51, $CHCl_3$) (lit.[9] mp 137–139 °C, $[\alpha]_D$ −39°); IR ν 1720, 1025 cm^{-1}; NMR δ 0.72 (s, 3, 18-CH_3), 1.01 (s, 3, 19-CH_3), 1.11 (d, 3, J = 7 Hz, 21-CH_3), 2.35 (d, 2, J = 7 Hz, 7-H_2), 3.5 (m, 2), 3.9 (m, 1), 4.73 (br s, 1, $W_{1/2}$ = 9 Hz, 2′-H), 5.36 (br s, 1, $W_{1/2}$ = 11 Hz, vinyl H), 9.55 (d, 1, J = 3 Hz, CHO). The isomer **7b** was not isolated in pure form.

Anal. Calcd for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.57; H, 10.31.

Acknowledgments. This work was supported, in part, by Grant AM17057 from the National Institute of Arthritis, Metabolism, and Digestive Diseases, and by Biomedical Sciences Support Grants RR05528 and RR07123 from the U.S. Public Health Service. The ^{13}C NMR spectra were obtained on an instrument supported in part by a National Science Foundation Equipment Grant No. CHE77-09059. We thank Dr. Warren G. Anderson, Mr. Cliff McDonald, and Mr. Frank Shea for NMR spectra, and Dr. Thomas A. Wittstruck for mass spectra.

Registry No.—**1a,** 53-43-0; **1b,** 19637-35-5; **1c,** 42151-23-5; **3a,** 67464-51-1; (20S)-**3b,** 67464-52-2; (20R)-**3b,** 67464-53-3; **3c,** 67464-54-4; (20S)-**4,** 67504-73-8; (20R)-**4,** 67504-74-9; (*E*)-**5a,** 58449-03-9; (*Z*)-**5a,** 58449-04-0; (*E*)-**5b,** 67488-41-9; (*Z*)-**5b,** 67464-55-5; **6a,** 67464-56-6; **6b,** 67464-57-7; **7a,** 22145-61-5; **7b,** 67488-42-0; *tert*-butyldimethylchlorosilane, 18162-48-6; propionitrile, 107-12-0.

References and Notes

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(8) The fact that the C-18 methyl signals of both **3b** and **4** are shifted downfield to approximately the same extent by Eu(fod)$_3$ indicates that complexation is not occurring exclusively with the C-17 hydroxyl group.
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(13) Microbiologically produced **2** has been converted, following the procedure described in this note, in good yields into the 1α-tetrahydropyran-2′-yloxy analogues of **3b, 5a, 6,** and **7.** However, to date only the analogue of **3b** has been obtained in crystalline form (mp 174–175 °C) [D. J. Aberhart and T. Y. Chau, unpublished]. Further work on the application of this approach to the synthesis of 1α-hydroxyvitamin D precursors will be reported in due course.
(14) The large discrepancy in the melting point of this product compared with that of Watt et al.[9] may be the result of a different ratio of 20-*E*/*Z* isomers. The compounds were prepared by different methods.

Synthesis of Thio Analogues of Prostaglandin H_2 and Prostaglandin F_2 from Prostaglandin A_2[1]

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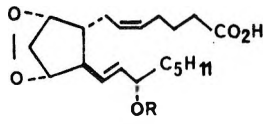
Received June 19, 1978

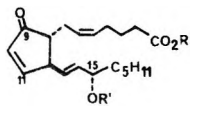
The prostaglandin endoperoxides PGG_2 (**1a**) and PGH_2 (**1b**) occupy a pivotal position in the biosynthesis of the primary prostaglandins, thromboxane A_2, and prostacyclin (PGI_2) from arachidonic acid.[2] The interesting spectrum of independent biological activity exhibited by the endoperoxides coupled with their lability has prompted the synthesis



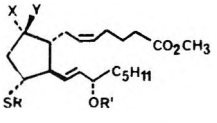
1 a) R = OH
b) R = H

of several potentially more stable analogues.[3,4] At the inception of a program in our laboratory aimed principally at the synthesis of the endo-disulfide analogue (6) of PGH_2, there was a surprising lack of C-9 and C-11 thio analogues of the prostaglandins in the literature. During the course of our work in this area, however, Hayashi et al.[3] reported a somewhat lengthy total synthesis of the endo-disulfide **6**, via the tetrahydropyranyl ether derivative of 9α,11α-dimercapto-9,11-dideoxyprostaglandin F_2 methyl ester (**5b**), and showed it to be a very effective biochemical mimic of PGH_2.

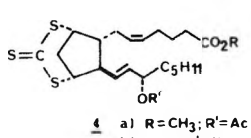
In this note we wish to present a short, stereoselective synthesis from (+)-PGA_2 (**2a**) of two endo-peroxide analogues, the novel *endo*-trithiocarbonate **4** and the endo-disulfide **6**, as well as 11α-mercapto-11-deoxyprostaglandin $F_{2\alpha}$ methyl ester (**3e**), 11α-mercapto-11-deoxyprostaglandin $F_{2\beta}$ methyl ester (**3d**), and 9α,11α-dimercapto-9,11-dideoxyprostaglandin F_2 (**5a**).[5]



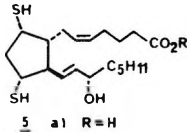
2 a) R = R' = H
b) R = CH_3, R' = Ac



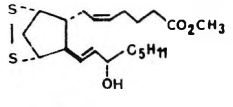
3 a) X, Y = O; R = R' = Ac
b) X = H; Y = OH; R = R' = Ac
c) X = OH; Y = H; R = R' = Ac
d) X = H; Y = OH; R = R' = H
e) X = OH; Y = H; R = R' = H
f) X = H; Y = OMs; R = R' = Ac



4 a) R = CH_3; R' = Ac
b) R = H; R' = H



5 a) R = H
b) R = CH_3



6

(+)-PGA_2 (**2a**), readily obtained in quantity by enzymatic hydrolysis of the lipophilic extract of *Plexaura homomalla*, *homomalla* (Var. S, collected off the Cuban coast) was converted in 92% yield to the corresponding diester **2b** by treatment with diazomethane followed by acetic anhydride in pyridine. Kinetically controlled conjugate addition of thiolacetic acid to **2b** smoothly produced a single product **3a** in 85% yield, which was assigned the α configuration from ample precedent.[6] Treatment of thiolacetate **3a** with zinc borohydride in DME[7] then afforded a 4 to 1 mixture of 9β (**3b**) and 9α (**3c**) alcohols, respectively, in 85% yield. After chromatographic separation of the C-9 alcohols, methanolysis gave the new C-11 mercapto analogues of $PGF_{2\alpha}$ and $PGF_{2\beta}$, compounds **3e** and **3d**, respectively. The stereochemical assignments in alcohols **3b–e** were made on the basis of the generally observed greater mobilities[5,9] on silica gel and larger C-9 carbinolic proton downfield chemical shifts[10] for the 9α alcohols relative to the corresponding 9β alcohols. Further proof was secured through reduction of **3a** with lithium perhydro-9b-borapheralylhydride, a reagent known to produce predominantly or exclusively PGF_α-type products from PGE derivatives,[6c,11] to afford the minor isomer **3c** as the major product.

The alcohol **3b** was also transformed to the corresponding mesylate **3f**, which underwent a smooth displacement reaction with attendant thiolacetate cleavage and cyclization upon treatment with sodium trithiocarbonate in aqueous methanol[12] to provide the bicyclic compound **4a** in 72% yield. Saponification of diester **4a** then gave the novel *endo*-trithiocarbonate analogue (**4b**) of PGH_2.[13]

The dimercapto derivative (**5a**) of PGF_2, which we had expected (as the triester) from the reaction of mesylate **3f** with sodium trithiocarbonate, could be obtained from trithiocarbonate **4b** using sodium in ethanol.[14] Esterification with diazomethane then produced **5b**.[3] Ester **5b** could also be secured by subjecting mesylate **3f** to treatment with potassium thiolacetate in DMF–Me_2SO,[3,5] followed by potassium carbonate in methanol.

The oxidative cyclization of the dimercaptan **5a,b** proved to be quite difficult. After numerous unsuccessful attempts to carry out this transformation, we found that the surprisingly simple method[15] of passing oxygen through a dilute methanolic solution of **5b** and 2.2 equiv of sodium methoxide effectively produced the thio analogue of PGH_2, endo-disulfide **6**.

Experimental Section

Isolation of the reaction products was accomplished by pouring the mixture into water, thoroughly extracting with the specified solvent, washing the combined extracts with a 10% aqueous HCl solution and/or a saturated aqueous sodium bicarbonate solution (if required), with water, and then with a saturated aqueous sodium chloride solution, drying the extracts over anhydrous sodium sulfate, filtering, and then concentrating under reduced pressure on a Buchi Rotovapor.

IR spectra were obtained using neat liquids between salt plates on a Beckman Acculab 4 spectrophotometer. A Beckman DBT recording spectrophotometer was used for the UV absorption spectra. NMR spectra were determined with a Jeol PMX-60 spectrometer using tetramethylsilane as the internal reference. Mass spectra were recorded on a MS-30AEI mass spectrometer generally at 70 eV using a direct insertion probe. Optical rotations were determined in $CHCl_3$ (C = 1) on a Perkin-Elmer 141 polarimeter. The circular dichroism (CD) curves were recorded on a Jouan 3 dichrograph instrument. Microanalyses were performed by the Central Service of the CNRS, Lyon. Thin layer chromatography was carried out using Merck $60F_{254}$ (0.25 mm) sheets. For column chromatography, Merck 230–400 mesh silica gel 60 and Mallinckrodt silicic acid silicar CC-4 and CC-7 were used.

(15*S*)-PGA_2 (2a) from *P. Homomalla* (Var. S).[15] *P. homomalla*, *homomalla* (Var. S) (1 kg), collected off Cuba and frozen within minutes of collection, was ground into a slurry. The slurry was stirred at room temperature for 24 h with 6–8 L of 0.1 M aqueous citric acid, and then 10 L of ethanol was added, the mixture was centrifuged and filtered, and the ethanol was evaporated in vacuo. A 1 M solution of citric acid was added to adjust the pH to 6.5–7 and the resulting solution was extracted with carbon tetrachloride. The aqueous solution was then acidified to pH 5–5.5 and the product was isolated with chloroform yielding 150–200 g of dark oil. This material was further purified by filtration column chromatography on silicic acid silicar

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CC-4 100–200 mesh eluting with a gradient of ethyl acetate in hexane, to afford a pale yellow oil containing 85–95% of PGA_2 (**2a**), having spectral (IR, NMR, UV) and biological characteristics identical with those reported in the literature.[16b,17] The purity of the PGA_2 was determined by TLC (system A IX).[9b]

(+)-Prostaglandin A_2 15-Acetate Methyl Ester (2b). A solution of 5 g (15.0 mmol) of PGA_2 (**2a**) in ether was treated with an ethereal solution of diazomethane to afford after filtration column chromatography on silicic acid silicar CC-7, 5 g of PGA_2 methyl ester as a pale yellow oil: $[\alpha]_D$ +148°; IR λ_{max} (film) 3450, 1730, 1705, 1580, 970 cm^{-1}; UV λ_{max} (MeOH) 217 nm (10 200); NMR δ_{Me_4Si} (CCl_4) 7.33 (dd, J = 2, 5 Hz, 1 H), 6.03 (dd, J = 2, 5 Hz, 1 H), 5.40 (m, 4 H), 3.95 (m, 1 H), 3.60 (s, 3 H), 3.12 (m, 1 H), 0.93 (t, J = 5 Hz, 3 H).

The above prostaglandin A_2 methyl ester (5 g, 14.4 mmol) was dissolved in 12.5 mL of pyridine and treated with 7.5 mL of acetic anhydride. After 2 h at room temperature, ice chips were added followed by 125 mL of cold water. After the reaction mixture was stirred for an additional 15 min, the product was isolated with ethyl acetate and then purified by filtration column chromatography on silicic acid silicar CC-7. Elution with 10% ethyl acetate in hexane gave fractions homogeneous by TLC (hexane–ethyl acetate, 7:3), affording 5.25 of prostaglandin A_2 acetate methyl ester (**2b**):[16b] 90%; $[\alpha]_D$ +102°; IR λ_{max} (film) 1735, 1705, 1590, 1240, 970 cm^{-1}; UV λ_{max} (MeOH) 217 nm (9980); NMR δ_{Me_4Si} (CCl_4) 7.33 (dd, J = 2, 6 Hz, 1 H), 6.03 (dd, J = 2, 6 Hz, 1 H), 5.3 (m, 5 H), 3.58 (s, 3 H), 3.15 (m, 1 H), 1.97 (s, 3 H), 0.89 (t, J = 5 Hz, 3 H).

(−)-11α-Thiolacetoxy-11-deoxyprostaglandin E_2 15-Acetate Methyl Ester (3a). To a stirred solution of 5 g (12.8 mmol) of **2b** in 25 mL of methanol at −78 °C under nitrogen was added 1.4 g of potassium thiolacetate dissolved in 50 mL of methanol and 9.2 mL of thiolacetic acid, and the resulting suspension was stirred for 30 min. The reaction mixture was then treated with aqueous sodium bicarbonate to neutral pH and diluted with 100 mL of water. The methanol was evaporated under reduced pressure and the product was isolated with methylene chloride and purified by filtration column chromatography on silicic acid silicar CC-7. Elution with 10% ethyl acetate–hexane gave fractions homogeneous by TLC (hexane–ethyl acetate, 7:3) affording 4.9 g (82%) of **3a** as a colorless oil:[6c] $[\alpha]_D$ −50°; IR λ_{max} (film) 1735, 1690, 1240, 970, 630 cm^{-1}; UV λ_{max} (MeOH) 232 nm (5030); NMR δ_{Me_4Si} (CCl_4) 5.33 (m, 5 H), 3.59 (s, 3 H), 3.10–2.60 (m, 1 H), 2.27 (s, 3 H), 1.97 (s, 3 H), 0.90 (t, J = 5 Hz, 3 H).

Anal. Calcd for $C_{25}H_{38}O_6S$: C, 64.35; H, 8.21. Found: C, 63.94; H, 8.25.

(−)-11α-Thiolacetoxy-11-deoxypostaglandin $F_{2\alpha+\beta}$ 15-Acetate Methyl Ester (3b,c). A solution of 4.6 g (9.9 mmol) of **3a** in 40 mL of dry dimethoxyethane (DME) was stirred at room temperature under nitrogen. A solution of 30 mL (1.5 equiv) of zinc borohydride (0.5 M, freshly prepared)[18] in DME was added dropwise over 5 min and stirring was continued for 30 min after which a saturated sodium hydrogen tartrate solution was added dropwise until no further evolution of gas was observed. Methylene chloride was then added and the resulting suspension was filtered through a coarse porosity sintered glass funnel. Isolation of the product with methylene chloride afforded 4.3 g of a mixture of alcohols. Analysis of the mixture by TLC (hexane–ethyl acetate, 1:1) showed only the two C-9 epimers, R_f 5.1 (9α) and R_f 4.5 (9β). The mixture was separated by column chromatography on silicic acid silicar CC-7. Elution with hexane–ethyl acetate, 9:1, gave 840 mg (18%) of the 9α-isomer **3c** as a colorless oil: $[\alpha]_D$ −31°; IR λ_{max} (film) 3500, 1740, 1690, 1240, 970, 640 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 5.33 (m, 5 H), 4.10 (m, 1 H), 3.62 (s, 3 H), 2.60 (m, 1 H), 2.27 (s, 3 H), 2.00 (s, 3 H), 0.85 (t, J = 5 Hz, 3 H).

Anal. Calcd for $C_{25}H_{40}O_6S$: C, 64.07; H, 8.60; S, 6.84. Found: C, 63.92; H, 8.62; S, 6.76.

Further elution with hexane–ethyl acetate, 85:15, gave 3.2 g (70%) of the 9β-isomer **3b** as a colorless oil: $[\alpha]_D$ −45°; IR λ_{max} (film) 3500, 1740, 1690, 1250, 970, 640 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 5.30 (m, 5 H), 3.90 (m, 1 H), 3.62 (s, 3 H), 2.67 (m, 1 H), 2.28 (s, 3 H), 2.00 (s, 3 H), 0.88 (t, J = 5 Hz, 3 H).

Anal. Calcd for $C_{25}H_{40}O_6S$: C, 64.07; H, 8.60; S, 6.84. Found: C, 64.08; H, 8.37; S, 6.70.

(+)-11α-Mercapto-11-deoxyprostaglandin $F_{2\alpha+\beta}$ Methyl Ester (3d,e). Methanolysis of the thiolacetate and acetate groups in **3b,c** (230 mg, 0.5 mmol) was effected using 20 mL of anhydrous methanol and 5 equiv of potassium carbonate at 20 °C for 30 min, followed by acidification with 1 N HCl (to pH 4–5) and isolation of the product with ether. Mercaptans **3d** (175 mg, 93%) and **3e** (168 mg, 89%) could be purified by column chromatography on silicic acid silicar CC-4 using hexane–ethyl acetate as the eluent.

(+)-11α-Mercapto-11-deoxyprostaglandin $F_{2\beta}$ Methyl Ester (3d): $[\alpha]_D$ +2.08°; IR λ_{max} (film) 3400, 2560, 1730, 1240, 970 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 5.42 (m, 4 H), 4.00 (m, 2 H), 3.63 (s, 3 H), 3.0 (m, 1 H), 0.87 (t, J = 5 Hz, 3 H).

Anal. Calcd for $C_{21}H_{36}O_4S$: C, 65.59; H, 9.44; S, 8.34. Found: C, 65.49; H, 9.43; S, 8.06.

(+)-11α-Mercapto-11-deoxyprostaglandin $F_{2\alpha}$ Methyl Ester (3e): $[\alpha]_D$ +11.19°; IR λ_{max} (film) 3450, 2560, 1730, 1240, 970 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 5.33 (m, 4 H), 4.06 (m, 2 H), 3.59 (s, 3 H), 2.70 (m, 1 H), 0.87 (t, J = 5 Hz, 3 H).

Anal. Calcd for $C_{21}H_{36}O_4S$: C, 65.59; H, 9.44; S, 8.34. Found: C, 65.89; H, 9.45; S, 8.14.

(−)-11α-Thiolacetoxy-11-deoxyprostaglandin $F_{2\beta}$ 9-Mesylate 15-Acetate Methyl Ester (3f). A stirred solution of 1.0 g (2.1 mmol) of alcohol **3b** in 10 mL of dry pyridine was cooled to 0 °C and 0.50 mL (6.3 mmol) of methanesulfonyl chloride was added dropwise. After 1 h at 0 °C the mixture was poured onto crushed ice and the product was isolated with ether to give 1.0 g of colorless oil (86%): $[\alpha]_D$ −41.3°; IR λ_{max} (film) 1740, 1695, 1250, 1180, 970, 630 cm^{-1}; UV λ_{max} (MeOH) 233 nm (5000); NMR δ_{Me_4Si} (CCl_4) 5.43 (m, 4 H), 5.15 (m, 1 H), 4.80 (m, 1 H), 3.63 (s, 3 H), 2.96 (s, 3 H), 2.26 (s, 3 H), 2.00 (s, 3 H), 0.93 (t, J = 5 Hz, 3 H).

Anal. Calcd for $C_{26}H_{42}O_8S_2$: C, 57.12; H, 7.74. Found: C, 57.41; H, 7.84.

(−)-9α,11α-Trithiocarbonate of 9,11-Dideoxyprostaglandin F_2 15-Acetate Methyl Ester (4a). Mesylate **3f** (900 mg, 1.65 mmol) in 10 mL of methanol was added dropwise to a stirred solution of aqueous sodium trithiocarbonate (33%, 8 mL)[12] under nitrogen. After stirring at 60 °C for 1 h, the mixture was carefully acidified with 0.5 M sulfuric acid to pH 4–5 and the product was isolated with ether and purified by filtration on silicic acid to afford 652 mg (82%) of **4a** as a viscous yellow oil: $[\alpha]_D$ −72°; CD (c 1; CH_3OH); $[\theta]_{455}$ −490; $[\theta]_{400}$ 0; $[\theta]_{350}$ +420; $[\theta]_{338}$ 0; $[\theta]_{319}$ −630; $[\theta]_{310}$ 0; $[\theta]_{294}$ +4110; $[\theta]_{275}$ +1230 (shoulder); $[\theta]_{262}$ 0; $[\theta]_{238}$ −9800; $[\theta]_{226}$ 0; IR λ_{max} (film) 1735, 1245, 1030, 980 cm^{-1}; UV λ_{max} (MeOH) 339 (12 300) 298 nm (7780); NMR δ_{Me_4Si} ($CDCl_3$) 5.35 (m, 5 H), 3.68 (s, 3 H), 3.6–2.9 (m, 2 H), 2.06 (s, 3 H), 0.90 (t, J = 5 Hz, 3 H); mass spectrum m/e 484 M^+ (39.88), $M^+ - OCH_3$ (13.19), $M^+ - S$ (21.88), $M^+ - HS$ (89.58), $M^+ - HOAc$ (43.25); molecular ion at m/e 484.1776, calcd, 484.1776.

