VOLUME 42 OCTOBER 14, 1977 NUMBER 21 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 7, 1977

JOCEAH 42(21) 3225–3462 (1977)
ISSN 0022-3263

THE JOURNAL OF Organic Chemistry®

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AUTHOR INDEX

THE JOURNAL OF Organic Chemistry®

VOLUME 42, NUMBER 21

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Conformational Analysis of Vitamin D and Analogues. ^{13}C and ^{1}H Nuclear Magnetic Resonance Study

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Received October 7, 1976

Complete and self-consistent assignment of the ^{13}C NMR spectra of the C_3-epimeric pairs of vitamin D_3, *trans*-vitamin D_3, its keto analogue, and dihydrotachysterol$_2$ were made. The conformational flexibility of ring A in these compounds and their esters was investigated using the ^{13}C as well as ^{1}H NMR data. The merits and the complementary nature of each approach are discussed in terms of the accuracy and reliability of the results. The relative excess of the equatorial conformer in the C_3 epimeric pairs of vitamin D_3 and its analogues was determined by both methods. This analysis indicates that in the case of vitamin D_3 and its C_3 epimer the methylene group affects the equilibrium population by stabilizing the chair conformation where the hydroxy group is axially oriented.

The recent discoveries of hormonal activity of vitamin D metabolites[1] have renewed the interest in the structure and chemistry of vitamin D and their analogues.[2] These ring B secosteroids exist as a mixture of two ring A conformations, which in solution are in dynamic equilibrium.

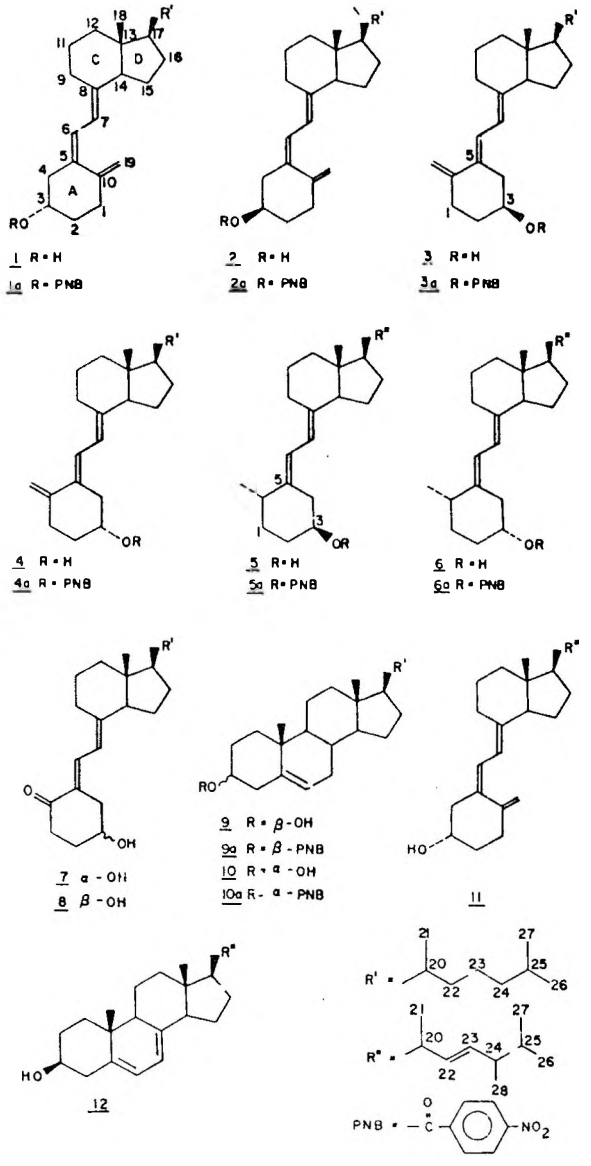
Detailed analysis of this equilibrium in vitamin D_2 (**11**) using ^{1}H NMR spectroscopy was performed by La Mar and Budd. This analysis was based on the correlation between the observable coupling constants of the proton at C_3–OH (J = 7.4 Hz)[3] and the limiting values of the axial–axial and equatorial–equatorial coupling constants for the cyclohexanol proton (J = 11.1 and 2.7 Hz).[4] Accordingly, the ratio of the two conformers, the one with the OH group in an equatorial and the other in an axial orientiation (Figure 1), was calculated to be ca. 50:50.[3] Using lanthanide-induced shifts this ratio was established to be 45:55 in favor of the OH-axial conformer, which, according to the temperature dependance of these shifts, was also the thermodynamically more stable conformer.[3] On the other hand, Wing et al.,[5,6] analyzing the conformational equilibrium of vitamin D_3 (**1**) by similar methods, established this ratio to be 54:43 in favor of the OH-equatorial conformer. This divergency of the results was attributed by the latter authors to the perturbation of the equilibrium ratio toward the OH-axial conformer by the complexing of the shift reagent with the substrate.[5,6]