(−)-9α,11α-Trithiocarbonate of 9,11-Dideoxyprostaglandin F_2 (4b). A 300-mg (0.62 mmol) sample of **4a** was saponified using 5 equiv of 1 M sodium hydroxide in methanol under nitrogen at 20 °C for 1 h. Acidification with 0.5 M sulfuric acid to pH 4–5 was followed by isolation of the crude product with ether. Purification by filtration on silicic acid then afforded 215 mg (81%) of **4b** as a viscous yellow oil: $[\alpha]_D$ −45°; IR λ_{max} (film) 3300, 1720, 1040, 980 cm^{-1}; UV λ_{max} (MeOH) 340 (12 500), 299 nm (8040); NMR δ_{Me_4Si} ($CDCl_3$) 5.33 (m, 6 H), 4.15 (m, 1 H), 3.6–2.9 (m, 2 H), 0.86 (t, J = 5 Hz, 3 H).

(−)-9α,11α-Dimercapto-9,11-dideoxyprostaglandin F_2 (5a) and Methyl Ester (5b): From Trithiocarbonate 4b. To a stirred solution of 250 mg (0.58 mmol) of **4b** in 10 mL of methanol at 0 °C under nitrogen was added sodium metal (667 mg, 29 g-atom) and stirring was continued for 30 min. After dilution with 50 mL of water, the solution was carefully acidified with 0.5 M sulfuric acid to pH 4–5 and the product was isolated with ethyl acetate to give 150 mg of crude **5a,** which was rapidly[5,15] purified by column chromatography on silicic acid silicar CC-4. Elution with 40% ethyl acetate in hexane gave fractions homogeneous by TLC (system A IX),[9b] affording 98 mg (43%) of **5a** as a pale yellow oil: $[\alpha]_D$ −22°; IR λ_{max} (film) 3400, 2570, 1700, 970 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 6.69 (s, 2 H), 5.40 (m, 4 H), 4.15 (m, 1 H), 3.50 (m, 1 H), 2.80 (m, 1 H), 0.85 (t, J = 5 Hz, 3 H).

A 125-mg (0.32 mmol) sample comparable to that above was dissolved in ether and esterified with ethereal diazomethane. Rapid[5,15] purification of the ester by filtration column chromatography on silicic acid silicar CC-7 using increasing concentrations of ethyl acetate in hexane afforded 118 mg (91%) of **5b** as a pale yellow oil.[3] $[\alpha]_D$ −7.2°; IR λ_{max} (film) 3400, 2560, 1730, 970 cm^{-1}; NMR δ_{MeSi_4} ($CDCl_3$) 5.39 (m, 4 H), 4.07 (m, 1 H), 3.61 (s, 3 H), 3.5 (m, 1 H), 2.80 (m, 1 H), 0.86 (t, J = 5 Hz, 3 H); mass spectrum m/e 400 M^+ (2.24), $M^+ - H_2O$ (9), $M^+ - SH$ (4), $M^+ - SH_2$ (10.52), $M^+ - (H_2O + SH)$ (14.52), $M^+ - (H_2O + SH_2)$ (16.68).

From Mesylate 3f. Mesylate **3f** (500 mg, 0.91 mmol) was treated with sodium thiolacetate (450 mg, 4.6 mmol) in Me_2SO–DMF (1:1) at 50 °C for 14 h.[3,5] The product was isolated with methylene chloride and purified by filtration column chromatography on silicic acid silicar CC-7 using hexane–ethyl acetate, 9:1, to afford 310 mg (64%) of 9α,11α-dithiolacetoxy-9,11-dideoxyprostaglandin F_2 15-acetate methyl ester as a colorless oil: IR λ_{max} (film) 1740, 1690, 1250, 970, 640 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 5.30 (m, 5 H), 4.03 (m, 1 H), 3.65 (s, 3 H), 2.33 (s, 3 H), 2.28 (s, 3 H), 2.03 (s, 3 H), 0.87 (t, J = 5 Hz, 3 H).

Methanolysis of the acetates (300 mg) was done as before (MeOH, K_2CO_3). The product **5b** (190 mg, 83%) was identical by NMR, IR,

and MS with that obtained by the method described above. Because of the observed instability[5,15] of mercaptans **5a,b**, the crude products were generally used without any chromatographic purification.

Disulfide Analogue of Prostaglandin H_2 Methyl Ester (6). To a stirred solution of 130 mg (0.32 mmol) of **5b** in 10 mL of methanol at room temperature was added 38 mg (0.70 mmol) of sodium methoxide, and then O_2 was bubbled through the resulting suspension.[15] After 1 h, the reaction mixture was diluted with 50 mL of H_2O and neutralized with 0.1 N HCl. The methanol was evaporated under reduced pressure, and the product was isolated with methylene chloride to afford 112 mg (87%) of nearly pure **6**, which was further purified by filtration column chromatography on silicic acid silicar CC-7. Elution with ethyl acetate–hexane, 1:3, gave fractions homogeneous by TLC (system A IX)[9b] affording 51 mg of **6** as a pale yellow oil:[3] $[\alpha]_D$ +8.81°; CD (*c* 1; CH_3OH); $[\theta]_{375}$ +1180; $[\theta]_{330}$ 0; $[\theta]_{256}$ +6500; $[\theta]_{242}$ 0; $[\theta]_{234}$ −5580; $[\theta]_{230}$ 0; IR λ_{max} (film) 3450, 1735, 970 cm^{-1}; Raman (neat) 520 cm^{-1}; NMR δ_{Me_4Si} ($CDCl_3$) 5.40 (m, 4 H), 4.00 (m, 1 H), 3.60 (s, 3 H), 0.87 (t, J = 5 Hz, 3 H); mass spectrum *m/e* (electron impact) 398 M^+ (95.34), $M^+ - H_2O$ (6.47), $M^+ - OCH_3$ (13.91), $M^+ - S$ (9.42), $M^+ - SH$ (5.54), $M^+ - (H_2O + OCH_3)$ (7.62), $M^+ - (H_2O + S)$ (13.66), $M^+ - (H_2O + SH)$ (13.60), $M^+ - C_5H_{11}$ (7.02), $M^+ - (OCH_3 + H_2O + SH_2)$ (47.68); mass spectrum (chemical ionization) 455 ($M^+ + C_4H_9$), 437 ($M^+ + C_4H_9 - H_2O$), 399 ($M^+ + 1$), 381 ($M^+ + 1 - H_2O$) base peak, 349 ($M^+ + 1 - H_2O - S$ or CH_3OH). Although the NMR spectrum shows some discrepancies with that of the reported compound[3] (identical IR), the clean chemical ionization mass spectrum (through *m/e* 800) would appear to preclude any alternative dimeric or polymeric structure:[5,15] *m/e* 398.1940, calcd, 398.1949.

Acknowledgment. We wish to thank Dr. Hayashi for kindly exchanging information. A fellowship to A.P. from the C.I.E.S. (Paris) is gratefully acknowledged.

Registry No.—**2a,** 13345-50-1; **2a** methyl ester, 31753-19-2; **2b,** 36323-03-2; **3a,** 67452-66-8; **3b,** 67452-67-9; **3c,** 67452-68-0; **3d,** 67452-42-0; **3e,** 67452-43-1; **3f,** 67452-44-2; **4a,** 67452-45-3; **4b,** 67452-46-4; **5a,** 67452-47-5; **5b,** 61955-20-2; **6,** 61955-22-4; methanesulfonyl chloride, 124-63-0; sodium trithiocarbonate, 534-18-9; 9α,11α-dithiolacetoxy-9,11-dideoxypostaglandin F_2 15-acetate methyl ester, 67452-48-6.

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Addition of Cyclic Secondary Amines to Benzo[*b*]thiophene and 3-Methylbenzo[*b*]thiophene

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Received May 4, 1978

Metal-catalyzed addition of primary and secondary amines to conjugated hydrocarbons is well documented,[1] and a general method of ethylating amines with ethylene using an alkali metal salt of the amine as catalyst has been described.[2] More recently, Eisenbraun and co-workers have shown that, in addition to reduction products, naphthalene and methylnaphthalenes undergo reductive amination in the presence of sodium and secondary amines.[3] We wish to report the addition of cyclic secondary amines to the C_2–C_3 bond of benzo[*b*]thiophene (**1**) and 3-methylbenzo[*b*]thiophene (**2**) in the presence of an alkali metal salt of the amine. A definite assignment for the position of attachment of nitrogen on C_2 for the adducts can be made using NMR data. 2-Alkylaminobenzo[*b*]thiophenes are readily obtained by aromatization of the adducts.

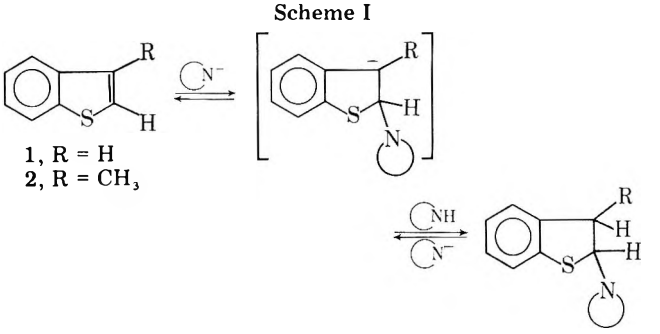
On stirring (18 h, 40 °C) benzo[*b*]thiophene **1** or **2** in a cyclic secondary amine in the presence of dispersed sodium, an adduct is obtained in high yield (see Table I). Similar addition is performed using an alkali metal salt of the amine instead of dispersed sodium. In this case, the anion of the amine is formed by reaction of the amine with *n*-butyllithium or sodium hydride.

We suggest nucleophilic addition of the anion of the amine as the first step of the reaction. The amine is needed for the protonation of the intermediate carbanion, as supported by the failure of addition of sodamide in toluene or the lithio salt of piperidine in hexane on **1** (Scheme I).

When similar reactions are performed on 2-methylbenzo[*b*]thiophene, 2,3-dimethylbenzo[*b*]thiophene, benzo[*b*]furan, or benzo[*b*]selenophene, no addition has been detected. Heterocycles are recovered unreacted except benzo[*b*]selenophene, which is reduced to ethylbenzene.

When a low molecular weight primary amine, e.g., propylamine,[4] is substituted for a cyclic secondary amine in reac-

Scheme I



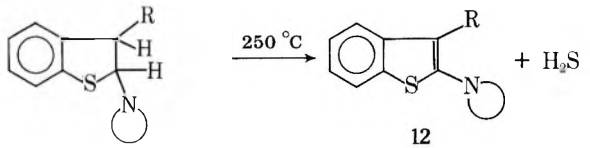
0022-3263/78/1943-4379$01.00/0

Table I. Addition of Amines to Benzo[*b*]thiophenes

Amine	Registry no.	Benzo[*b*]thiophene recovered, %	Adduct	Registry no.	Yield,[a] %
		Benzo[*b*]thiophene (1)			
Pyrrolidine[b]	123-75-1	10	**3**	66966-29-8	50
Piperidine[b]	110-89-4	12	**4**	41216-62-0	51
Piperidine[c]		21	**4**		46
Morpholine[b]	110-91-8	15	**5**	66902-30-5	45
Morpholine[d]		29	**5**		41
Diethylamine[b]	109-89-7	75	**6**[e]	66902-29-2	5
		3-Methylbenzo[*b*]thiophene (2)			
Pyrrolidine[b]		5	**7**		52
Piperidine[b]		4	**8**		55
Morpholine[b]		12	**9**		42
Propylamine[b,f]	107-10-8	5	**10**[e]	66902-24-7	2
Cyclohexylamine[b,f]	108-91-8	72	**11**[e]	66902-23-6	4

[a] Yield is based on consumed benzo[*b*]thiophene. [b] Reaction in the presence of dispersed sodium. [c] Anion formed by reaction of amine with *n*-butyllithium. [d] Anion formed by reaction of amine with sodium hydride. [e] Characterized only through mass spectra. [f] At room temperature.

Scheme II



5 9 12 13

tion with dispersed sodium, **1** is reduced to ethylbenzene (60%), 2-ethylthiophenol (20%),[5] and *o*-ethylphenyl disulfide (10%), and **2** gives cumene (90%). With cyclohexylamine or an acyclic secondary amine, small amounts of reduction products are formed but yields of adduct are very low.[6]

No reaction with other nucleophilic anions, e.g., an alkali metal salt of thiophenol or alcohols, can be detected.

The NMR data for adducts **7**, **8**, and **9** on 3-methylbenzo[*b*]thiophene allow the definite assignment for the position of attachment of the amino group on C_2 and suggest that these adducts are a mixture of trans (major product 95%) and cis isomers.[7]

In each case, on VPC analysis of the crude amino derivatives a small amount of 2-alkylaminobenzo[*b*]thiophene (**12**, **13**)[9] can be detected. These products are readily obtained by aromatization of the adducts with stoichiometric amounts of sulfur[10] (Scheme II).

Experimental Section

Benzo[*b*]thiophene was purchased and recrystallized. 3-Methylbenzo[*b*]thiophene was synthesized according to Werner[11] and distilled. All amines were distilled twice from KOH under dry nitrogen.

All melting points are uncorrected. IR spectra were determined using a PE 157G instrument, NMR spectra were recorded on a 60 CHL Jeol spectrometer in $CDCl_3$ using Me_4Si as an internal standard, and mass spectra were determined using a MS 12 spectrometer (University of Bordeaux, France) or a RIBERMAG 10.10. VPC analyses were performed on a F & M 810 GC 6 ft × 0.25 in column packed with 10% SE-30 on Chromosorb W.

Reactions with Dispersed Sodium. General Procedure. To 3.5 g (0.15 g-atom) of dispersed sodium in 60 mL of amine was added a 0.03 M solution of the benzo[*b*]thiophene (**1**, 4 g; **2**, 4.5 g) in 10 mL of amine. The mixture turned red-brown within half an hour and was stirred at 40 °C under dry nitrogen for 18 h. Unreacted sodium generally agglomerated and was removed. The reaction mixture was poured into ice water, acidified with aqueous HCl, and extracted with ether to discard unreacted benzo[*b*]thiophene. The aqueous layer was made basic with KOH and extracted with ether. The adduct-carrying ether layer was dried (Na_2SO_4) and concentrated. The crude adduct was purified by chromatography on alumina and was recrystallized from heptane–toluene when a solid.

2-Pyrrolidino-2,3-dihydrobenzo[*b*]thiophene (3). Reaction of **1** with pyrrolidine: 3.1 g (50%); IR (CCl_4) 3060, 2950, 2870, 2810, 1585, 1460, 1445, 1360, 1120, 1060, 740 cm^{-1}; NMR ($CDCl_3$) δ 1.6 (m, 4 H), 2.4 (m, 4 H), 3.2 (q, 1 H, $J_{3,3'}$ = 16.5 Hz, $J_{2,3'}$ = 8 Hz, C_3-H), 3.4 (q, 1 H, $J_{3,3'}$ = 16.5 Hz, $J_{2,3}$ = 2.5 Hz, C_3-H), 5.3 (dd, 1 H, C_2-H), 6.9 (m, 4 H, aromatic H); mass spectrum, *m/e* (relative intensity) 205 (M^+, 24), 172 (9), 170 (5), 136 (30), 135 (67), 134 (100), 133 (8), 121 (38), 91 (76), 90 (20), 89 (31), 78 (20), 77 (33), 70 (57), 69 (33).

Anal. Calcd for $C_{12}H_{15}NS$: C, 70.20; H, 7.36; N, 6.82; S, 15.61. Found: C, 70.37; H, 7.42; N, 6.80; S, 15.97.

2-Piperidino-2,3-dihydrobenzo[*b*]thiophene (4). Reaction of **1** with piperidine: 3.35 g (51%); IR (CCl_4) 3060, 2940, 2860, 2805, 1580, 1460, 1445, 1230, 1205, 1120, 1060, 990, 860, 740 cm^{-1}; NMR ($CDCl_3$) δ 1.4 (m, 6 H), 2.35 (m, 4 H), 3.2 (q, 1 H, $J_{3,3'}$ = 16.5 Hz, $J_{2,3'}$ = 7.5 Hz, C_3-H), 3.6 (q, 1 H, $J_{3,3'}$ = 16.5 Hz, $J_{2,3}$ = 3 Hz, C_3-H), 5.1 (dd, 1 H, C_2-H), 7 (m, 4 H, aromatic H); mass spectrum, *m/e* (relative intensity) 219 (M^+, 48), 186 (8), 137 (8), 136 (31), 135 (48), 134 (30), 96 (38), 91 (23), 85 (15), 84 (100).

Anal. Calcd for $C_{13}H_{17}NS$: C, 71.20; H, 7.82; N, 6.39. Found: C, 70.93; H, 7.82; N, 6.18.

2-Morpholino-2,3-dihydrobenzo[*b*]thiophene (5). Reaction of **1** with morpholine: 3 g (45%); mp 75–76 °C; IR (CCl_4) 3060, 2960, 2850, 1580, 1460, 1445, 1120, 1060, 1020, 995, 920 cm^{-1}; NMR ($CDCl_3$) δ 2.45 (m, 4 H), 3.3 (q, 1 H, $J_{3,3'}$ = 16.5 Hz, $J_{2,3'}$ = 8 Hz, C_3-H), 3.6 (q, 1 H, $J_{3,3'}$ = 16.5 Hz, $J_{2,3}$ = 2.5 Hz, C_3-H), 3.65 (m, 4 H), 7.1 (m, 4 H, aromatic H); mass spectrum, *m/e* (relative intensity) 221 (M^+, 67), 188 (4), 136 (32), 135 (100), 134 (75), 121 (8), 98 (32), 91 (37), 86 (30), 77 (12).

Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33; O, 7.23; S, 14.49. Found: C, 64.90; H, 6.91; N, 6.45; O, 7.53; S, 14.31.

2-Pyrrolidino-3-methyl-2,3-dihydrobenzo[*b*]thiophene (7). Reaction of **2** with pyrrolidine: 3.4 g (52%); IR (CCl_4) 3060, 2950, 2860, 2805, 1585, 1460, 1440, 1355, 1250, 1070, 1020, 870, 790, 740 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (d, 3 H, J = 7 Hz, CH_3), 1.7 (m, 4 H), 2.55 (m, 4 H), 3.4 (dq, 1 H, $J_{2,3}$ = 3 Hz, C_3-H), 5.0 (d, 1 H, C_2-H), 7.0 (m, 4 H, aromatic H); mass spectrum, *m/e* (relative intensity) 219 (M^+, 49), 186 (8), 149 (49), 148 (100), 147 (35), 135 (21), 134 (28), 115 (11), 96 (21), 91 (13), 84 (21), 70 (75).

Anal. Calcd for $C_{13}H_{17}NS$: C, 70.93; H, 7.68; N, 6.51; S, 14.87. Found: C, 71.19; H, 7.80; N, 6.38; S, 14.62.

2-Piperidino-3-methyl-2,3-dihydrobenzo[*b*]thiophene (8). Reaction of **2** with piperidine: 3.85 g (55%); IR (CCl_4) 3060, 2930, 2850, 2800, 1580, 1460, 1445, 1230, 1205, 1115, 1105, 1060, 990, 860, 740 cm^{-1}; NMR ($CDCl_3$) δ 1.3 (d, 3 H, J = 7.5 Hz, CH_3), 1.4 (m, 6 H), 2.35 (m, 4 H), 3.4 (dq, 1 H, $J_{2,3}$ = 3 Hz, C_3-H), 4.6 (d, 1 H, C_2-H), 7 (m, 4 H, aromatic H); mass spectrum, *m/e* (relative intensity) 233 (M^+, 45), 150 (22), 149 (66), 148 (100), 147 (22), 135 (22), 134 (22), 110 (20), 96 (20), 85 (25), 84 (78).

Anal. Calcd for $C_{14}H_{19}NS$: C, 72.05; H, 8.21; N, 6.00; S, 13.74. Found: C, 71.85; H, 8.06; N, 6.21; S, 13.57.

2-Morpholino-3-methyl-2,3-dihydrobenzo[*b*]thiophene (9).

Reaction of **2** with morpholine: 2.85 g (42%); mp 64–65 °C; IR (CCl_4) 3060, 2960, 2850, 1580, 1460, 1440, 1250, 1130, 1115, 1010, 905, 860, 690 cm^{-1}; NMR ($CDCl_3$) δ 1.3 (d, 3 H, J = 7 Hz, CH_3), 2.45 (m, 4 H), 3.4 (dq, 1 H, $J_{2,3}$ = 2.5 Hz, C_3-H), 3.6 (m, 4 H), 4.65 (d, 1 H, C_2-H), 7.1 (m, 4 H, aromatic H); mass spectrum, *m/e* (relative intensity) 235 (M^+, 36), 202 (4), 149 (100), 148 (92), 147 (60), 135 (28), 134 (64), 114 (16), 115 (24), 105 (16), 103 (16), 100 (34), 91 (25), 77 (28).

Anal. Calcd for $C_{13}H_{17}NOS$: C, 66.34; H, 7.28; N, 5.95; O, 6.80; S, 13.62. Found: C, 66.35; H, 7.16; N, 6.16; O, 6.99; S, 13.74.

Reaction of Piperidine and Benzo[*b*]thiophene by Means of *n*-Butyllithium. *n*-Butyllithium (0.15 M, 20% solution in hexane) was added to 60 mL of piperidine under nitrogen. The temperature of the mixture was maintained at 40 °C, and a solution of 4 g (0.03 M) of benzo[*b*]thiophene in 10 mL of amine was added. Reaction and isolation were performed as previously described. 2-Piperidino-2,3-dihydrobenzo[*b*]thiophene (**4**) was purified by chromatography, 3 g (46%).