The method of correlation of the observed spin-coupling constants with the Karplus equation was extended to ring A substituted vitamin D_3 derivatives, as well as to the 10,19-dihydrovitamin analogues, possessing a diene instead of a triene chromophore.[6-9] For some of these compounds this method gave consistent results, but for others it failed, since the multiplet structure due to the proton at C_3 was insufficiently resolved to allow such analysis.[8] Even in favorable cases, the use of the Karplus relation has a relatively large experimental error, up to 10% of the value obtained for the population ratio. As a result, the interpretation of the differences in the conformational equilibria of compounds, whose population ratio varies slightly, will be difficult. An additional error may be introduced by using cyclohexanol as a model for all the compounds investigated, although some of these possess at least one exocyclic double bond which may change the limiting coupling-constant values.

Our decision to utilize the ^{13}C NMR data for the conformational analysis stems from the fact that there are intrinsically large ^{13}C chemical-shift differences[10] between ring A carbon atoms in the respective conformers. The use of the sophisticated NMR techniques enables us to obtain ^{13}C chemical shifts with a high degree of precision, better than 0.03 ppm. Thus, a suitable choice of conformational analysis utilizing these ^{13}C chemical shifts may yield results with relatively small experimental error. For example, the limiting range of ^{13}C chemical shifts used in the present work was 4.62 ± 0.07 ppm (ca. 1.5% error) as compared to the limiting range of 8.4 ± 0.4 Hz[4] (ca. 5% error) for the proton coupling constant observed in vitamin D_3 (**1**) (vide infra).

In the present work, we have investigated the ^{13}C NMR spectra of vitamin D_3 (**1**) and its C_3 epimer **2**. Other compounds studied include *trans*-vitamin D_3 (**3**), its keto analogue **7**, and dihydrotachysterol$_2$ (**5**) as well as their respective C_3 epimers **4**, **8**, and **6**. In addition, the ^{13}C NMR spectra of the *p*-nitrobenzoate esters of these compounds (**1a** to **6a**) were recorded and analyzed. To help in the analysis we have also studied the NMR spectra of cholesterol (**9**), epicholesterol (**10**), and their *p*-nitrobenzoate esters **9a** to **10a** and vitamin D_2 (**11**).

The ^{13}C NMR spectra of all the compounds studied gave well-resolved lines which could be fully assigned. We have first described in detail the assignments for the various com-



pounds, for which we have used several techniques including ^{13}C chemical-shift additivity parameters, effects of lanthanide shift reagents (LIS), single-frequency off-resonance decoupling (SFORD), and comparison with known structures.[11] We have then interpreted the ^{13}C resonances of the A ring in terms of the conformational equilibria between the two chair conformers, and use the experimental results to determine the relative populations of the epimeric pairs. Finally, we have compared our results with those obtained from other sources and discussed them in terms of the possible steric factors which affect the conformational equilibria.

While this work was in progress the ^{13}C NMR of vitamin D analogues, including vitamin D_2 and D_3, *trans*-vitamin D_2, isotachysterol$_2$, isovitamin D_2 and their acetates were reported by Tsukida et al.[12] They have also estimated the conformational equilibrium of the two chair forms by an approach which differs from ours.

Experimental Section

With the exception of the following compounds, the samples used in this study were either commercially available or synthesized by previously described methods.