Reaction of Morpholine and Benzo[*b*]thiophene by Means of Sodium Hydride. A mixture of 60 mL of morpholine and 3.6 g (0.15 M) of NaH was refluxed under nitrogen until the evolution of hydrogen ceased and was cooled to 40 °C. The addition of benzo[*b*]-thiophene and the reaction procedure were as previously described. 2-Morpholino-2,3-dihydrobenzo[*b*]thiophene (**5**) was recrystallized from heptane–toluene, 2.7 g (41%).

2-Morpholinobenzo[*b*]thiophene (12). A 1.1-g (0.005 mol) amount of **5** and 0.16 g (0.005 mol) of sulfur were heated at 250 °C until the evolution of H_2S ceased (5 min). The reaction mixture was taken into benzene and decolorized with Norit. Evaporation of benzene and recrystallization from toluene–heptane gave a colorless solid: 0.65 g (60%); mp 179–180 °C; IR (CCl_4) 3060, 2960, 2900, 2855, 2815, 1530, 1440, 1120, 1030, 930, 900, 870, 650 cm^{-1}; NMR (CCl_4) δ 3.2 (m, 4 H), 3.9 (m, 4 H), 6.2 (s, 1 H, C_3-H), 7.3 (m, 4 H, aromatic H); mass spectrum, *m/e* (relative intensity) 219 (M^+, 100), 204 (6), 162 (23), 161 (93), 160 (38), 147 (14), 135 (8), 134 (26), 133 (9), 89 (20), 80 (12).

Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39; O, 7.30; S, 14.62. Found: C, 65.71; H, 5.95; N, 6.35; O, 7.55; S, 14.58.

2-Morpholino-3-methylbenzo[*b*]thiophene (13). From aromatization of 100 mg of **9** with 15 mg of sulfur: 65 mg (65%); mp 79–80 °C; IR (CCl_4) 3060, 2960, 2900, 2855, 2820, 1575, 1435, 1190, 1120, 1045, 1015, 980, 880 cm^{-1}; NMR (CCl_4) δ 2.3 (s, 3 H, CH_3), 3.0 (m, 4 H), 3.9 (m, 4 H), 7.4 (m, 4 H, aromatic H); mass spectrum, *m/e* (relative intensity) 234 (18), 233 (M^+, 100), 232 (27), 218 (5), 188 (5), 176 (11), 175 (50), 174 (58), 173 (16), 161 (12), 160 (30), 159 (10), 147 (30), 134 (11).

Anal. Calcd for $C_{13}H_{15}NOS$: mol wt 233.0874. Found (high-resolution mass spectrum): mol wt 233.0876.

Registry No.—**1**, 95-15-8; **2**, 1455-18-1; *cis*-**7**, 66902-28-1; *trans*-**7**, 66902-27-0; *cis*-**8**, 66902-26-9; *trans*-**8**, 66902-22-5; *cis*-**9**, 66902-21-4; *trans*-**9**, 66902-20-3; **12**, 18774-55-5; **13**, 66902-25-8.

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(6) When the reaction is performed with *n*-butyllithium and a primary amine, no reduction products are formed but the yield of adduct remains disappointingly low.
(7) Cis and trans isomers of adducts **7**, **8**, and **9** cannot be separated, even at an analytical scale. The assumption that the major product is the trans isomer is based on literature data assuming that the chemical shift of H_2 should be higher in the cis isomer than in the trans isomer and that $J_{2,3}$ is higher when H_2 and H_3 are cis than when they are trans.[8]
(8) (a) L. M. Jackman and S. Sternhell, "Application of NMR Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, Oxford, 1969, p 233; (b) J. J. Christol, T. W. Russel, J. R. Mohrig, and D. C. Plorde, *J. Org. Chem.*, **31**, 581 (1966).
(9) The yield is less than 1% based on consumed benzo[*b*]thiophene.
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Facile Synthesis of 2-Substituted Imidazoles

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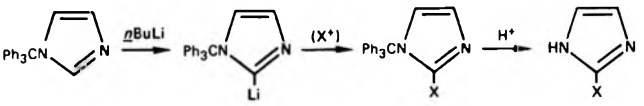
Received June 13, 1978

Continuing studies in the biochemistry and pharmacology of ring-fluorinated imidazoles have revealed striking differences in behavior between 2- and 4-fluoro isomers in each series.[1] For example, 2-fluorohistidine displays a wide range of biological activities[2] while 4-fluorohistidine shows little or no activity in the same systems. As part of our efforts to elucidate the causes of these differences, we wished to extend our testing to isomer pairs of the other haloimidazoles—particularly the halohistidines. The 4 (or 5)-halo derivatives can be obtained by direct electrophilic substitution,[3] but no methods are available for preparation of the 2-halo isomers. While 2-fluoro-[4] and 2-chloroimidazoles[5] have been prepared by photochemical decomposition of 2-diazoniumimidazoles, the method fails for bromine or iodine, and there exists no obvious procedure for the introduction of the latter halogens.[6] We have now developed a general synthesis, not only for 2-haloimidazoles, but for a variety of other 2-substituted imidazoles.

In 1-alkyl or 1-arylimidazoles (methyl, benzyl, phenyl), H-2 is the most acidic hydrogen and a carbanion is readily generated at C-2 by reaction with *n*-butyllithium; this carbanion has been used for addition to carbonyl groups[7] as well as to other electrophilic reagents.[8] Unfortunately, the 1-substituent is not easily removed from the product in these cases. *N*-Benzylimidazole can be debenzylated with sodium in liquid ammonia,[9] but bromine or iodine at C-2 undoubtedly would be removed at the same time. We have found that 1-tritylimidazole[10] also forms a carbanion (**1**) with *n*-butyllithium,



1 **2** **3**

that the carbanion reacts readily with various electrophiles to form 1-trityl-2-X-imidazoles (**2**), and that the trityl group is easily removed by mild acid hydrolysis to give 2-X-imidazoles (**3**).

Tables I and II describe compounds prepared by this general method. Yields of **2** are consistently high,[11] except where X is halogen. Attempts to improve yields in the halogenation steps by variation in conditions or source of halogen were unsuccessful. Unreacted tritylimidazole accounted for most of the material loss in these cases. The presence of a single imidazole proton resonance in the NMR spectrum of each **3** supports assignment of the substituent to the 2-position. For **3c**, **3d**, and **3g**, structural assignments were confirmed by comparison with authentic samples. In no case was there formed a detectable quantity of the isomeric 4(5)-X-imidazole, based on NMR and chromatographic evidence.

The preparation of 2-aminoimidazole through the phenyltriazene (**2g**), based on a procedure for the preparation of 1-alkyl-2-aminoimidazoles,[12] has special significance in that it allows a nonreductive introduction of the 2-amino function into a preformed imidazole ring. (In our hands, the catalytic reduction of 2-arylazo-4-X-imidazoles often results in simultaneous loss of the 4-X substituent.[5]) Consistent with the results of others,[12] our attempts to aminate **1** with methoxyamine,[13] *O*-mesitylenesulfonylhydroxylamine,[14] or *O*-2,4-dinitrophenylhydroxylamine[15] were unsuccessful.

Table I. Products of the Reaction of 1-Trityl-2-lithioimidazole with Electrophilic Agents

registry no.	cpd[a]	electrophilic agent	registry no.	X	yield, %	mp, °C	NMR, ppm (J, Hz)[b]
67478-46-0	**2a**	*N*-iodosuccinimide[c]	516-121	I	40	170–172	6.81 (d) (*J* = 1.5), 6.98 (d) (*J* = 1.5), 7.05–7.38 (m)
	2a	I_2[c]	7553-56-2	I	41		
67478-47-1	**2b**	*N*-bromosuccinimide[c]	128-08-5	Br	35	208–209	6.82 (d) (*J* = 1.5), 6.99 (d) (*J* = 1.5), 7.08–7.40 (m)
67478-48-2	**2c**	*N*-chlorosuccinimide[c]	128-09-6	Cl	<5	208–210	6.87 (d) (*J* = 1.5), 7.01 (d) (*J* = 1.5), 7.15–7.65 (m)
	2c	*tert*-butyl hypochlorite[d]	507-40-4	Cl	39		
23593-68-2	**2d**	CH_3I[e]	74-88-4	CH_3	95	217–218.5	1.64 (s), 6.69 (d) (*J* = 1.4), 6.89 (d) (*J* = 1.4), 7.05–7.40 (m)
67478-49-3	**2e**	$ClCO_2C_2H_5$[d]	541-41-3	$CO_2C_2H_5$	90	204.5–206.5	0.94 (t) (*J* = 7), 3.84 (q) (*J* = 7), 7.09 (d) (*J* = 1.5), 7.1–7.5 (m)
67478-50-6	**2f**	$HCON(CH_3)_2$[e]	68-12-2	CHO	98	189–190	7.07 (d) (*J* = 1.5), 7.20–7.50 (m), 9.40 (s)
67478-51-7	**2g**	PhN_3[d]	622-37-7	N=NNHPh	95	124–135 (d)	6.82 (d) (*J* = 1.5), 7.08 (d) (*J* = 1.5), 7.13–7.48 (m)

[a] Identity and purity of all compounds were confirmed by chemical ionization mass spectrometry and by combustion analysis. (Satisfactory analytical data (C, H, N) were submitted.) Purifications were effected by recrystallization from ethyl acetate/cyclohexane mixtures. [b] Spectra measured in $CDCl_3$ on a Varian A60 spectrometer. [c] Added in 5 mL of tetrahydrofuran. [d] Added neat. [e] Added neat, threefold excess.

Table II. Preparation of 2-X-imidazoles by Acid Catalyzed Cleavage of 1-Trityl-2-X-imidazoles

registry no.	cpd[a]	X	cleavage[b]	yield, %	mp, °C	purification	NMR, ppm in Me_2SO-d_6 (*J*, Hz)[c]
3034-62-6	**3a**	I	A	99	190–192	sublimation	7.08 (s)
16681-56-4	**3b**	Br	A	>99	197–198[d]	sublimation	7.08 (s)
16265-04-6	**3c**	Cl	A	98	166–167[e]	sublimation	7.07 (s)
693-98-1	**3d**	CH_3	B	97	130–133[f]	sublimation	2.29 (s), 6.89 (s)
33543-78-1	**3e**	$CO_2C_2H_5$	A	>99	178–179	ethanol	1.30 (t) (*J* = 7), 3.35 (q) (*J* = 7), 7.32 (s)
10111-08-7	**3f**	CHO	C	99	190–196[g]	ethyl acetate	7.41 (s), 9.63 (s)
52737-40-3	**3g**	$NH_2 \cdot HCl$	D	73	144–146[h]	ethanol	6.88 (s)

[a] All new compounds had satisfactory elemental analyses. Identity of all compounds was checked by mass spectrometry. [b] (A) 1 mmol refluxed 30 min in 5 mL of 5% acetic acid in methanol; (B) 1 mmol refluxed 4 h in 1 mL of 1 N HCl and 0.5 mL of ethanol; (C) 1 mmol refluxed for 1 h in 5 mL of 5% acetic acid in methanol; (D) 1 mmol refluxed for 3 h in 10 mL of methanol and 0.2 mL of concentrated HCl. [c] NMR spectra were measured on a JEOL Model FX 100 spectrometer. [d] Lit. mp 207 °C: H. King and W. O. Murch, *J. Chem. Soc.*, **123**, 621 (1923). [e] Lit.[6] mp 165–166 °C. [f] Lit. mp 137 °C: O. Wallach, *Justus Liebigs Ann. Chem.*, **214**, 257 (1882). [g] Lit. mp 204 °C: H. Shubert and H.-D. Rudolf, *Angew. Chem. Int. Edit. Engl.*, **5**, 674 (1966). [h] Lit. mp 152 °C: R. G. Fargher and F. L. Pyman, *J. Chem. Soc.*, **115**, 217 (1919).

The procedure described in this report is now being applied to the preparation of 2,4-disubstituted imidazoles and to 2-substituted histidines and histamines. The variety of X groups introduced is also being expanded.

Experimental Section

Preparation of 1-Trityl-2-X-imidazoles (2). The preparation of 1-trityl-2-iodoimidazole (**2a**) illustrates the general procedure. 1-Trityl-2-lithioimidazole (I) was prepared by the addition of 1.5 mL of 1.6 M *n*-butyllithium in hexane (Aldrich) to a solution of 620 mg (2 mmol) of 1-tritylimidazole in 25 mL of tetrahydrofuran (freshly distilled from lithium aluminum hydride) at 0 °C under a nitrogen atmosphere. The solution, which gradually turned red, was stirred at room temperature for 1.5 h, was then cooled to 0 °C, and 508 mg (2 mmol) of iodine in 5 mL of tetrahydrofuran was added dropwise over 5 min. After an additional 10 min at 0 °C, the reaction mixture was poured into 25 mL of water. After concentration of the solution by rotary evaporation, ether extraction, and silica gel chromatography (1:1 ether–petroleum ether), **2a** was obtained in 40% yield.

Products described in Table I were prepared from 2 mmol of tritylimidazole. No problems are encountered when the reaction is carried out on a larger scale.

Preparation of 2-X-Imidazoles (3). 2-Iodoimidazole[16] (**3a**) was prepared from **2a** by refluxing a solution of 350 mg (0.80 mmol) of **2a** in 5 mL of 5% acetic acid in methanol for 30 min. After evaporation of the solvent, water was added to the residue. After chilling, the solution was filtered and the filtrate evaporated to give 155 mg of crystalline **3a** (99%), the homogeneity of which was demonstrated by thin-layer chromatography and chemical ionization mass spectrometry.

Variations in hydrolysis condition are given in Table II. The course of the reaction in each case was monitored by silica gel thin-layer chromatography.

Registry No.—1, 67478-52-8; 1-tritylimidazole, 15469-97-3.

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Reactivity of Oxoindole-$\Delta^{3,\alpha}$-acrylates toward Diazoalkanes: An Unusual Ring Expansion

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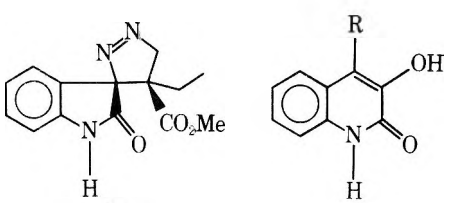
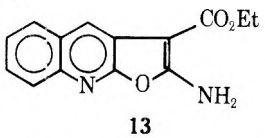
Received April 4, 1978

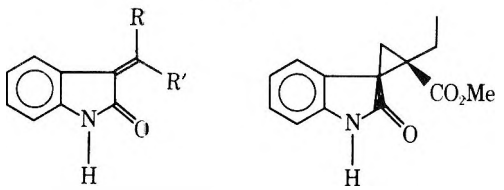
As part of our work on the regiospecific behavior of enedicarbonyl compounds[1a] we decided to examine the reaction of diazoalkanes[1b] with oxoindol-$\Delta^{3,\alpha}$-acrylates (**1**). With diazomethane acrylate **1** (X = H)[2] provided pyrazoline **3a** (X = H). The observed NMR coupling of the pyrazoline methylene and methine protons was sufficient evidence to assign structure **3a** and not **2a** to the product. Steric (tertiary vs. secondary carbon) as well as electronic (polarization of the C–C double bond) effects are such that the [1,3]-dipolar addition of diazomethane involves initial C–C bond formation α to the ester, with the reaction proceeding via a nonsynchronous intermediate such as **4** and not **5**.[3] When heated above its melting point or in refluxing xylene, pyrazoline **3a** (X = H) underwent N_2 loss giving spirocyclopropane **7a** (X = H). Reaction of acrylate **1**, X = H, with phenyldiazomethane provided the corresponding spirocyclopropane **7b** (X = H) as a single diastereomer.

Exposure of acrylate **1** (X = CN)[6] to diazomethane did not afford either a pyrazoline (**2** or **3**) or a spirocyclopropane (**7**). Instead, only quinolone **11a** (X = CN) could be isolated (92%). Rearrangement of the intermediate resulting from loss of N_2, **8**, and isomerization of the resulting exocyclic double bond out of conjugation with the cyanoester and into aromatization would account for the observed product.[7] The addition of a cyano group[8] has thus reversed the polarization of the C–C double bond while equalizing the steric effects of substitution such that the diazomethane addition now involves initial C–C bond formation β to the ester moiety (**5**). The rearrangement of isatins to quinolones has precedent in the literature.[9] Eistert and coworkers had reported that the reaction of isatin and *N*-methylisatin with diazoalkanes ($RCHN_2$) led in good yield to 4-R-substituted 3-hydroxycarbostyrils (**12**).

An equilibrium mixture of **11a** (X = CN) and tricyclic **13** was established after only 12 h in Me_2SO at ambient temperature. Dissolution of either **11a** or **13** in Me_2SO resulted in the same mixture. The ^{13}C chemical shifts for compounds **11a** (X = CN) and **13** were consistent with structural assignments made on the basis of other spectral data.[10] The ^{13}C NMR spectrum of **11a** displayed a single aliphatic, methine carbon which disappeared on isomerization in Me_2SO to **13**. In addition the A ring aromatic carbons β to N shifted downfield on isomerization, an indication of the imino ether tautomeric form. The rather high-field (80.2 ppm) absorption of the furan ring C α to the ester in **13** is consistent with a high-electron density resulting from mesomeric O and NH_2 participation. Furthermore, hydrolysis of **11a** (X = CN) followed by decarboxylation provided the known quinolone-3-acetic acid (**11a**, X = H), identical in all respects[11a] with the compound prepared by literature techniques.[11b]







14a, R = Et; R′ = CO_2Me
b, R = CO_2Me; R′ = Et

15

In a similar manner, reaction of **1** (X = CN) with $PhCHN_2$[12] provided the corresponding rearrangement product **11b** (X = CN) mp >325 °C in a yield of 42%. Reaction of **14a**[9c] with diazomethane, on the other hand, provided pyrazoline **9** resulting from C–C bond formation α to the ester. When heated in refluxing xylene this pyrazoline underwent smooth conversion to spirocyclopropane **15**. The double bond carbons of compound **14a** are more sterically equivalent (tertiary vs. tertiary) than in the case where X = H and yet initial C–C bond formation has still occurred α to the ester. This result lends support to the argument that only when C–C double bond polarization of the oxoindol-$\Delta^{3,\alpha}$-acrylates has been reversed (as in the case where X = CN)[13] such that dipolar species react initially at the carbon β to the ester will rearrangement to the quinolone ring system occur. Furthermore, the sequence provides an efficient procedure for the synthesis of quinolone-3-acetates. Additional work relating to this rearrangement and the regioselectivity of such dipolar addition reactions is now in process.

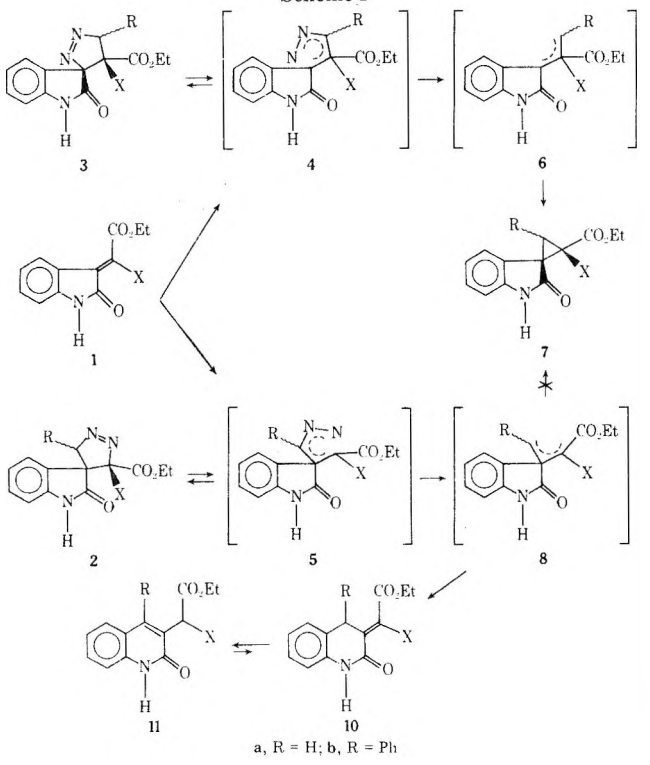
Experimental Section

The IR spectra were recorded on a Perkin-Elmer Model 257 or 457 grating spectrophotometer and NMR spectra were recorded using either a Varian T-60 or EM-360 spectrometer. ^{13}C NMR spectra were recorded using a Varian XLFT-100 spectrometer. Chemical shifts (δ) are recorded relative to Me_4Si; coupling constants (J) are given in hertz. Mass spectra were recorded using either an LKB 9000 or an AEI MS-30-D5-50 spectrometer. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. In all workup procedures, the drying process involved swirling over $MgSO_4$ and filtering prior to evaporation.

Ethyl 4′,5′-Dihydro-2-oxospiro(3*H*-indole-3,3′-pyrazole)-4′-carboxylate (3a, X = H). To a solution of acrylate **1**[2] (X = H) (21.9 g, 0.1 mol) in anhydrous Et_2O (700 mL) at 0 °C was added CH_2N_2 (ca. 5.1 g, 0.12 mol) (from 36 g of Diazald).[20] After an additional 18 h at ambient temperature, the excess CH_2N_2 was quenched with HOAc and the solution was washed with aqueous $NaHCO_3$, dried, and

0022-3263/78/1943-4383$01.00/0

Scheme I



a, R = H; b, R = Ph

evaporated. Recrystallization of the residue from *i*-PrOH gave 17.6 g (68%) of white solid: mp 113.5–114.5 °C; NMR ($CDCl_3$) δ 1.74 (t, J = 7 Hz, 3 H), 3.45 (t, J = 8 Hz, 1 H), 3.83 (q, J = 7 Hz, 2 H), 5.12 (d, J = 8 Hz, 2 H), 6.70–7.50 (m, 4 H), and 10.83 (broad s, 1 H); IR (KBr) 3420, 1730, and 1625 cm^{-1}.

Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.2; H, 5.1; N, 16.2. Found: C, 60.4; H, 5.5; N, 16.3.

Ethyl 1′,2′-Dihydro-2′-oxospiro(cyclopropane-1,3′-[3*H*]-indole)carboxylate (7a, X = H). Pyrazoline **3a** (X = H) (17.6 g, 0.068 mol) was heated in refluxing toluene (300 mL) for 4 h. Evaporation of the solvent and crystallization of the residue from cold *i*-PrOH gave 9.9 g (63%) of white crystals: mp 154–6 °C; NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3 H), 2.13 (d of ABq, 2 H), 2.89 (d of d, J = 7.8 Hz, 1 H), 4.17 (q, J = 7 Hz, 2 H), 6.90–7.50 (m, 4 H), and 9.82 (broad s, 1 H); IR (CH_2Cl_2) 3430, 1730, and 1625 cm^{-1}.

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.5; H, 5.7; N, 6.1. Found: C, 67.1; H, 5.6; N, 6.2.

Ethyl 1′,2′-Dihydro-2′-oxoxpiro(2-phenylcyclopropane-1,3′-[3*H*]indole)carboxylate (7b, X = H). To a solution of $PhCHN_2$ (prepared[21] from 7.8 g of benzalhydrazone) in Et_2O (300 mL) was added acrylate 1 (X = H) (6.54 g, 30 mmol) and the mixture was allowed to stir at ambient temperature for 18 h. After quenching of the excess $PhCHN_2$ with HOAc, filtration gave a white solid. Recrystallization from *i*-PrOH provided 5.7 g (62%) of white needles: mp 175–177 °C; NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3 H), 3.20 (d, J = 8 Hz, 1 H), 3.73 (d, J = 8 Hz, 1 H), 4.24 (q, J = 7 Hz, 2 H), 6.90–7.50 (m, 9 H), and 10.56 (broad s, 1 H); IR ($CHCl_3$) 1725 and 1515 cm^{-1}.

Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.2; H, 5.6; N, 4.6. Found: C, 74.1; H, 5.6; N, 4.5.

Ethyl 1,2-Dihydro-2-oxo-3-quinolinemalononitrile (11a, X = CN). To a solution of acrylate 1 (X = CN) (2.4 g, 10 mmol) in Et_2O (100 mL) and EtOH (20 mL) at 0 °C was added diazomethane (ca. 0.5 g, 12 mmol, from 3.5 g of Diazald[20]) and, after an additional 18 h at ambient temperature, the reaction mixture was quenched with HOAC, washed with aqueous $NaHCO_3$ and brine, dried, and evaporated. Recrystallization of the residue from *i*-PrOH–CH_2Cl_2 provided 2.35 g (92%) of a white solid: mp 147.5–149 °C; NMR ($CDCl_3$) δ 1.24 (t, J = 7 Hz, 3 H), 4.33 (q, J = 7 Hz, 2 H), 5.19 (s, 1 H), 7.10–7.70 (m, 4 H), 8.06 (s, 1 H), and 12.69 (broad s, 1 H); IR ($CHCl_3$) 3370, 2250, 1760, and 1670 cm^{-1}; UV (MeOH) 230 (31 910), 271 (7850), and 332 (5990) nm.

Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.6; H, 4.7; N, 10.9. Found: C, 65.5; H, 4.6; N, 10.8.

Upon dissolution in Me_2SO an equilibrium mixture of **11a** and **13** was established after 12 h at ambient temperature. Crystallization from *i*-PrOH–CH_2Cl_2 left **13** in the filtrate. Evaporation and recrystallization of this residue from *i*-PrOH gave **13**: mp 171.5–172.5 °C; NMR (Me_2SO) δ 1.52 (t, J = 7 Hz, 3 H), 3.26 (s, 2 H, H_2O), 4.41 (q, J = 7 Hz, 2 H), 7.40–8.00 (m, 4 H), and 8.06 (s, 1 H); IR (CH_2Cl_2) 3500, 3380, 1685, and 1640 cm^{-1}; UV (MeOH) 215 (32 700), 259 (23 810), and 343 (13 460) nm.

Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.6; H, 4.7; N, 10.9. Found: C, 65.3; H, 5.2; N, 10.8.

Hydrolysis of Malonitrile (11a) (X = CN). A mixture of malononitrile (**11a**, X = CN; 150 mg), H_2O (2 mL), and concentrated H_2SO_4 (1.5 mL) was heated at reflux for 18 h, cooled and poured onto ice water (30 mL). Filtration of the resulting solids gave **11a** (X = H), mp 273–275 °C; mmp 273–75 °C; lit.[11] mp 271–3 °C.

Ethyl 4-Phenyl-1,2-dihydro-2-oxo-3-quinolinemalononitrile (11b, X = CN). To a solution of $PhCNH_2$ (prepared from 2.65 g of benzalhydrazone) in Et_2O (100 mL) was added acrylate 1 (X = CN) (2.42 g, 10 mmol) in EtOH (15 mL). After 18 h at ambient temperature, the mixture was quenched with HOAc, washed with aqueous $NaHCO_3$, and extracted with 2 N NaOH. Acidification of the hydroxide extract with 2 N HCl (to pH 2) left a white solid, which after recrystallization from EtOH gave 1.39 g (42%) of a white solid: mp >325 °C; NMR ($CDCl_3$–Me_2SO) 1.21 (t, J = 7 Hz, 3 H), 4.20 (q, J = 7 Hz, 2 H), 5.39 (s, 1 H), 7.20–7.90 (m, 9 H), and 12.10 (broad s, 1 H); IR (KBr) 2240, 1750, and 1660 cm^{-1}.

Anal. Calcd for $C_{20}H_{16}N_2O_3$: C, 72.3; H, 4.9; N, 8.4. Found: C, 72.4; H, 4.4; N, 8.2.

Methyl (*Z*)-2-Oxoindole-$\Delta^{3,\alpha}$-butyrate (14a). The procedure of Mori[12c] provided a 2:1 mixture of *E* and *Z* isomers which had to be separated by chromatography over silica gel. The compound of larger R_f value was the *E* isomer, **14b**: deep yellow crystals; mp 119–20 °C; NMR ($CDCl_3$) δ 1.34 (t, J = 7 Hz, 3 H), 3.39 (q, J = 7 Hz, 2 H), 4.08 (s, 3 H), 6.88–7.50 (m, 4 H), and 9.46 (broad s, 1 H); IR ($CHCl_3$) 3450, 1710, and 1610 cm^{-1}.

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 66.5; H, 5.7; N, 6.1. Found: C, 66.2; H, 5.3; N, 6.3.

The lower R_f value material, *Z* isomer (**14a**), was isolated as yellow crystals: mp 131–2 °C; NMR ($CDCl_3$) δ 1.39 (t, J = 7 Hz, 3 H), 2.87 (q, J = 7 Hz, 2 H), 4.02 (s, 3 H), 6.90–7.60 (m, 4 H), and 9.52 (broad s, 1 H); IR ($CHCl_3$) 3450, 1715, and 1615 cm^{-1}.

Anal. Found: C, 66.3; H, 5.5; N, 6.2.

Methyl 4′,5′-Dihydro-4′-ethyl 2-oxospiro(3*H*-indolo-3,3′-pyrazole)-4′-carboxylate (9). To a solution of (*Z*)-acrylate **14a** (1.30 g, 6 mmol) in Et_2O (40 mL) at 0 °C was added CH_2N_2 (ca. 0.26 g, 6.2 mmol) (from 1.82 g of Diazald[20]) and the resulting mixture was stirred at ambient temperature for 18 h. After HOAc quench, the solution was washed with $NaHCO_3$, dried, and evaporated to give 1.40 g (83%) of a light-brown oil: NMR ($CDCl_3$) δ 0.87 (t, J = 7 Hz, 3 H), 1.68 (q, J = 7 Hz, 2 H), 3.64 (s, 3 H), 4.95 (d, J = 18 Hz, 1 H), 5.41 (d, J = 18 Hz, 1 H), 6.90–7.60 (m, 4 H), and 9.28 (broad s, 1 H); IR ($CHCl_3$) 3430, 1725, and 1615 cm^{-1}.

Anal. Calcd for $C_{14}H_{15}N_3O_3$: C, 61.5; H, 5.5; N, 15.4. Found: C, 62.0; H, 6.0; N, 15.7.

Treatment of the (*E*)-acrylate **14b** in a small similar manner provided the corresponding spiropyrazole in 63% yield: mp 133–5 °C dec; NMR ($CDCl_3$) 0.90 (t, J = 7 Hz, 3 H), 1.98 (q, J = Hz, 2 H), 3.40 (s, 3 H), 4.81 (d, J = 18 Hz, 1 H), 5.46 (d, J = 18 Hz, 1 H), 6.70–7.35 (m, 4 H), and 9.12 (broad s, 1 H); IR ($CHCl_3$) 3430, 1710, and 1620 cm^{-1}.

Methyl (*Z*)-1′,2′-Dihydro-2-ethyl-2′-oxospiro(cyclopropane-1,3′-3*H*-indole)carboxylate (15). A solution of the (*Z*)-spiropyrazoline (**9**) (1.40 g, 5.1 mmol) in xylene (75 mL) was heated at reflux for 8 h. After cooling, evaporation of the solvent and distillation (180–90 (0.025 mm)) gave 0.77 g (61%) of a light yellow oil: NMR ($CDCl_3$) δ 1.06 (t, J = 7 Hz, 3 H), 2.39 (ABq, 2 H), 2.93 (q, J = 7 Hz, 2 H), 3.74 (s, 3 H), 6.90–7.40 (m, 4 H), and 10.00 (broad s, 1 H); IR (CH_2Cl_2) 3420, 1720, and 16.20 cm^{-1}.

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.2; N, 5.7. Found: C, 68.6; H, 6.6; N, 5.6.

Registry No.—**1** (X = H), 21728-28-9; **1** (X = CN), 59225-18-2; **3a** (X = H), 67487-94-9; **7a** (X = H), 67487-95-0; **7b** (X = H), 67487-96-1; **9**, 67487-97-2; **11a** (X = H), 53244-93-2; **11a** (X = CN), 67487-98-3; **11b** (X = CN), 67487-99-4; **13**, 67488-03-3; **14a**, 67488-00-0; **14b**, 67488-01-1; **15**, 67488-02-2; CH_2N_2, 334-88-3; $PhCHN_2$, 766-91-6.

References and Notes

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(2) H. A. Brandman, *J. Heterocycl. Chem.*, **10**, 383 (1973).

(3) While our discussion (Scheme I) makes use of a nonsynchronous concerted mechanism[4] governed by frontier orbitals, a synchronous or even a diradical mechanism[5] would have served equally well to explain both the regiospecificity of addition and the unusual ring expansion.

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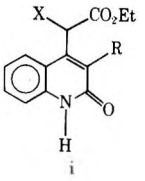
(7) Structure i was dismissed on the basis of spectral data.



i

(8) For a discussion of the effects of an added CN moiety on pyrazoline stability see F. D. Popp and A. Catalia, *J. Org. Chem.*, **26**, 2738 (1961), and references cited therein.
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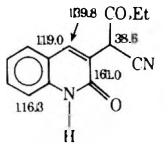
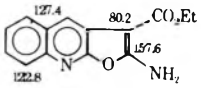
(10) Structures **11a** and **13.**



11a



13

(11) (a) mp 273–5 °C; mmp 273–5 °C; as well as comparative TLC, MS, and solution IR; (b) H. A. Lloyd, L. V. Matternas and E. C. Horning, *J. Am. Chem. Soc.*, **77**, 5932 (1955); UV (MeOH) 227 (32 700), 269 (8220), and 326 (7350).
(12) R. J. Mohrbacher and N. H. Cromwell, *J. Am. Chem. Soc.*, 79, 401 (1957).
(13) A referee suggested that the ethyl moiety might sterically drive the ester function out of planarity with the double bond, thus destablizing any partial charge in a transition state such as **5.**

Thallium in Organic Synthesis. 53. Simple Procedures for the Replacement of a Phenolic OH Group by N=NAr, N=O, H, NH_2, and C Substituents[1,2]

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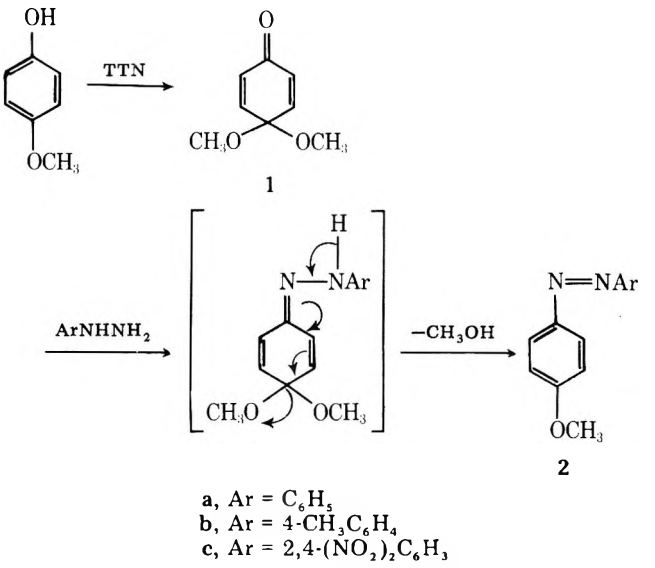
Evans et al.[3] have recently described an ingenious synthetic approach to the Amaryllidaceae alkaloid cherylline via a quinone methide prepared by a Wittig-type reaction of 4,4-dimethoxycyclohexadienones. We have recently described a general, efficient, and mild procedure for the oxidation of a variety of 4-substituted phenols to 4-substituted 4-methoxycyclohexadienones utilizing thallium(III) nitrate (TTN) in methanol or methanol/trimethyl orthoformate as solvent.[4] We now report a series of simple transformations of these cyclohexadienones which effect overall replacement of the OH group of the precursor phenol by N=NAr, N=O, H, NH_2, and C substituents.

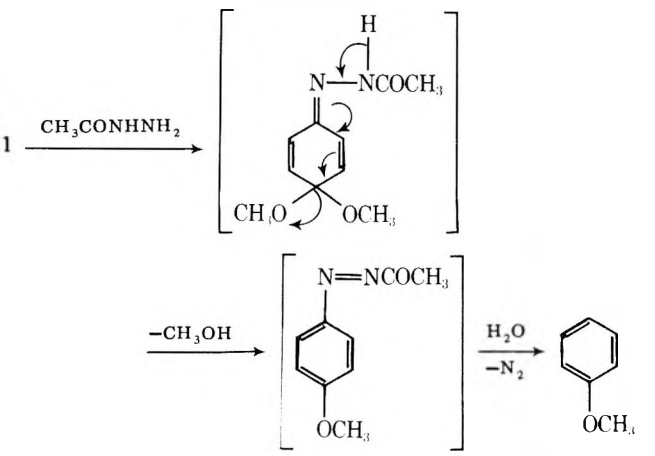
In 1963 Hecker and Lattrell[5] reported the conversion of several 4-hydroxy-4-substituted cyclohexadienones (prepared by thallium(III) or lead(IV) acetate oxidation of the corresponding phenols) to 2,4-dinitrophenylazobenzenes by reaction with 2,4-dinitrophenylhydrazine. Because of the inaccessibility of the requisite precursor cyclohexadienones, however, there has been no subsequent synthetic exploitation

Scheme I



a, Ar = C_6H_5
b, Ar = 4-$CH_3C_6H_4$
c, Ar = 2,4-$(NO_2)_2C_6H_3$

Scheme II



of this type of transformation, but it appears to be general. Thus, treatment of **1** with phenylhydrazine smoothly gave 4-methoxyazobenzene **2a** in 90% yield (Scheme I). Similarly, reaction of **1** with 4-methyl- and 2,4-dinitrophenylhydrazine gave 4-methyl-4′-methoxyazobenzene (**2b**) and 2,4-dinitro-4′-methoxyazobenzene (**2c**) in 92 and 98.5% yield, respectively. This transformation can also be carried out without isolation of the intermediate cyclohexadienone; 3,4-dimethylphenol, for example, was converted to 3,4-dimethylazobenzene in 55% overall yield. Extrapolation of these results to the replacement of a phenolic OH group by H was somewhat less successful. Reaction of **1** with acethydrazide followed by addition of water resulted in the evolution of nitrogen, and anisole was isolated in 50% yield (Scheme II); 6-hydroxytetralin was similarly converted to tetralin in 31% yield.[6] Despite the moderate yields, this simple transformation could represent a mild procedure for effecting a potentially useful reduction.[7]

The principle illustrated in these transformations—conversion of **1** to an imine possessing an acidic α-hydrogen atom which can be lost in a subsequent, and spontaneous, aromatization step—appears to be capable of considerable extension. Thus, treatment of **1** with hydroxylamine led directly to 4-methoxynitrosobenzene in 91% yield (Scheme III). The overall conversion of 4-methoxyphenol to 4-methoxynitrosobenzene can also be carried out as a one-pot operation without isolation of the intermediate cyclohexadienone, although this procedure gave a somewhat lower yield (70%). Using the latter technique, 4-methylphenol, 3,4-dimethyl-

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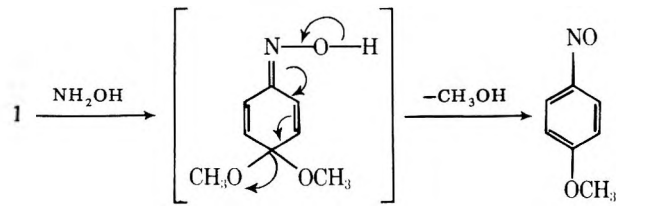
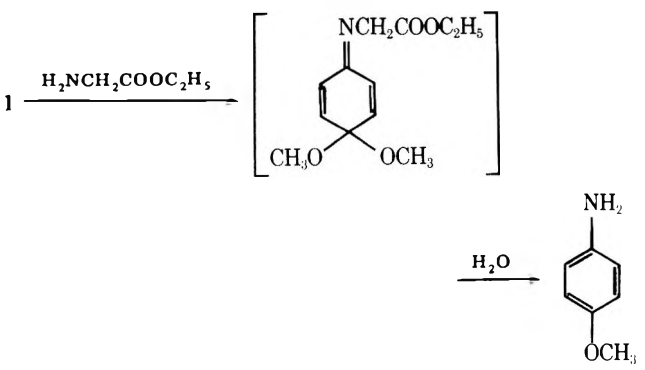
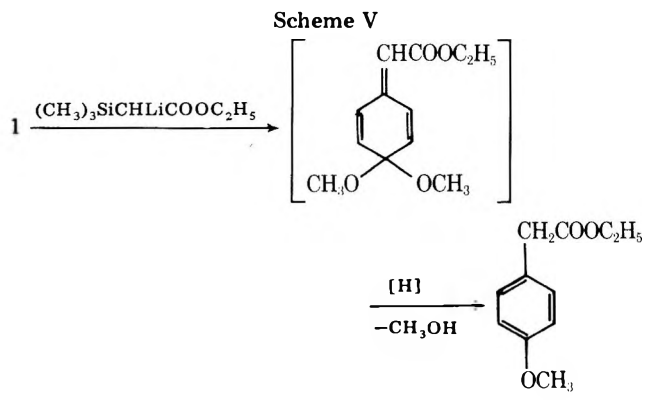
Scheme III



Scheme IV



Scheme V



phenol, 2-chloro-4-methoxyphenol, 4-hydroxybiphenyl, and 6-hydroxytetralin were converted to the aromatic nitroso compounds (in which the nitroso group has replaced the OH substituent of the phenolic precursor) in 41, 62, 54, 40, and 31% yield, respectively.

The cyclohexadienone 1 can also be converted to 4-methoxyaniline (isolated as the acetanilide) in 56% yield by reaction with ethyl glycinate followed by acid hydrolysis of the (presumed but not isolated) imine (Scheme IV). This mild conversion of a phenol to an aniline derivative should be contrasted with the extremely vigorous conditions required by current methodology.[8]

Finally, by analogy with the recently described conversion by Evans et al.[3] of 1 to *N*,*N*-dimethyl-α-(4,4-dimethoxycyclohexa-2,5-dienylidene)acetamide with the lithium enolate of *N*,*N*-dimethyl-α-trimethylsilylacetamide, we have found that reaction of 1 with the lithium enolate of ethyl α-trimethylsilylacetate gave the corresponding quinone methide dimethyl ketal (Scheme V). Catalytic reduction then led directly to ethyl 4-methoxyphenylacetate (68%). This transformation, and that reported by Evans, represent an attractive potential synthetic method for arylation of carbanions.

Experimental Section[9]

General Procedure for the Conversion of 4,4-Dimethoxycyclohexadienone to 4-Methoxyazobenzenes. A solution of the arylhydrazine hydrochloride (7 mmol) in methanol (20 mL) containing pyridine (3.75 mmol) was added dropwise to a stirred solution of 4,4-dimethoxycyclohexadienone (5 mmol) in methanol (20 mL) cooled to 0 °C. The mixture was stirred at room temperature for 2.5 h; 6 drops of boron trifluoride etherate were then added and stirring was continued for a further 8–10 h. The reaction mixture was diluted to a total volume of 200 mL with methylene chloride and the resulting solution washed with water (50 mL), saturated aqueous sodium bicarbonate solution, and water (50 mL); it was then dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure. Chromatography of the residue on silica gel using methylene chloride as the eluent gave the pure (mp, IR, NMR, TLC) 4-methoxyazobenzene.

One-Pot Procedure for the Conversion of Phenols to Azobenzenes: Preparation of 3,4-Dimethylazobenzene. A solution of thallium(III) nitrate trihydrate (2.22 g, 5 mmol) in anhydrous methanol (20 mL) was added dropwise to a stirred solution of 3,4-dimethylphenol (0.61 g, 5 mmol) in anhydrous methanol (20 mL) cooled to −78 °C. The temperature of the reaction mixture was allowed to rise to room temperature, and stirring was continued for 1 h. The reaction mixture was then cooled to 0 °C, a solution of phenylhydrazine (0.76 g, 7 mmol) in methanol (20 mL) containing pyridine (0.5 g, 6.25 mmol) was added dropwise, and stirring was continued at room temperature for 4 h. Six drops of boron trifluoride etherate was then added and stirring was continued for a further 12 h. The product was isolated using the technique described above; this gave 0.58 g (55%) of pure 3,4-dimethylazobenzene, mp 63–65 °C. Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.92; H, 6.64; N, 13.02.

Conversion of 4,4-Dimethoxycyclohexadienone to Anisole. 4,4-Dimethoxycyclohexadienone (0.77 g, 5 mmol) was dissolved in anhydrous methanol (20 mL) containing 2 g of Davidson Type 4A molecular sieves. In a separate flask, anhydrous acethydrazide (0.55 g, 7.5 mmol) was dissolved in anhydrous methanol (20 mL) containing 2 g of Davidson Type 4A molecular sieves and concentrated hydrochloric acid (0.25 g). The two solutions were stirred for 30 min; then the latter was added to the former, which had been chilled to 0 °C. The mixture was stirred for 1.5 h, 20 drops of boron trifluoride etherate were then added during 3 min, and stirring was continued for 2.5 h. Water (100 mL) was added all at once and the molecular sieves were removed by filtration; the filtrate was stirred for 30 min, after which 10% hydrochloric acid (5 mL) was added. The resulting mixture was stirred at room temperature for 6 h, then at 60 °C for 1 h; water (100 mL) was added and the aqueous solution was extracted with ether (3 × 100 mL). The combined ether extracts were washed with water (50 mL) and aqueous sodium bicarbonate solution (50 mL) and dried ($MgSO_4$) and the solvent was removed by distillation under reduced pressure. The residue was chromatographed on silica gel using methylene chloride as eluent; this gave 270 mg (50%) of pure (IR, GLC) anisole.

Conversion of 6-Hydroxytetraline to Tetralin. 6-Hydroxytetralin (5 mmol) was oxidized to the cyclohexadienone by the procedure described above for the oxidation of 3,4-dimethylphenol with thallium(III) nitrate trihydrate. The cyclohexadienone was not isolated, but was treated in situ with acethydrazide as described in the preparation of anisole; this gave pure (IR, GLC) tetralin in 31% yield.

General Procedure for the Conversion of Phenols to Nitroso Compounds. A solution of thallium(III) nitrate trihydrate (2.22 g, 5 mmol) in methanol (15 mL) was added to a stirred solution of the phenol (5 mmol) in methanol (15 mL) cooled to −78 °C. The temperature of the reaction mixture was allowed to rise to room temperature, and stirring was continued for 1 h. A solution of hydroxylamine hydrochloride (6.5 mmol) and pyridine (11.5 mmol) in methanol was then added dropwise and the mixture was stirred for a further 5 h.[10] Six drops of boron trifluoride etherate were then added,[11] and stirring was continued overnight. The reaction mixture was diluted to a volume of 150 mL with ether and filtered to remove inorganic salts; the filtrate was washed with aqueous sodium chloride solution (75 mL). The aqueous layer was extracted with ether (2 × 75 mL), and the combined ether extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel using methylene chloride as eluent to give the pure product.

Conversion of 4,4-Dimethoxycyclohexadienone to 4-Nitrosoanisole. A solution of hydroxylamine hydrochloride (0.84 g, 12 mmol) and pyridine (1 g, 12.5 mmol) in methanol (25 mL) was added dropwise to a stirred solution of 4,4-dimethoxycyclohexadienone (1.54 g, 10 mmol) in methanol (50 mL), and the reaction mixture was stirred at room temperature for 5 h. Product isolation as described above gave 1.24 g (91%) of pure (IR, NMR, TLC) 4-nitrosoanisole.

Conversion of 4,4-Dimethoxycyclohexadienone to 4-Methoxyacetanilide. A mixture of ethyl glycinate hydrochloride

(1.05 g, 7.5 mmol) and sodium bicarbonate (0.55 g, 6.5 mmol) in ethanol (50 mL) and water (10 mL) was added to a solution of 4,4-dimethoxycyclohexadienone (0.77 g, 5 mmol) in ethanol (50 mL), and the resulting mixture was heated under reflux for 1 h. Ten drops of 10% hydrochloric acid was added and the mixture was heated under reflux for 24 h; 6 N hydrochloric acid (80 mL) was then added and reflux continued for 2 h. The reaction mixture was then cooled, neutralized with sodium bicarbonate, and extracted with chloroform (3 × 150 mL). The organic extracts were dried ($MgSO_4$) and evaporated to give crude 4-methoxyaniline. This was acetylated with acetic anhydride and the crude anilide (86%) purified by chromatography and crystallization; this gave 0.46 g (56%) of pure (IR, NMR) 4-methoxyacetanilide, mp 130–132 °C.

Conversion of 4,4-Dimethoxycyclohexadienone to Ethyl 4-Methoxyphenylacetate. The lithium enolate of ethyl α-trimethylsilylacetate[12] (5.5 mmol) was prepared in THF using the procedure described by Evans[3] for the preparation of the corresponding acetamide. A solution of 4,4-dimethoxycyclohexadienone (5 mmol) in THF (3 mL) was added to the enolate solution, and the mixture was stirred at 0 °C for 5 h. It was then added to a mixture of saturated aqueous sodium bicarbonate solution (40 mL) and methylene chloride (150 mL) which had been prechilled to 0 °C. The organic layer was separated, washed with 5% aqueous sodium chloride solution (40 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The crude quinone methide ketal (1.10 g) was catalytically hydrogenated (5% Pd/charcoal) at atmospheric pressure in ethyl acetate and the product chromatographed on silica gel using methanol/methylene chloride (3:97) as eluent. This gave 0.22 g of 4-methoxyphenol and 0.43 g (68% based on dienone consumed) of pure (IR, NMR, GLC) ethyl 4-methoxyphenylacetate.

Registry No.—**1**, 935-50-2; **2a**, 2396-60-3; **2b**, 29418-44-8; **2c**, 51640-06-3; $ArNHNH_2$ (Ar = Ph), 100-63-0; $ArNHNH_2$ (Ar = 4-$CH_3C_6H_4$), 539-44-6; $ArNHNH_2$ (Ar = 2,4-$(NO_2)_2C_6H_3$), 119-26-6; TTN, 13746-98-0; 3,4-dimethylphenol, 95-65-8; 3,4-dimethylazobenzene, 67425-70-1; acethydrazide, 1068-57-1; anisole, 100-66-3; 6-hydroxytetralin, 1125-78-6; tetralin, 119-64-2; hydroxylamine hydrochloride, 5470-11-1; 4-nitrosoanisole, 100-17-4; 4-methoxyacetanilide, 51-66-1; ethyl glycinate hydrochloride, 623-33-6; 4-methoxyaniline, 104-94-9; ethyl 2-trimethylsilylacetate lithium enolate, 54886-62-3; 4-methoxyphenol, 150-76-5; ethyl 4-methoxyphenylacetate, 14062-18-1.

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(8) See, e.g., D. F. Morrow and M. E. Butler, *J. Org. Chem.*, **29**, 1893 (1964); R. A. Scherrer and H. R. Beatty, *ibid.*, **37**, 1681 (1972); R. A. Rossi and J. F. Bunnett, *ibid.*, **37**, 3570 (1972); R. Bayles, M. C. Johnson, R. F. Maisey, and R. W. Turner, *Synthesis*, 31, 33 (1977).
(9) Mp's were determined using a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer Model 467 grating infrared spectrophotometer, and NMR spectra using a Varian A-60 60 MHz spectrometer. GLC was performed on an F and M Model 810R-29 S/N B-273 gas chromatograph equipped with a Honeywell Electronik 15 strip chart recorder. TLC refers to the use of Baker-flex silica gel 1B2-F thin-layer chromatography sheets. Microanalyses were performed by Hoffmann-La Roche, Inc., Nutley, N.J.
(10) When 4-methoxyphenol is used as the substrate the reaction temperature should be held at 0 °C both before the addition of the hydroxylamine and for 1 h afterwards to prevent acid-catalyzed decomposition of the quinone ketal.
(11) Azoxyarenes are produced as by-products in small amounts in these reactions and are difficult to separate from the desired nitroso compounds. Addition of boron trifluoride eliminates this problem.
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Eutectic Potassium–Sodium–Aluminum Chloride as a Mild Catalyst for Ene Reactions: Simple Synthesis of the Sex Pheromone from Douglas Fir Tussock Moth

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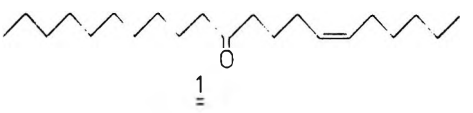
Received March 13, 1978

Several syntheses of the sex pheromone of the Douglas fir tussock moth (**1**) have recently been published.[1-4] These



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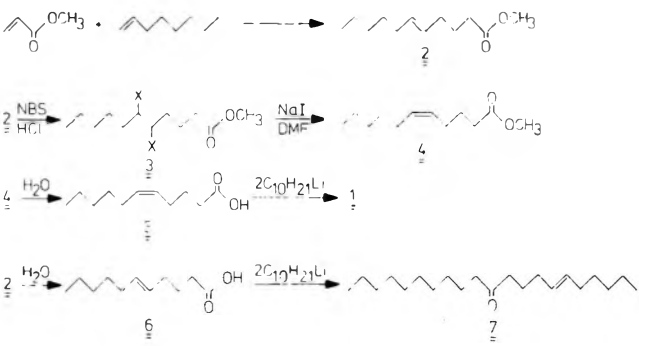
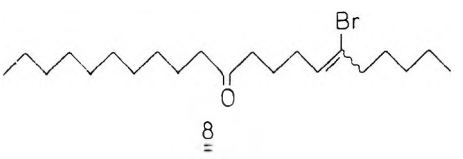
syntheses make use of fairly complicated reactions and sophisticated starting materials. During our studies of acid-catalyzed ene reactions, we have explored a simpler synthesis both for the natural isomer and the also active[5] *E* isomer (**7**). The principles of this synthesis are outlined in Scheme I.

Scheme I



The ene reaction between methyl acrylate and 1-octene has been reported not to occur with aluminium chloride.[6] This is probably due to isomerization of the 1-octene to other internally substituted octenes and subsequent formation of branched adducts. In contrast to this, the eutectic mixture of $AlCl_3$, NaCl, and KCl has been found to be a superior catalyst for the reactions of methyl acrylate with 1-olefins. Using this catalyst, a 40% yield of ene adducts was obtained as a 94:6 mixture of normal and branched isomers. Careful GC analysis (see Experimental Section) showed that the ratio of **2**/**4** was 86:14. After hydrolysis of the product mixture and reaction with decyllithium,[7] the *E* isomer **7** can be obtained by recrystallization. The conversion of the acid mixture to **5** could not be carried out satisfactorily via the straightforward bromination–dehydrobromination[8]–hydrogenation[9] reaction sequence. The overall yields were low, and the presence of **8**,



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in the product mixture, from the reaction with decyllithium indicated the interference of the carboxylate group somewhere in the bromination–dehydrobromination sequence.

Inversion of the **2**/**4** ratio could, however, be carried out very smoothly by conversion of the ester mixture to the corresponding vicinal bromochloride[10] and subsequent elimination[11] to form the inverted olefin. GC analysis showed that the inversion is not 100% stereospecific in this case since the ratio **2**/**4** of the inverted mixture was 20:80. Hydrolysis and reaction

with decyllithium then yields the pheromone.

These results show that the synthetic scope of the ene reaction of acrylate can be considerably extended by this modified Lewis acid catalyst.

Experimental Section

GC analysis was performed on a Hewlett-Packard 402 gas chromatograph with a column packed with 5% FFAP on Chromosorb W at 150–170 °C. The branched ketones were separated from the straight chain ketones on a 3.8% UCW 98 on Chromosorb W column at 240 °C. The isomers **2** and **4** were separated on a PYE GCV apparatus equipped with a CW20M 50 m SCOT column. IR spectra were recorded with Perkin-Elmer 237 and 257 instruments. NMR spectra were obtained in CCl_4 using a Varian EM 360 spectrometer with tetramethylsilane as an internal standard. Melting points were recorded on a hot stage and are uncorrected. All yields are based on isolated products.

Ene Reaction between 1-Octene and Methyl Acrylate. $AlCl_3$ (5.85 g), KCl (0.848 g), and NaCl (0.803 g) were heated while well protected from moisture in a tube of Pyrex glass until a clear solution was obtained. After cooling to room temperature, the glass tube was placed in an acetone–CO_2 bath and 40 mL of methyl acrylate, 17 mL of 1-octene, and a few crystals of hydroquinone were added. When the contents had reached −78 °C, the tube was sealed by melting and put in a boiling water bath for 16 h. The workup procedure consisted of pouring the mixture on ice and dilute hydrochloric acid, extraction with ether, washing of the ether phase, and drying. Evaporation of the solvent and distillation afforded 8.6 g (40%) of 5-hendecenoic acid methyl ester: **2**/**4** ratio was 86:14; IR showed strong absorption at 970 cm^{-1}, suggesting mainly the *E* isomer; NMR δ 5.4–5.15 (m, 2 H), 3.55 (s, 3 H), 2.35–0.80 (m, 17 H), and distorted triplets centered at δ 2.15 and 0.9 corresponding to the allylic CH_2 (s) and the CH_3 at the end of the chain were observed; MS *m/e* 198 ($M^{+}\cdot$), 166 ($M - CH_3OH)^{+}\cdot$, 124 ($C_5H_4CH{=}CHCH{=}CH_2^{+}\cdot$) (McLafferty), 74 ($CH_3O{-}C(OH){-}CH_2^{+}\cdot$) (McLafferty).

Vicinal Bromochloro Ester 3. **2** (1.1 g, 5.55 mmol) was dissolved in 11 mL of CH_2Cl_2, and the solution was cooled to −78 °C in an acetone–CO_2 bath during saturation with HCl gas. Then 1.04 g of *N*-bromosuccinimide, which had been crystallized from water, was added in one portion. The temperature was then allowed to rise to −20 °C, maintaining HCl saturation. After 0.5 h at −20 °C, the mixture was poured on ice–$NaHSO_3$, extracted three times with ether, washed with $KHCO_3$ solution and water, and finally dried. Evaporation of the solvent gave 1.6 g of a colorless oil in 92% crude yield. GLC analysis of the product, which was not purified, showed that it was 93% pure. No olefin remained. IR 1740 cm^{-1} (CO); NMR δ 4.2–3.9 (broad unresolvable multiplet, 2 H), 3.67 (s, 3 H), 2.5–0.8 (m, 17 H). The NMR spectrum was very similar to the spectrum of **2**.

Formation of the Inverted Olefinic Ester Mixture. The product from the above reaction, 1.6 g, was dissolved in 60 mL of dry DMF, and 15 g of NaI was added with stirring. The temperature was then raised to 110–115 °C. After 4 h at this temperature, the mixture was poured out in H_2O and the water–DMF solution was extracted three times with light petroleum. The petroleum phase was then washed with $NaHSO_3$ solution and water and dried with magnesium sulfate. Evaporation of the solvent gave 0.99 g (99%) of a product that contained less than 1% of the bromochloro ester: **2**/**4** ratio was 20:80; IR showed weak absorption at 970 cm^{-1}, attributable to the *E* isomer present; NMR and mass spectra were practically identical with the spectra of the trans compound.

Ester Hydrolysis. The ester (0.81 g) was hydrolyzed in 5 mL of H_2O and 2 mL of EtOH with 0.3 g of KOH for 16 h at room temperature with occasional heating on a water bath at the beginning of the reaction. The usual workup procedure gave 0.77 g (95%) of acid as a colorless oil: IR showed typical broad carboxylic acid bonds at 3000–2000 cm^{-1}; NMR spectrum was similar to the NMR spectrum of the ester, except for the disappearance of the O–CH_3 and the appearance of a COOH proton at δ 11.05.

(*Z*)-6-Heneicosen-11-one (1). To 150 mg of lithium powder in 10 mL of ether was added 2.2 g of decylbromide in 3 mL of ether during 1 h at −10 to −15 °C. After additional stirring for 2 h, GLC analysis after hydrolysis of a sample showed only decane.

This decyllithium solution was then added dropwise at 0 °C with vigorous stirring to a solution of the acid in 10 mL of THF. The mixture was stirred for 16 h at room temperature and refluxed for 0.5 h. The solution was then slowly added to 100 mL of water with vigorous stirring. Extraction of the water phase three times with ether, washing, drying with magnesium sulfate, and evaporation of the ether and the majority of the decane gave 1.4 g of product. Acidification of the water phase and extraction with ether afforded 0.12 g of acid. GC analysis of the ketone revealed the existence of about 3.9% of the branched isomer. This product (0.8 g) was then chromatographed on SiO_2 with 10% ether in light petroleum as eluant. A slight enrichment could be achieved; 0.46 g of ketone was obtained, the GC analysis of which showed 2.5% of the branched isomer. This corresponds to a yield of 62% based on the acid and 75% based on consumed acid.

The *E* and *Z* ketones **7** and **1** could not be satisfactorily separated on any column tried, including the SCOT column. The *E*/*Z* ratio should, however, be 20:80 since neither the hydrolysis nor the reaction with decyllithium concerns the double bond: IR 1720 cm^{-1} (CO) and weak absorption at 970 cm^{-1}; NMR δ 5.25 (m, 2 H), 2.2 (t, 4 H), 1.9 (m, 4 H), 1.8–1.1 (m, 24 H), 1.1–0.8 (overlapping distorted triplets, 6 H); MS (70 eV) *m/e* 308 ($M^{+}\cdot$), 197 ($C_{10}H_{21}CO{-}C_2H_4^{+}\cdot$), 169 ($C_{10}H_{21}CO^{+}\cdot$), 124 ($C_5H_4CH{=}CHCH{=}CH_2^{+}\cdot$) (McLafferty).

(*E*)-6-Heneicosen-11-one (7). By hydrolyzing the ester mixture obtained in the ene reaction, the *E* ketone was synthesized the same way as described above. From 1.84 g (10 mmol) of acid there was obtained after recrystallization from ethanol 1.7 g of **7**: 55% yield based on total acid and 73% yield based on not recovered acid (0.45 g of acid could be recovered); mp 36 °C; IR showed strong absorption at 970 cm^{-1} (trans double bond); NMR and mass spectra were practically identical with the spectra of the cis compound.

Registry No.—**1**, 54844-65-4; **2**, 67270-84-2; **3**, 67254-48-2; **4**, 54471-23-7; **6**, 67270-85-3; **7**, 54844-66-5; methyl acrylate, 96-33-3; 1-octene, 111-66-0; decyl bromide, 112-29-8; $AlCl_3$, 7446-70-0; NaCl, 7647-14-5; KCl, 7447-40-7.

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Stereochemical Control of Transpositional Allylic Oxidation[1,2]

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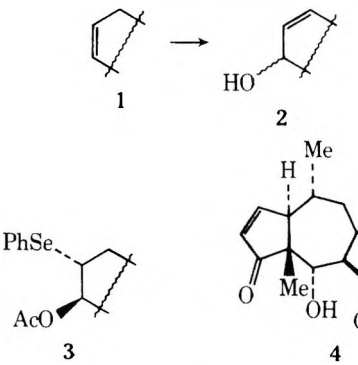
Received April 4, 1978

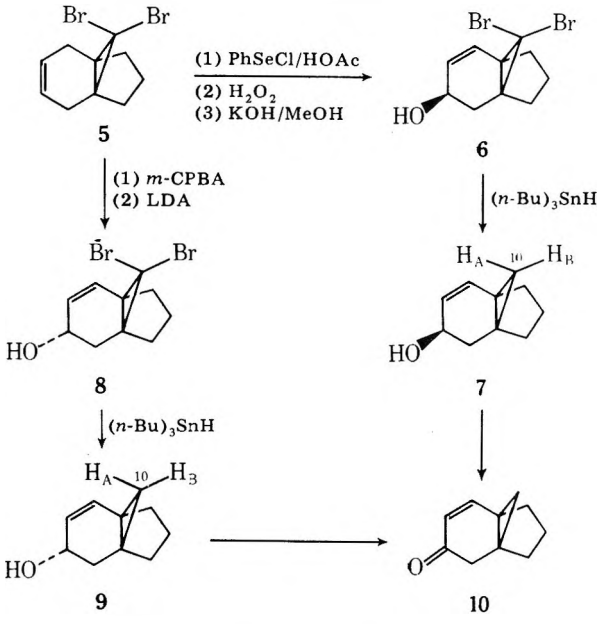
The facility of transpositional allylic oxidation (eq 1) was greatly increased by the discovery by Reich,[4] and also Sharpless[5a] and Clive,[5b] that PhSeX could be utilized for effecting the process. Based on ^1H NMR spectra of intermediates of type **3**, Reich[4] concluded that the PhSeOAc addition to **1** oc-



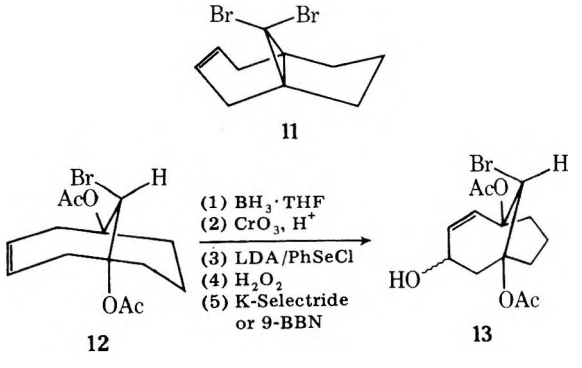
1 2 3 4 (1)

curred in a trans fashion. If so, the configuration of the hydroxyl group in **2**, as produced from base-mediated epoxide ring-opening,[6] might be epimeric with that formed via the organoselenium adduct.

In the course of our work aimed at the total synthesis of helenalin (**4**),[7] we had occasion to investigate this supposition, the results of which we now report. When 10,10-dibromo[4.3.1]propell-3-ene (**5**)[8] was phenylselenenylated, oxidized, and hydrolyzed, only one allylic alcohol (**6**) was obtained; reduction of **6** with tin hydride afforded **7**. Alternatively, epoxidation of **5** produced a single epoxide, ring opening of which gave **8**; tin hydride reduction of **8** led to **9**, shown to be epimeric with **7** by the fact that both could be oxidized to **10**. Regardless of the stereochemistry of **6** and **8**, it is apparent that the two methods utilized provided the two possible allylic alcohols stereoselectively (i.e., there was no crossover). The stereochemistry of **6** and **8** was proven by measuring the Eu(dpm)$_3$-shifted ^{1}H NMR spectra of **7** and **9**, respectively (see Table I). It is thus concluded that initial attack on **5** occurs from the less hindered side away from the bromine atom; in the case of selenenylation, acetate subsequently attacks from the side syn to the bromine atom.



We note some rather subtle conformational effects are at work in additions to **5**, for attack is apparently initiated in the seemingly uncomfortable atomic arrangement shown in **11**.



On the other hand, the related molecule **12** (known to exist as shown at least in the solid state[9]) did not react with PhSeCl/HOAc, even under forcing conditions. In this case, transpositional allylic oxidation was achieved by the rather circuitous route indicated, where trans additions were avoided.[10] The difficulty with **12** is the bromine atom; its removal afforded a normally reactive olefin.[12]

Table I. Eu(DPM)$_3$-Induced ^{1}H NMR Shifts (LIS) (in ppm)

compd	H	[shift reagent]/[compd] 0.1	0.2	0.3
7[a]	H_A	1.32	4.11	7.28
	H_B	1.05		3.33
9[b]	H_A[c]	0.28	0.73	1.23
	H_B[c]	0.44	0.82	1.09

[a] Measured in CCl_4 solution. [b] Measured in $CDCl_3$ solution. [c] The assignments of H_A and H_B may be reversed.

Experimental Section

Infrared spectra were recorded on a Beckman IR-4250 spectrometer. The proton magnetic resonance spectra were obtained on Varian A-60, Varian HA-100, and Hitachi Perkin-Elmer R-20B spectrometers, using the indicated solvents and tetramethylsilane as an internal standard. The mass spectra were obtained on a high resolution MS-9 mass spectrometer. Some purifications were accomplished with a Waters M-6000 high-pressure liquid chromatograph utilizing 1 ft μ-Porasil or 8 ft Porasil-A preparative columns. Melting points are uncorrected.

***exo*-10,10-Dibromo[4.3.1]propell-2-en-4-ol (6).** To a stirring solution of 2.92 g (10 mmol) of **5**[8] and 1.92 g (10 mmol) of benzeneselenenyl chloride in 10 mL of HOAc was added a solution of 1.96 g (20 mmol) of KOAc in 15 mL of HOAc under nitrogen at room temperature. The initially red solution turned yellow immediately. After stirring for 4 h, the mixture was diluted with H_2O and extracted with ethyl acetate. The combined extracts were washed with H_2O and saturated K_2CO_3 solution, dried, and concentrated to yield a yellow oil which was dissolved in 40 mL of dry THF and cooled in ice; 10 mL of 30% H_2O_2 was then added dropwise at 0–4 °C. Stirring was continued for 17 h. The resulting mixture was diluted with H_2O and extracted with ethyl acetate. The combined extracts were washed with saturated NaCl solution and dried, and the solvent was removed to afford 3.26 g of solid material. This was recrystallized from ether/hexane to give 2.96 g (85%) of *exo*-10,10-dibromo[4.3.1]propell-2-ene 4-acetate: mp 79–82 °C; IR (CCl_4) 3045, 1745, 1630, 1235 cm^{-1}; ^{1}H NMR (CCl_4) δ 5.7 (brd s, 2 H), 5.35–4.95 (m, H_4), 2.8–1.5 (m, 11 H, including an acetate s at δ 2.0). Anal. Calcd for $C_{12}H_{14}O_2Br_2$: *m/e* 347.9374. Found: *m/e* 347.9361.

To a solution of 2.04 g of the above acetate in 10 mL of MeOH was added 68 mL of a 1.0 M KOH/95% MeOH solution. The resulting reaction mixture was stirred for several hours (or overnight), whereafter H_2O was added, the MeOH evaporated, and 100 mL of $CHCl_3$ added. The $CHCl_3$ layer was washed with H_2O (until neutral) and then dried over K_2CO_3. Filtration and solvent evaporation afforded 1.78 g (99%) of **6**: mp 102.5–103 °C; IR ($CDCl_3$) 3613 (free OH), 3050, 1635, 1088 cm^{-1}; ^{1}H NMR (CCl_4) δ 5.84 (brd s, 2 H), 4.25 (apparent quartet, H_4), 2.8–1.4 (m, 9 H). Anal. Calcd for $C_{10}H_{12}Br_2O$: C, 38.99; H, 3.93. Found: C, 38.87; H, 3.87.

***exo*-[4.3.1]Propell-2-en-4-ol (7).** A mixture of 50 mg (0.16 mmol) of **6** and 118 mg (0.41 mmol) of *n*-Bu_3SnH[13] was heated in an 80 °C oil bath for ca. 7 h. After cooling, the resulting material was chromatographed on a preparative thin-layer plate utilizing 95% ethereal hexane as the developing solvent. Obtained was 19 mg (81%) of **7**: IR (CCl_4) 3630 (s, free OH), 3595–3170 (brd, OH), 3040, 3010, 1640. 1030 cm^{-1}; ^{1}H NMR (CCl_4) δ 6.60 (d, H_2, J = 10 Hz), 5.48 (dd, H_3, J = 5 and 10 Hz), 4.15 (q, H_4 J = 5 Hz), 2.3–1.1 (m, 9 H), 0.76 (center of AB quartet, 2 H_{10}, J = 5 Hz). Anal. Calcd for $C_{10}H_{14}O$: *m/e* 150.1045. Found: *m/e* 150.1042.

***endo*-10,10-Dibromo[4.3.1]propell-2-en-4-ol (8).** To a solution of 7.0 g (23.5 mmol) of **5**[8] in 20 mL of $CHCl_3$ was added, at 0 °C, a solution of 5.0 g (24.5 mmol) of *m*-chloroperbenzoic acid (*m*-CPBA) in 60 mL of $CHCl_3$. After stirring the reaction mixture for 4 h at room temperature, a dilute $NaHSO_3$ solution was added to destroy any excess *m*-CPBA. After dilution with ether, the organic phase was washed with a 5% NaOH solution and a saturated NaCl solution and dried over K_2CO_3. Filtration and evaporation of solvent afforded a white solid identified as *endo*-3,4-epoxy-10,10-dibromo[4.3.1]propellane (7.2 g, 98%): mp 102–104 °C; IR (CCl_4) 1190 cm^{-1}; ^{1}H NMR (CCl_4) δ 2.9 (brd s, 2 H), 2.6–1.4 (m, 10 H). Anal. Calcd for $C_{10}H_{12}Br_2O$: *m/e* 305.9255. Found: *m/e* 305.9256.

A solution of 0.24 mL (3.6 mmol) of Me_2NH in 5 mL of THF was cooled to 0 °C in a flame-dried flask. To this was added 2.7 mL (3.6 mmol) of 1.33 M *n*-BuLi (previously titrated with diphenylacetic acid). After stirring the resulting mixture for 15 min, a solution of 0.74 g (2.4 mmol) of the above synthesized epoxide in 10 mL of THF was

added dropwise via syringe. After completion of the addition, stirring was continued for 5 min, after which the mixture was diluted with ether, washed with 1 N HCl and then a saturated NaCl solution, dried over Na_2CO_3, filtered, and stripped of solvent. The residue was chromatographed on a silica gel column. Elution with 80% ethereal hexane afforded 0.16 g of starting epoxide; further elution with 67% ethereal hexane provided 0.45 g (78%) of **8**: mp 88.5–89.5 °C; IR (KBr) 3500–3100 (OH), 3020, 2920, 1630, 1430, 1010 cm^{-1}; ^1H NMR (CCl_4) δ 5.98 (center of apparent d with 2 Hz splitting, 2 H), 4.15 (m, H_4), 2.5–1.5 (m, 9 H). Anal. Calcd for $C_{10}H_{12}Br_2O$: C, 39.00; H, 3.95; Br, 51.88. Found: C, 39.17; H, 3.93; Br, 51.83.

***endo*-[4.3.1]Propell-2-en-4-ol (9).** Into a dry NMR tube was introduced 0.106 g of benzene (internal standard), 0.354 g (2.0 mmol) of *n*-Bu_3SnH,[13] and 0.083 g (0.27 mmol) of **8**. The mixture became instantly warm, but was then cooled in liquid N_2 and sealed. The tube was then placed in an NMR probe and the reaction followed over a 24-h period (tube was left in probe continuously). After 3 h, integration indicated that ca. 38% of monobromocyclopropyl products and ca. 55% of **9** had been formed. After 24 h, only ca. 8% of monobromocyclopropyl products remained, while ca. 92% of **9** had been produced. The tube was then opened, and pure **9** was isolated via thin-layer chromatography: IR (CCl_4) 3610 (free OH), 3340 (brd, OH), 3060, 3015, 3000, 2920, 1630, 1450, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.05 (dd, H_2, $J_{2,3}$ = 10 Hz, $J_{2,4}$ = 2.5 Hz), 5.38 (dd, H_3, $J_{3,4}$ = 1.5 Hz), 4.15 (m, H_4), 2.7–0.8 (m, 9 H), 0.60 (center of AB quartet, 2 H_{10}, J = 5 Hz). Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.99; H, 9.40.

[4.3.1]Propell-2-en-4-one (10). The oxidations of **7** and **9** were performed according to the method of Brown.[14]

(1) From 7. To a stirring solution of 38.5 mg (0.26 mmol) of **7** in 1 mL of Et_2O at 0 °C was added 0.17 mL of chromic acid solution (prepared according to Brown[14]). The reaction mixture was stirred for 10 min at 0 °C, following which the cooling bath was removed and the solution allowed to stir for an additional 2 h. The now green solution was diluted with ether, washed with saturated $NaHCO_3$ and then saturated NaCl, and dried over $MgSO_4$. Filtration and evaporation gave 25 mg of crude yellow oil. Thin-layer chromatographic purification (90% ethereal hexane) gave 20.5 mg (54%) of **10**: IR (CCl_4) 3070, 3030, 1680, 1660, 1610, 1400 cm^{-1}; ^1H NMR (CCl_4) δ 7.10 (d, H_2, $J_{2,3}$ = 10 Hz), 5.56 (d, H_3), 2.82 (d, $H_{5\text{-endo}}$, $J_{5\text{-exo},5\text{-endo}}$ = 18 Hz), 2.32 (d, $H_{5\text{-exo}}$), 2.1–1.3 (m, 6 H), 1.17 (d, H_{10A}, $J_{10A,10B}$ = 5 Hz), 0.37 (d, H_{10B}). Anal. Calcd for $C_{10}H_{12}O$ (P − 1, relative intensity 19% of P): *m/e* 147.0810. Found: *m/e* 147.0804.

(2) From 9. The above procedure was used to oxidize 0.039 g (0.26 mmol) of **9** in 3 mL of Et_2O. The yield of **10** was ca. 30 mg (78%).

***syn*-10-Bromo-1,6-diacetoxybicyclo[4.3.1]dec-2-en-4-ol (13).** In a 250-mL flask was dissolved 10 g (30 mmol) of **12** in 80 mL of ether. After cooling to 0 °C, 62 mL (62 mmol) of a 1 M BH_3·THF solution was added dropwise. The solution was then allowed to warm to 25 °C and stirred an additional 2 h. The solution was again cooled to 0 °C, and the excess borane was cautiously destroyed with water. After the addition of 100 mL of ether, a solution of 18 g (60 mmol) of sodium dichromate in 12 mL of concentrated H_2SO_4 and 160 mL of H_2O was added, following which the solution was allowed to warm to 25 °C and stirred for 16 h. The solution was then transferred to a separatory funnel, 100 mL of ether added, and the organic layer washed with two 100-mL portions of H_2O and one 100-mL portion of saturated $NaHCO_3$ solution. The organic solution was then dried over Na_2SO_4, and, after filtering, the solvent was removed on a rotary evaporator. Recrystallization from ether/hexane afforded 8.3 g (80%) of *syn*-10-bromo-1,6-diacetoxybicyclo[4.3.1]decan-3-one as white crystals: mp 93–94 °C; IR ($CDCl_3$) 3000, 2920, 2890, 1740, 1710, 1375, 1240, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.75 (m, H_{10}), 3.21 (center of AB q, J = 14 Hz, 2 H_2), 2.8–1.5 (m, 10 H), 2.02 (s, 6 H, OAc).

In a 50-mL, flame-dried, three-neck flask fitted with an N_2 inlet and outlet (static pressure of N_2 maintained during the reaction) and an addition funnel (septum) was dissolved 5 g (14.5 mmol) of the above ketone in 100 mL of dry THF, and the solution was cooled to −78 °C. In a separate flask was prepared 15 mmol of LDA by the addition of 2.1 mL (15 mmol) of diisopropylamine to 9.4 mL (15 mmol) of 1.6 N *n*-BuLi in 50 mL of dry THF at −10 °C. After stirring for 15 min, the base solution was transferred to the addition funnel and diluted with another 50 mL of ether. The base solution was then added dropwise, and after the addition was complete the solution was stirred at −78 °C for 20 min followed by rapid quenching with a solution of 3.75 g (20 mmol) of phenylselenenyl chloride in 30 mL of dry THF. The solution was then warmed to 0 °C, and a solution of 5 mL of 30% H_2O_2, 5 mL of H_2O, and 0.3 mL of HOAc was added dropwise. After the addition, the solution was allowed to warm to 25 °C and stirred for 5 h. Another 5 mL of H_2O_2 was then added, and the solution was allowed to stir an additional 5 h. Much of the excess solvent was removed on a rotary evaporator, and 100 mL of ether was then added. The solution was transferred to a separatory funnel and the aqueous layer extracted twice with 100-mL portions of ether. The ether fractions were combined, washed twice with 100-mL portions of saturated NH_4Cl solution, and dried over Na_2SO_4. After filtering, the solvent was removed on a rotary evaporator and the product chromatographed on silica gel (hexane/ether) to afford 3 g (60%) of *syn*-10-bromo-1,6-diacetoxybicyclo[4.3.1]dec-2-en-4-one as white crystals: mp 107–108 °C; IR ($CDCl_3$) 2960, 1740, 1670, 1370, 1240, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.42 (dd, H_2, $J_{2,3}$ = 14 Hz, $J_{2,10}$ = 2.5 Hz), 6.02 (d, H_3), 5.76 (narrow m, H_{10}), 3.31 (narrow m, 2 H_5), 2.7–1.5 (m, 6 H), 2.10 (s, 3 H, OAc), 2.02 (s, 3 H, OAc). Anal. Calcd for $C_{14}H_{17}O_5Br$: *m/e* 344.0260. Found: *m/e* 344.0261.

(1) K-Selectride.[15] The above enone (100 mg, 0.3 mmol), dissolved in 10 mL of dry THF, was then placed in a 50-mL, flame-dried, three-neck flask fitted with an N_2 inlet and outlet (static pressure of N_2 maintained during the reaction) and an addition funnel septum). After cooling the solution to −78 °C, 1.2 mL (0.6 mmol) of potassium tri-*sec*-butylborohydride[15] (K-Selectride, 0.5 M in THF) was added dropwise. After the addition was complete, the solution was stirred for 1.5 h at −78 °C followed by quenching with saturated NH_4Cl solution. The solution was then transferred to a separatory funnel and extracted with three 50-mL portions of ether. The ether fractions were combined, washed twice with 50-mL portions of H_2O, and dried over Na_2SO_4. After filtering and removal of the solvent on a rotary evaporator, the resulting oil was purified by LC to afford 75 mg (72%) of **13**, mp 94–96 °C, assigned the endo configuration at C_4 (i.e., hydroxyl away from Br) on the basis of its ^1H NMR spectrum (see below).

(2) 9-BBN.[16] Following Brown's procedure,[16] 1.0 g (2.9 mmol) of the enone in 30 mL of THF was reduced with 9-BBN (6.0 mL, 0.5 M in THF) to afford 0.81 g of crude oil which was chromatographed on silica gel (35% ether/65% hexane as eluent) to give **13a** and **13b.**

syn-10-Bromo-1,6-diacetoxybicyclo[4.3.1]dec-2-en-*endo*-4-ol (**13a**): 121 mg (12%); mp 94–96 °C; IR ($CDCl_3$) 3620, 3460, 2980, 1740, 1295, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.95 (dd, H_2, $J_{2,3}$ = 13 Hz, $J_{2,10}$ = 2.5 Hz), 5.59 (m, H_3, H_{10}), 5.5–5.1 (m, H_4), 3.0–1.5 (m, 9 H), 2.02 (s, 3 H, OAc), 2.01 (s, 3 H, OAc). Anal. Calcd for $C_{14}H_{19}O_5Br$: *m/e* 346.0416. Found: *m/e* 346.0427.

syn-10-Bromo-1,6-diacetoxybicyclo[4.3.1]dec-2-en-*exo*-4-ol (**13b**): 328 mg (33%); mp 124–127 °C; IR ($CDCl_3$) 3620, 3450, 1735, 1250, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.80 (brd s, H_2, H_3), 5.67 (brd s, H_{10}), 5.0–4.5 (m, H_4), 3.2–1.4 (m, 9 H), 2.13 (s, 6 H, OAc). Anal. Calcd for $C_{14}H_{19}O_5Br$: *m/e* 346.0416. Found: *m/e* 346.0420.

Registry No.—**5**, 38749-47-2; **6**, 67421-43-6; **7**, 67421-44-7; **8**, 67462-75-3; **9**, 67462-76-4; **10**, 67421-45-8; **12**, 58738-40-2; **13a**, 67421-46-9; **13b**, 67426-17-9; i, 17048-59-8; ii, 67421-49-2; iii, 67462-77-5; *exo*-10,10-dibromo[4.3.1]propell-2-ene 4-acetate, 67421-47-0; *endo*-3,4-epoxy-10,10-dibromo[4.3.1]propellane, 67421-48-1; *syn*-10-bromo-1,6-diacetoxybicyclo[4.3.1]dec-2-en-4-one, 67452-69-1; *syn*-10-bromo-1,6-diacetoxybicyclo[4.3.1]decan-3-one, 67426-16-8.

References and Notes

(1) This is Part 20 of the "Propellanes" series.
(2) This work was supported in part by the NSF, the ISU Research Foundation, and a Departmental Young Faculty Development Award.
(3) Alfred P. Sloan Fellow, 1976–1978.
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(5) (a) K. B. Sharpless and R. F. Lauer, *J. Org. Chem.*, **39**, 429 (1974); (b) D. L. J. Clive, *J. Chem. Soc., Chem. Commun.*, 100 (1974).
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(9) P. Warner, S. Lu, E. Myers, P. DeHaven, and R. A. Jacobson, *J. Am. Chem. Soc.*, **99**, 5102 (1977).
(10) Singlet oxygen did not react with **12**, while the epoxide generated from **12** did not react with LDA/Et_2O or with benzene selenolate anion.[11] Even Br_2 (CH_2Cl_2) did not add to **12**, but rather reacted slowly at room temperature to afford allylic substitution products.
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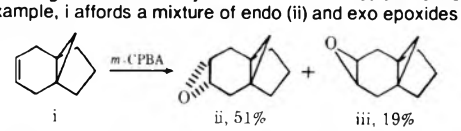
(12) Indeed the high stereoselectivity observed for **5** is also due to the bromines. For example, i affords a mixture of endo (ii) and exo epoxides (iii).



i ii, 51% iii, 19%

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Selective Lithiation/Carbonation of Polyhalobenzenes: An Improved Synthesis of Furosemide-7-^{14}C

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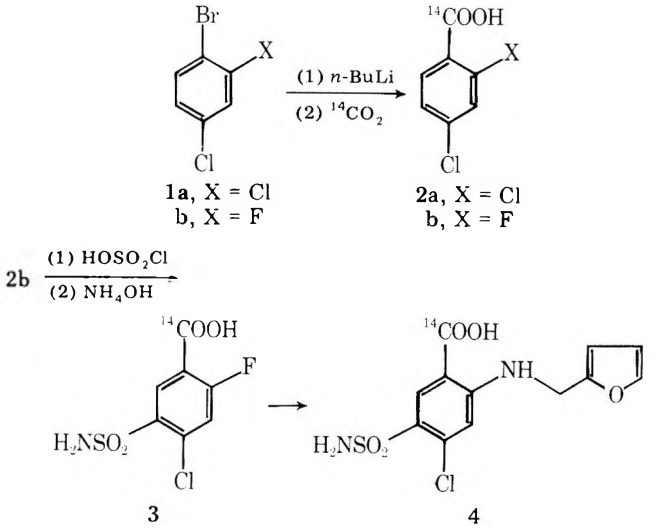
Received June 19, 1978

Furosemide (4) usually has been prepared from 4-chloro-2-fluorobenzoic acid (**2b**) by chlorosulfonation and ammonolysis to the sulfonamide (**3**) followed by reaction with furfurylamine.[1-3] In an earlier synthesis of furosemide-7-^{14}C,[4] the required labeled intermediate **2b** was prepared from 4-chloro-2-fluoroaniline and dipotassium diamminocupricyanide-^{14}C by a modified Sandmeyer reaction followed by hydrolysis of the resulting 4-chloro-2-fluorobenzo-^{14}C-nitrile.



The more direct preparation of **2b** from 4-chloro-2-fluorobromobenzene (**1b**) by butyllithium exchange and carbonation was not attempted because the closely related 2,4-dichlorobromobenzene (**1a**) reportedly did not afford 2,4-dichlorobenzoic acid (**2a**) by that procedure.[5]

We now report that, in fact, both **1a** and **1b** do undergo selective lithiation/carbonation to afford the corresponding acids **2a** and **2b** in high yields. The conversion of carbon-14 labeled **2b** to furosemide-7-^{14}C (**4**) by a simplified version of the earlier process[4] is also described.

Reaction of **1a**[6] in ether with *n*-butyllithium at −80 °C for a short time followed by carbonation at −80 °C with carbon-14 dioxide afforded the acid **2a** in 98% yield based on carbon-14 dioxide. Similarly, lithiation/carbonation of **1b**[7] gave **2b** in quantitative radiochemical yield. Treatment of the labeled **2b** with chlorosulfonic acid followed by concentrated ammonium hydroxide afforded labeled **3** in 91.5% yield (crude). Reaction of the crude **3** with furfurylamine gave crude furosemide-7-^{14}C (**4**) in 32% yield.

Experimental Section

Melting and boiling points are uncorrected. Radioactivity was measured by the liquid scintillation technique using a Packard Tricarb Model 2010 spectrometer. Radiochemical purity was determined on thin-layer chromatograms with a Packard Model 7201 radiochromatogram scanner system. Spectra were recorded on standard instruments. All reactions were conducted under nitrogen unless otherwise indicated.

2,4-Dichlorobenzoic-7-^{14}C Acid (2a). A solution of 1-bromo-2,4-dichlorobenzene[8] (**1a**; 1.02 g, 4.5 mmol) in anhydrous diethyl ether (15 mL) contained in an ordinary round-bottom flask was frozen with liquid nitrogen, and a solution of *n*-butyllithium in hexane (3 mL, 2.8 mmol) was added and frozen. The flask was evacuated and then warmed to −80 °C with stirring. From 2 to 5 min after the reaction mixture became a homogeneous solution, it was refrozen with liquid nitrogen and carbon-14 dioxide (1.51 mmol) was transferred into the flask. The mixture was warmed to −80 °C, stirred for 20 min, made alkaline with 0.9 N sodium hydroxide solution (10 mL, 9 mmol), and thoroughly extracted with ether, which was discarded. Acidification of the aqueous phase with dilute sulfuric acid and extraction with ether afforded **2a** (282 mg, 1.48 mmol), 98% yield based on carbon-14 dioxide. Nonradioactive material prepared by the same procedure from ordinary carbon dioxide was found to be identical with authentic 2,4-dichlorobenzoic acid by melting point, IR, and TLC (silica gel; dichloromethane-ethyl acetate–acetic acid, 8:1:1 v/v/v).

4-Chloro-2-fluorobenzoic-7-^{14}C Acid (2b). In the same manner, 4-chloro-2-fluorobromobenzene[7] (**1b**; 440.3 mg, 2.1 mmol) was metalated with *n*-butyllithium (1.17 mmol) and carbonated with carbon-14 dioxide (1.08 mmol; specific activity 59.1 mCi/mmol) to afford **2b** in quantitative yield (209 mg). The product was radiochemically pure (TLC on silica gel; benzene–ethyl acetate–formic acid, 8:1:1 v/v/v). Material prepared with ordinary carbon dioxide in the same way was identical with authentic 4-chloro-2-fluorobenzoic acid.[1]

4-Chloro-2-fluoro-5-sulfamoylbenzoic-7-^{14}C Acid (3). The dry 4-chloro-2-fluorobenzoic-7-^{14}C acid was heated with freshly distilled chlorosulfonic acid (0.655 mL, 9.7 mmol) at 155 °C for 2 h. When cool, the entire reaction mixture was diluted with dichloromethane (4 mL) and transferred to a 10 mL addition funnel using additional dichloromethane (4 mL). The addition funnel was attached to a 100-mL flask containing concentrated ammonium hydroxide (4 mL) cooled to −30 °C, the dichloromethane solution was added dropwise very slowly with stirring, and the mixture was allowed to warm to room temperature. Evaporation of the dichloromethane under reduced pressure left an aqueous phase which was transferred to a liquid–liquid extractor, acidified with 6 N hydrochloric acid (1 mL), and extracted with diethyl ether for 20 h to afford the crude product (**3**; 248 mg, 0.98 mmol). Thin-layer chromatography (silica gel; ethylene dichloride–ethyl acetate, 2:3) showed the product to be approximately 60% of **3**, which was used in the next step without purification.

4-Chloro-*N*-furfuryl-5-sulfamoylanthranilic-7-^{14}C Acid (Furosemide-7-^{14}C; 4). The crude **3** (248 mg) was stirred with dioxane (1 mL) and freshly distilled furfurylamine (0.32 mL) at 110 °C for 2.5 h. Concentration of the reaction mixture under reduced pressure left a dark brown residual oil which was stirred vigorously with ethyl acetate (3 mL) and extracted six times with water (3 mL). Concentration of the aqueous extracts left a residue which was crystallized from methanol–water, 1:1 (4 mL), to give crude **4** (114.5 mg; radiochemical purity 95% by TLC using silica gel plates developed with acetonitrile–acetic acid, 99:1; R_f 0.68). Recrystallization of 15.1 mg of crude **4** with 20.2 mg of unlabeled furosemide (**4**) from methanol–water, 1:1 (2 mL), afforded 23 mg of radiochemically pure **4** of specific activity 57.2 μCi/mg.

Registry No.—**1a**, 1193-72-2; **1b**, 1996-29-8; **2a**, 67700-16-7; **2b**, 54416-83-0; **3**, 54416-34-1; **4**, 54416-85-2; $^{14}CO_2$, 51-90-1; furfurylamine, 617-89-0.

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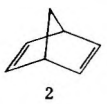
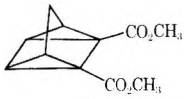
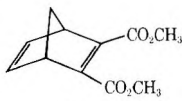
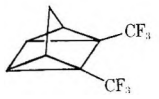
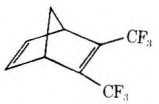
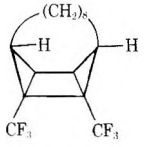
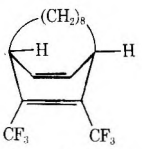
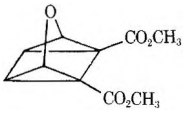
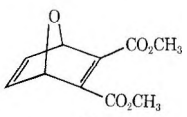
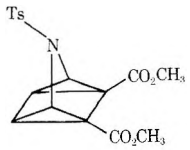
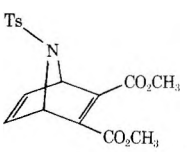
Communications

The Ease of Oxidation of Highly Strained Polycyclic Molecules

Summary: A quantitative measure of the ease of oxidation of highly strained polycyclic compounds has been provided and the effect of substituents has been evaluated.

Sir: Although recent years have witnessed a plethora of studies on the chemical and physical properties of highly strained polycyclic molecules, including studies on their ease of reduction,[1] relatively little is known about the stability of such systems under oxidative conditions. It might have been assumed that highly strained polycyclic ring systems would be stable to oxidation, since examples of the synthesis of bicyclo[1.1.0]butane derivatives under oxidative conditions existed.[2] However, one of us[3] recently demonstrated that quadricyclane (1) could be oxidized by silver ion in methanol. It has also been shown that 1 was subject to electrochemical oxidation in methanol.[4,5] We now wish to report that highly strained polycyclic molecules can be oxidized with surprising ease.

Table I. Half-Wave Oxidation Potentials for a Series of Strained Polycyclic Compounds and Their Isomers vs. SCE

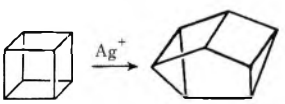
column I		column II	
compd	$E_{1/2}$, V	compd	$E_{1/2}$, V
 1	0.91	 2	1.56[a]
 3	1.64	 4	2.06
 5	2.19	 6	~2.51[b]
 7	~2.60[b]	 8	2.41
 9	1.95	 10	2.26
 11	1.95, 2.36	 12	2.20, 2.37[c]
 13	2.12	 14	1.95[d]
 15	1.91	 16	2.03[e]

[a] Lit.[6] value 1.54 V. [b] Values above 2.5 V are less accurate than the other values listed because they appear as shoulders on the curve for solvent oxidation. [c] Curves for these two values overlap. Thus, these values are slightly less accurate than the rest of the values in this table. [d] Lit.[6] value 2.02 V. [e] Lit.[7] value 1.96 V.

Table I lists the half-wave oxidation potentials for a series of strained polycyclic molecules and their isomers. The values were obtained versus a saturated calomel electrode (SCE) using single sweep voltametry (sweep rate 100 mV/s) on a Princeton Applied Research Model 174 polarographic analyzer equipped with platinum electrodes. The solvent was high purity acetonitrile which contained 0.1 M lithium perchlorate (supporting electrolyte) and ~10^{-3} M substrate.

As can be seen from Table I, quadricyclane (1) has an amazingly low oxidation potential. Hence, it is not surprising that it was easily oxidized by silver ion in methanol. Even substitution of 1 by strong electron-withdrawing groups, such as in **3**, failed to raise the oxidation potential to what one might expect for an olefin (to say nothing about what might be predicted for a saturated hydrocarbon).[8]

It is of interest to compare the ease of oxidation of the compounds in column I with their isomers in column II. Compounds **1**, **3**, and **5** are all more easily oxidized than are their photochemical precursors **2**, **4**, and **6**, respectively. Compounds **1**, **3**, and **5** are all converted back to the corresponding dienes in the presence of certain transition-metal catalysts.[9,10] Since a catalyst facilitates an isomerization in these examples, it can be safely assumed that the dienes are more thermodynamically stable than the corresponding quadricyclanes. Thus, superficially it would appear that the less stable compounds were the more easily oxidized. Consideration of the interconversion of **7** and **8** would seem to support this concept. In this case, the diene was more easily oxidized than the quadricyclane, **7**. In line with relative stabilities, **8** was converted into **7**, both photochemically and in the presence of a transition-metal complex.[10] Similar comparisons can be made for the interconversion of **13** and **14**[11] and for the catalytic isomerization of **15** to **16**.[12] While these two cases are more complicated in that a hydrogen transfer was involved, in each case the thermodynamically more stable isomer is the more difficult to oxidize. On the basis of this comparison, one might be tempted to equate ease of oxidation with thermodynamic stability or strain energy. We hasten to warn that such extrapolations, if valid at all, are only valid within certain very narrow limitations. Electron transfer undoubtably occurs from the highest occupied molecular orbital (HOMO) of the strained ring system in an anodic oxidation.[13] Such orbital energies do not correlate in general with either thermodynamic stability or strain energy. This is amply demonstrated by comparison of **17** with **18**. Whereas, **18** is

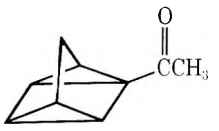


17 18

more easily oxidized than **17** ($E_{1/2}$ vs. SCE_{18} = 1.73 V; $E_{1/2}$ vs SCE_{18} = 1.54 V), **17** was readily isomerized to **18** in the presence of silver ion.[14] This represents a clear-cut case where the thermodynamically more stable isomer is also the more easily oxidized!

Comparison of **3**, **9**, and **11** illustrates the effect of heteroatom incorporation into the strained polycyclic molecule on its ease of oxidation. To a first approximation, the oxygen

bridge of **9** and the nitrogen bridge of **11**[15] function primarily as slightly electronegative substituents. In connection with substituent effects, the oxidation curve of **19** was of interest. Two half-wave potentials were observed. The lower wave



19

showed $E_{1/2}$ at 1.00 V while the second appeared at $E_{1/2}$ = 1.87 V. Two different oxidative processes are indicated. It is interesting to speculate as to whether these two waves reflect the oxidation of the two different cyclopropyl moieties.[16]

In summary, we have provided a quantitative measure of the ease of oxidation of highly strained polycyclic compounds. The effect of substituents has been evaluated. We are continuing to study both the mechanistic detail and products of these facile oxidations.

Acknowledgment. We are indebted to the National Science Foundation and the General Electric Foundation for a grant to P.G.G. which supported this investigation.

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(15) The second wave which was observed for both **11** and **12** was attributed to the aryl sulfonamide moiety. Little change occurred in the oxidation in changing from **11** to **12**.
(16) This would require that the two different cyclopropyl rings of **19** have different half-wave oxidation potentials. This should be the case, since two different cation radicals would be generated from the oxidation of the two different rings. Obviously, the two waves which were observed reflect the existence of two close lying high-energy occupied molecular orbitals. The question which requires answering is whether these two high-energy orbitals are associated with the two different cyclopropyl moieties, respectively. We are currently carrying out studies designed to determine the answer to this question.

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Received July 5, 1978

A New Synthesis of Amides and Macrocyclic Lactams

Summary: New and general routes to amides and lactams of up to 32 atoms in circumference are described based on boron-containing active esters.

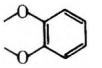
Sir: We wish to report that carboxylic acids react rapidly and smoothly with catecholborane to afford 2-acyloxy-1,3,2-benzodioxaborolanes (**1c**). As one aspect of a general program to prepare clinically interesting maytansinoids and ansamycins,[1] we herein document the use of this mild reaction as the essential carboxyl-activation step for the synthesis of amides and macrocyclic lactams.[2]

Simple acyloxyboranes such as **1a** and **1b** react with amines to furnish amides in moderate yield, but uniformly low conversion.[3] Mechanistic studies by Pelter in 1970 revealed that the leaving groups **2a,b** ejected in this process fragment to liberate 1 equiv of ROH which competitively destroys the active intermediate by attack at the boron atom of **1**.[4]

$$RCO_2BR_1R_2 + R_3NH_2 \longrightarrow RCONHR_3 + HOBR_1R_2$$

1a, R_1, R_2 = alkoxy — **2**

b, R_1, R_2 = 

c, R_1, R_2 = 

We reasoned that acyloxyborane **1c** might circumvent these difficulties, since its leaving group, 2-hydroxy-1,3,2-benzodioxaborolane, ought to resist disproportionation. Moreover, any breakdown of **2c** would form a relatively nonnucleophilic phenol still attached to boron. We further expected the aromatic ring's electron-withdrawing character to enhance the reactivity of the active ester. Modulation of this effect through substitution of polar groups on the arene would enable a high degree of control in designing preparatively useful reagents.

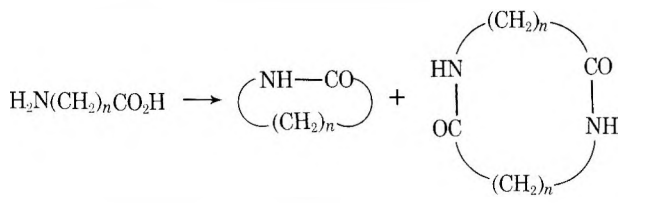
Catecholborane (**3**)[5] is available from Aldrich Chemical Company[6] and converts carboxylic acids (THF, room temperature, 30–60 min) to the corresponding acyloxybenzodioxaborolanes (IR λ_{max} 1740 cm^{-1}) free of anhydride byproduct. At ambient temperatures catecholborane is ideally suited for the C-activation of complex substrates, since it is inert toward alkyl and aryl halides, alkenes, alkynes, amides, anhydrides, disulfides, esters, nitriles, nitro compounds, sulfides, and sulfones.[7] Subsequent addition of an amine to **1c** rapidly forms the amide in greatly improved yield (Table I). Even optically active acids such as *N*-benzoyl-L-leucine can be coupled with no measurable loss (<2%) of enantiomeric

Table I. Formation of Amides from Nonanoic Acid Using Catecholborane

amine	product[a]	% yield[b]
benzylamine	$C_8H_{17}CONHCH_2Ph$	92
pyrrolidine	$C_8H_{17}CON$⟨⟩	85
butylamine	$C_8H_{17}CONHCH_2CH_2CH_2CH_3$	84
morpholine	$C_8H_{17}CON$⟨O⟩	74
benzylmethylamine	$C_8H_{17}CON(CH_3)CH_2Ph$	74
glycine ethyl ester	$C_8H_{17}CONHCH_2CO_2CH_2CH_3$	63

[a] Obtained by inverse addition of the acyloxyborane to the amine (2 equiv) in THF at −78 °C. [b] Product identity was established by comparison with authentic samples. In some cases filtration through a short column of silica gel was necessary to obtain pure product.

Table II. Formation of Lactams from ω-Amino Acids Using Catecholborane



ω-amino acid: n =	lactam: size (% yield)	dimer: size (% yield)[a]	dimer properties
3	5 (>95)		
5	7 (85)		
6	8 (6)	16 (18)	mp 246–249 °C,[b] *m/e* 255 (M^+), 128 (base)
7		18 (10)	mp 273–275 °C,[b] *m/e* 282 (M^+), 142 (base)
11	13 (6)	26 (25)	mp 203–206 °C, *m/e* 394 (M^+, base)
12	14 (9)	28 (22)	mp 152–154 °C, *m/e* 422 (M^+, base)
14	16 (13)	32 (17)	mp 168–171 °C, *m/e* 478 (M^+, base)

[a] All monomers were identified by comparison with authentic samples. Dimers were fully characterized by IR, NMR, and mass spectrometry. [b] This melting point was identical with that of a known sample of dimer (ref 12).

purity.[8] Both 3-methoxy- and 4-nitrocatechol also form the derived boranes in standard fashion and a preliminary survey of their reactivity suggests that the former comprises a somewhat superior coupling reagent.

Our interest in closing rings at the site of an amide bond requires a reagent that is capable of carboxyl activation without interference by a basic amino group. The direct addition of catecholborane to a homogeneous 1:1 mixture of nonanoic acid and benzylamine in THF simulates lactamization conditions and produces the desired nonanoic acid *N*-benzylamide in 85% yield. These "in situ" couplings are general and small amounts of pyridine (2–3 equiv) accelerate them, possibly by transforming the acyloxyborane to a more reactive acylpyridinium salt.

Most parent ω-amino acids are but sparingly soluble in nonaqueous solvents, nevertheless we can prepare their lactams by the acyloxyborane technique under heterogeneous conditions. For example, when 6-aminocaproic acid (1.85 mmol) is suspended in pyridine (30 mL) at 80 °C and treated with catecholborane (2.78 mmol), the solid slowly dissolves and caprolactam is formed in 85% yield. γ-Aminobutyric acid similarly affords 2-pyrrolidinone (>95%). Table II summarizes our experience with a series of homologous substrates. Substantial proportions of medium-ring monomers are not formed, although the cyclization becomes more favorable in the case of 14- and 16-membered lactams. In each of these experiments, controls clearly establish that no ring closure whatsoever occurs if the borane is omitted.[9]

Our results contrast with similar studies on the formation of macrocyclic lactones[10] and may reflect more stringent geometric demands imposed on the ring and on the ring-forming process by the planar amide bond. However the heterogeneous conditions we describe are of unknown (but probably high) dilution and make an accurate assessment of rate data impossible. Recently we have discovered the combination of soluble ω-amino acid tetra-*n*-butylammonium salts with *B*-chlorocatecholborane in pyridine also produces lactams and that under such homogeneous circumstances, dimer formation does not occur at up to 0.05 M concentrations. Thus, for example, the 6-, 12-, and 15-carbon ω-amino acid salts furnish only the corresponding monomeric lactams in yields of 65, 15, and 17%, respectively. This result suggests either that two independent cyclization mechanisms are operating or that the observed dimers arise from complex surface effects. In future work we hope to explore these possibilities.

Acknowledgment is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We also thank the National Institutes of Health and Eli Lilly and Company for partial financial assistance.

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S-Oxides of Tetrathiafulvalenes

Summary: The first tetrathiafulvalene *S*-oxides have been synthesized. These include the mono *S*-oxides of tetrathiafulvalene, dibenzotetrathiafulvalene, and tetrakis(carbomethoxy)tetrathiafulvalene. The polarographic properties of these novel sulfoxides are described.

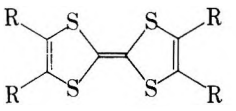
Sir: Tetrathiafulvalene (**1**, TTF) and its derivatives have been the subject of intensive chemical and physical study in recent years, due to the fact that many compounds of this group can form crystalline, electrically conducting charge-transfer salts.[1,2] This property is dependent upon the relative ease with which the TTF system can be oxidized by a variety of means to give the radical cation (**4**) or the dictation (**5**).[3,4] This type of one-electron or two-electron oxidation is, indeed, the only known transformation of the basic TTF system with the exception of the recently described[5] lithium–hydrogen interchange reaction of TTF. We now report the first synthesis of a new type of TTF oxidation product, namely a tetrathiafulvalene *S*-oxide.

Table I. Polarographic Half-Wave Potentials[a]

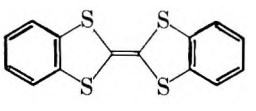
	$E_{1/2}^1$	$E_{1/2}^2$	$\Delta E_{1/2}$
6	+0.936	+1.10	0.164
7	+1.05	+1.21	0.160
8	+1.39	+1.55	0.160
TTF[8]	+0.342	+0.721	0.379

[a] Reversible oxidations in MeCN with added Et_4NClO_4 (0.05 *m*) vs. Ag/Ag^+ (0.1 N in MeCN) with a glassy carbon electrode as the working electrode; the resulting values are given in volts with respect to the saturated calomel electrode.

Reaction of TTF (**1**) with 1 equiv of *m*-chloroperbenzoic acid in a cooled (5–10 °C) two-phase system (CH_2Cl_2/aqueous



1, R = H
3, R = COOMe



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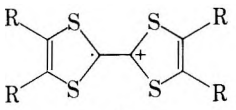

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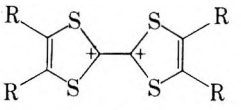

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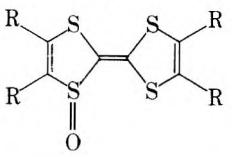
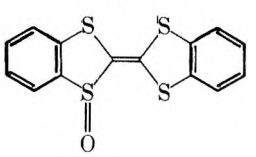


6, R = H
8, R = COOMe



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Na_2HPO_4) gave the pale yellow tetrathiafulvalene *S*-oxide **6**,[6] (68%): mp >90 °C dec; UV λ_{max} (EtOH) 208 (log ϵ 3.92), 265 sh (3.38), 295 (3.50), 350 sh (3.77), 388 nm (3.98). In a similar manner, dibenzotetrathiafulvalene (**2**) was converted (57%) to the lemon yellow *S*-oxide **7**: mp >195 °C dec; UV λ_{max} (EtOH) 208 (log ϵ 3.54), 220 sh (4.36), 296 (3.95), 406 nm (4.19). The highly electron-deficient tetrakis(carbomethoxy)tetrathiafulvalene (**3**) was less easily oxidized, but underwent a similar transformation at room temperature to give orange needles of *S*-oxide 8 (57%): mp >120 °C dec; UV λ_{max} (EtOH) 210 (log ϵ 4.65), 236 (4.52), 303 (4.07), 370 nm (4.17).

All three *S*-oxides (**6, 7,** and **8**) were quantitatively deoxygenated to the corresponding tetrathiafulvalenes (**1, 2,** and **3**) by P_2S_5 in CH_2Cl_2 at room temperature;[7] **8** was reduced most rapidly and **6** was reduced most slowly.

The infrared spectra (KBr) of compounds **6, 7,** and 8 all showed a strong band in the 9.7–9.9-μm region, attesting to the presence of the sulfoxide function. The asymmetry due to the single sulfoxide oxygen was clearly discernible in the NMR spectra of **6** and **8.** The NMR spectrum of **6** (Me_2SO-d_6) showed a clear AB quartet (J = 8 Hz) for R_1 (δ 7.65) and R_2 (δ 6.83); the effect of the sulfoxide oxygen is still noticeable, though barely so, in the second dithiole ring, in which protons R_3 and R_4 appear as apparent close singlets at δ 7.0 and 6.98, respectively. A close examination reveals an AB quartet (J = 8 Hz) for R_3 (δ 6.95) and R_4 (7.08). The NMR spectrum of tetraester **8** ($CDCl_3$) shows a similar influence of the sulfoxide function on the R_1 ester methyl resonance, which is deshielded (δ 3.90) in comparison to the remaining three ester methyls (singlet at δ 3.85).

The first ($E_{1/2}^1$) and second ($E_{1/2}^2$) polarographic half-wave potentials and their difference ($\Delta E_{1/2}$) for the *S*-oxides are given in Table I.

The $E_{1/2}^1$ values show that **6, 7,** and **8** undergo oxidation to their respective monocations less readily relative to the corresponding unoxidized parent donors,[4] while the oxidation sequence due to substituent effects remains the same: **6** > **7** > **8.** Further, a given sulfoxide monocation oxidizes to the dication more easily than the corresponding parent monocation. These systematic differences in oxidation properties of the parent donors and their *S*-oxides are related to the fact that the total free energy (ΔF) for oxidation in solution is a sum of electronic (ΔF_e), solvation (ΔF_s), and intramolecular distortion (ΔF_d) terms, $\Delta F = \Delta F_e + \Delta F_s + \Delta F_d$. The presence of the SO group would then change the molecular contributions to each of the three terms. For example, in addition to overall changes in the molecular electronic states (ΔF_e), the pyramidal bonding around S at each S–O site would markedly distort the TTF ring structure (ΔF_d) and introduce larger dipole moments within each ring (ΔF_s).

Dilute acetonitrile solutions of sulfoxides **6** and **7** give a greenish coloration on treatment with tetracyanoquinodimethane (TCNQ), suggestive of the formation of charge-transfer salts. The preparation of crystalline salts has so far been hampered by the thermal instability of **6** and **7,** as well as their very low solubility in dry nonprotic solvents.

Acknowledgment. This work was supported by grants from the National Science Foundation, CHE 76-83417, the MRL program grant DMR 76-00678, and NATO. We also thank Mr. Paul J. Nigrey for technical assistance.

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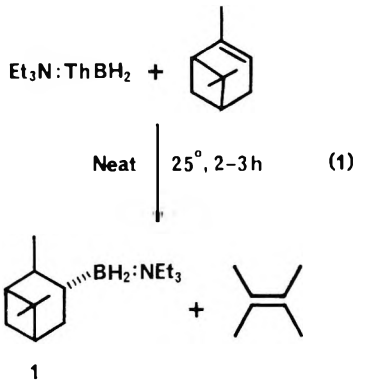
Simple Synthesis of Monoisopinocampheylborane of High Optical Purity

Summary: N,N,N′,N′-Tetramethylethylenediamine (TMED) reacts rapidly at 34 °C with diisopinocampheylborane (IPC_2BH) to displace α-pinene and produce the solid 1:2 adduct of the base and monoisopinocampheylborane (TMED·$2BH_2IPC$). Treatment of this adduct with boron trifluoride etherate precipitates the amine and generates free monoisopinocampheylborane in optical purities approaching 100%, much higher than that of the α-pinene (~94%) utilized in the synthesis of the IPC_2BH.

Sir: Recently the reaction of neat triethylamine–thexylboranes (Et_3N·$ThBH_2$) with neat α-pinene was reported to yield the triethylamine–monoisopinocampheylborane (Et_3N·BH_2IPC) (**1**) adduct (eq 1).[1] Triethylamine could be removed with either THF·BH_3[2] or Et_2O·BF_3[1] to produce the free monoisopinocampheylborane ($IPCBH_2$). Unfortunately, both Et_3N·BH_3 and Et_3N·BF_3 are highly soluble in the usual THF medium and are difficult to separate from the desired product.[1,2] This difficulty can be overcome by isolating the intermediate and placing it in a pentane solution from which



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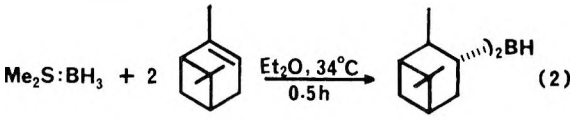
Et_3N-BF_3 can be crystallized out at −5 °C.[1] A further handicap is the fact that Et_3N-BH_2IPC is a liquid which cannot be purified readily. The $IPCBH_2$ reagent, which is highly promising for asymmetric hydroboration[2] and reductions,[3] has been previously synthesized in high optical purity by a relatively long and time-consuming process.[4] It appeared desirable, therefore, to develop a more simple, more direct synthesis of optically pure $IPCBH_2$. The discovery that $IPCBH_2$ forms a crystalline bis adduct with TMED[5] prompted us to explore the reaction between IPC_2BH and TMED as a potential solution to this problem.

The present procedure utilizes borane–methyl sulfide (BMS) in Et_2O for the rapid preparation of IPC_2BH,[6] a fast displacement of α-pinene by TMED, and a convenient removal of TMED from the product with Et_2O-BF_3. An unexpected development was the discovery that the bis adduct of TMED with $IPCBH_2$ separates in much higher optical purity than the α-pinene used to synthesize IPC_2BH. With this method the synthesis and storing of optically pure $IPCBH_2$ becomes a simple, rapid process. Diisopinocampheylborane (2) was prepared in 0.5 h by the reaction of α-pinene with BMS in Et_2O at 34 °C (eq 2). Addition of 0.5 equiv. of TMED at 34



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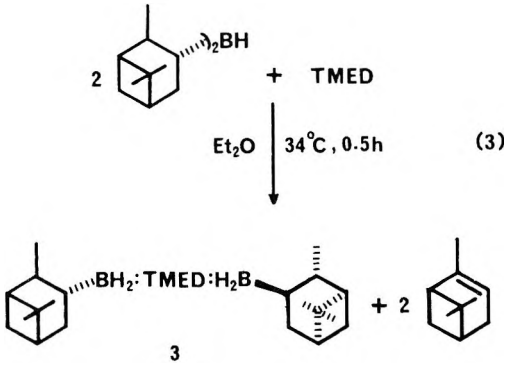
°C results in the displacement of α-pinene and the formation of TMED-$2BH_2IPC$ (3) (eq 3). The reaction is essentially



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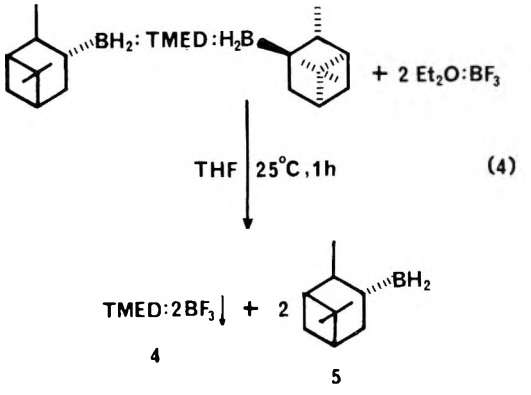
complete in 0.5 h. The reaction mixture is then transferred to a centrifuge tube. Upon cooling, the bis adduct 3 is thrown out as a crystalline solid. α-Pinene and methyl sulfide are removed by centrifugation, followed by decantation of the supernatant liquid. After washing with pentane, 3 is isolated in ~80% yield. Spectral (^1H NMR and ^{11}B NMR) data revealed that the derivative 3 is very pure. Methanolysis provided pure IPC-$B(OMe)_2$ by ^1H NMR. The isopinocampheol obtained after oxidation of 3 showed $[\alpha]^{25}_D$ −35.79° (c 0.9, C_6H_6), a value equal to the highest optical rotation previously achieved.[4] At this stage it is appropriate to point out that the α-pinene used in the preparation of 2 possessed only ~94% optical purity, and the intermediate 2 was not purified prior to the synthesis of 3.[4] Hence, an important outcome of this method is the fact that from an optically impure substrate the adduct 3 can be prepared in exceptionally high optical purity, approaching 100%.

Amine–boranes react sluggishly with olefins at 25 °C.[2] Thus, the removal of TMED from the adduct 3 is necessary to facilitate the hydroboration reaction. Fortunately, TMED can be very effectively removed from the adduct 3 with Et_2O-BF_3.[5] Thus, when Et_2O-BF_3 is added to a THF solution of 3 at 25 °C, TMED-$2BF_3$ (4) precipitates out within 1 h, leaving $IPCBH_2$ (5) in solution for ready hydroboration of olefins (eq 4).[2] The $IPCBH_2$ solution can be separated by decantation in nearly quantitative yield. Since the compound 4 is very inert, its removal is not crucial for further hydroboration.



4 5

The following procedure for the preparation of $IPCBH_2$ is typical. With the usual experimental setup, all operations were carried out under nitrogen in a 100-mL flask.[7] The flask was charged with borane–methyl sulfide (2.0 mL, 20.0 mmol) and anhydrous diethyl ether (11.3 mL). The reaction mixture was heated under reflux. Addition of (+)-α-pinene (7.36 mL, 46 mmol)[8] led to the quantitative formation of IPC_2BH (~20 mmol) in 0.5 h. TMED (1.51 mL, 10 mmol) was added to the refluxing solution and the refluxing was continued for another 0.5 h. The reaction mixture was then transferred to a centrifuge tube. On cooling the adduct 3 crystallized out. Methyl sulfide and α-pinene were removed by centrifugation, followed by decantation.[7] Solids were washed with pentane (3 × 5 mL) and dried under vacuum (12 mm) to provide 3.32 g (~80%) of TMED-$2BH_2IPC$: mp 140–141 °C (recrystallized from Et_2O); ^1H NMR ($CDCl_3$, Me_4Si) δ 1.00 (d, 6 H, J = 7 Hz), 1.1 (s, 6 H), 1.16 (s, 6 H), 2.63 (s, 12 H), 3.20 (s, 4 H); ^{11}B NMR (THF, relative to Et_2O-BF_3) δ +1.80 (br s). Oxidation of 3 with alkaline hydrogen peroxide afforded isopinocampheol, $[\alpha]^{27}_D$ −35.79° (c 0.9, C_6H_6). To liberate the free monoalkylborane 5, the adduct 3 (3.32 g, 8.0 mmol) was dissolved in THF (16 mL) and Et_2O-BF_3 (1.97 mL, 16 mmol) was added with constant stirring. After 1 h the solid TMED-$2BF_3$ was centrifuged and the supernatant liquid was analyzed for free monoalkylborane 5. Hydrolysis of an aliquot (1 mL) evolved hydrogen (~1.6 mmol, 100%). Another aliquot (10 mL) after oxidation with alkaline hydrogen peroxide provided isopinocampheol (8 mmol) by GLC analysis.

This new procedure thus describes a direct, rapid synthesis of IPC_2BH, optically pure TMED-$2BH_2IPC$, and $IPCBH_2$. The air stable solid adduct TMED-$2BH_2IPC$ alleviates handling and storing problems. Finally, the Et_2O-BF_3 procedure is generally useful for removal of TMED from the TMED-RBH_2 adducts, now readily available.

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(9) Postdoctoral Research Associate on Grant No. GM 10937 from the National Institutes of Health.

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Received June 1, 1978

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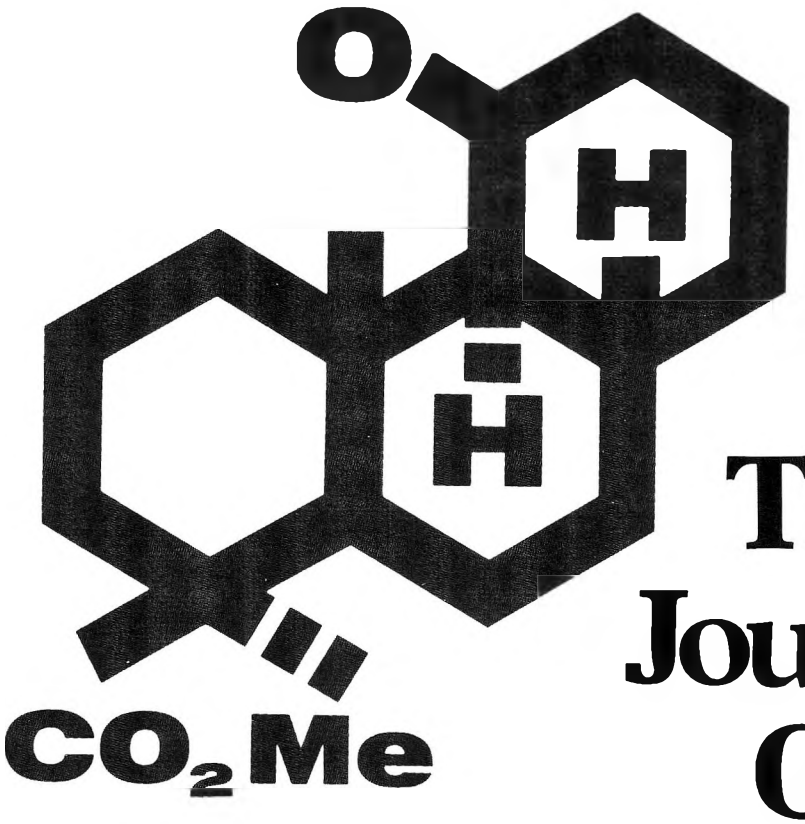

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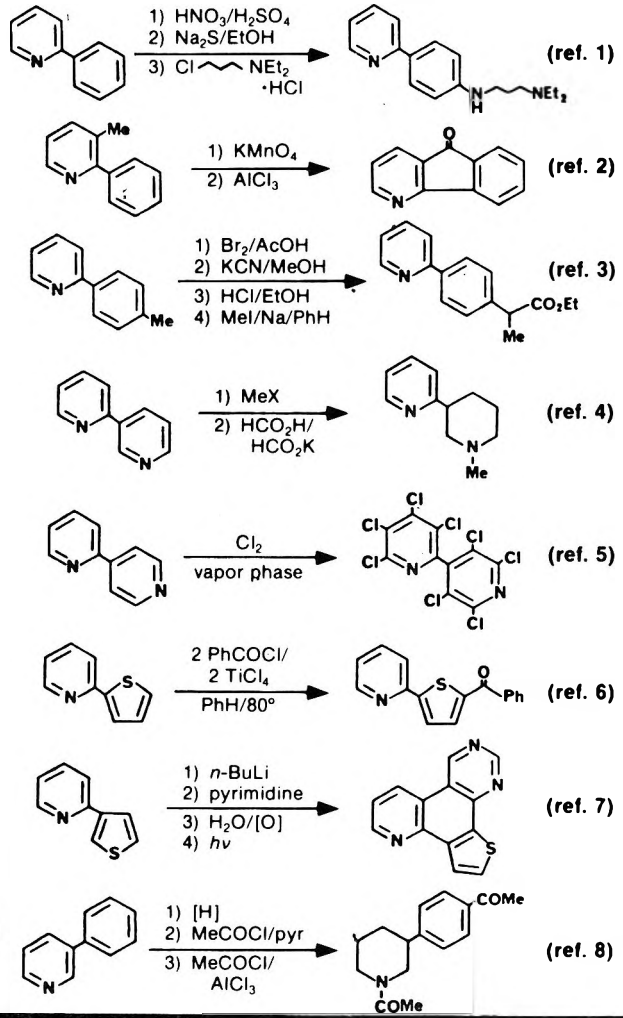

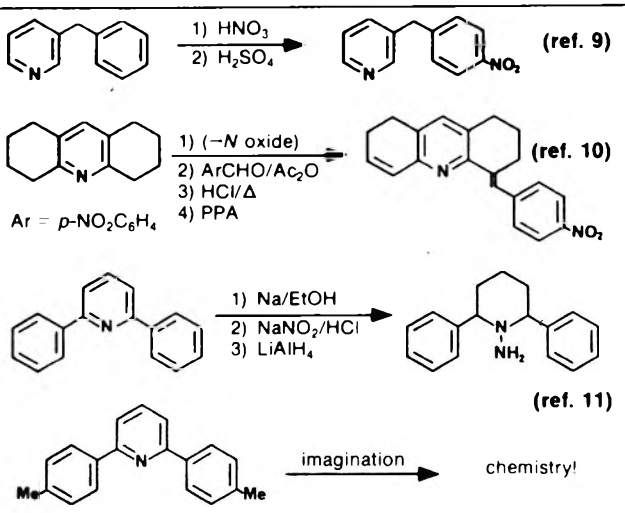

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P3,340-2	2-Phenylpyridine	10g $9.30; 50g $30.00
19,886-2	3-Methyl-2-phenylpyridine	10g $10.00; 50g $34.00
19,887-0	2-(*p*-Tolyl)pyridine	5g $8.10; 25g $28.00
19,888-9	2,3'-Dipyridyl	5g $8.10; 25g $28.00
19,889-7	2,4'-Dipyridyl	5g $8.10; 25g $28.00
19,890-0	2-(2-Thienyl)pyridine	5g $8.10; 25g $28.00
19,894-3	2-(3-Thienyl)pyridine	2.5g $9.75; 10g $27.00
20,973-2	3-Phenylpyridine	5g $7.50; 25g $25.00
20,974-0	3-Benzylpyridine	5g $7.50; 25g $25.00
19,891-9	1,2,3,4,5,6,7,8-Octahydro-acridine	10g $10.00; 50g $34.00
19,892-7	2,6-Diphenylpyridine	10g $10.00; 50g $34.00
19,893-5	2,6-Di-(*p*-tolyl)pyridine	5g $8.10; 25g $28.00