Epivitamin D_3 (2). A solution of 0.136 g (0.78 mmol) of diethyl azocarboxylate in 3 mL of dry tetrahydrofuran (THF) was added dropwise, under nitrogen atmosphere, to a cold solution (0 °C) of 0.200 g of vitamin D_3 (1) (0.52 mmol), 0.205 g of triphenylphosphine (0.78 mmol), and 0.130 g of *p*-nitrobenzoic acid (0.78 mmol) in 8 mL of dry THF. The resulting mixture was stirred at room temperature for ca. 6 h. The solvent was evaporated at room temperature, and the residue was chromatographed on silica gel using ether–hexane (1:9 mixture) as eluent. The product was crystallized from a methanol–ether solution to give 0.050 g of *p*-nitrobenzoate of epivitamin D_3 (**2a**): mp 117–118 °C; $[\alpha]_D$ −44° (*c* 0.89 in $CHCl_3$), −1° (C_6H_6). To a solution of 0.040 g of **2a** in 2 mL of methanol and 1 mL of ether a 5% KOH in methanol solution (2 mL) was added. The resulting mixture was stirred for 3 h at room temperature. The organic material was extracted with ether. The organic layer was washed three times with saturated NaCl solution and dried over $MgSO_4$. The solvent was evaporated to dryness and the residue was chromatographed on silica gel, using a ether–hexane (3:7) mixture as eluent, to afford 0.025 g of epivitamin D_3 (**2**): $[\alpha]_D$ −0.5° (*c* 0.9 in C_6H_6); UV λ_{max} 264 nm (ϵ 18 000).[9b,13]

Epi-*trans*-vitamin D_3 (4). The synthesis of **4** from **3** followed the same procedure as outlined above to give the *p*-nitrobenzoate epi-*trans*-vitamin D_3 (**4a**): mp 104–105 °C; $[\alpha]_D$ −95° (*c* 0.9 in $CHCl_3$). After hydrolysis, **4a** yielded the required product, epi-*trans*-vitamin D_3 (**4**): $[\alpha]_D$ −30° (*c* 0.85 in C_6H_6); UV λ_{max} 272 nm (ϵ 22 000).[9b,13]

Epidihydrotachysterol$_2$ (6). **6** was obtained by the same method from dihydrotachysterol$_2$ (**5**). The *p*-nitrobenzoate ester **5a**, mp 100–101 °C, $[\alpha]_D$ = −141° (*c* 1.0 in $CHCl_3$), was hydrolyzed to give epidihydrotachysterol$_2$ (**6**); UV λ_{max} 242, 251, and 261 nm (ϵ 34 500, 40 000, and 26 000); exact mass calcd for $C_{28}H_{46}O$: 398.6782; found; 398.6784.

NMR Spectra. All ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer, operating at 20 MHz. Flip angles of 45° or less were employed with 8K transform which gave ca. 1 Hz per data point for a 4000-Hz sweep width. Peak positions were determined by a software control and are considered to be accurate to within 0.03 ppm. The LIS experiments were done by adding small portions of Eu(fod)$_3$[14] (ca. 50 mg) to a $CDCl_3$ solution containing the compound under investigation (ca. 200 mg/mL), which was then filtered. All ^1H NMR spectra were recorded on a Bruker HFX-90 spectrometer operating in FT mode with a 8K transformer which gave ca. 0.2 Hz per data point for a 900-Hz sweep width. Peak positions are considered to be accurate to within 2×10^{-3} ppm.

Results

(a) Assignment of the ^{13}C Resonances. The ^{13}C chemical shifts for all observed peaks and their assignments are summarized in Table I. In the table, the numbering of the carbon atoms are given in the first column to the left. The other columns give the chemical shifts for the various compounds studied in ppm relative to Me_4Si as internal standard. All measurements were performed in deuterated chloroform and recorded at room temperature. The concentration of the solution ranged between 0.5 and 0.1 M.

To illustrate the procedure of assignment, we discuss in some detail the analysis of vitamin D_3. The relevant information is summarized in Table II. The carbon atoms of the side chain and of rings C and D were generally assigned by comparison with previous results for ergosterol (**12**) and cholesterol (**9**), discussed in detail in ref 11. Olefinic carbon atoms (i.e., C_5, C_6, C_7, C_8, C_{10}, C_{19}) could be easily distinguished from the rest of the carbon atoms by their large downfield shifts, and were further subdivided according to the multiplicity of the signals in the coupled spectra (C_{19} triplet (t), C_6 and C_7 doublets (d), and C_5, C_8, and C_{10} singlets (s), see column 2 in Table II). Within each subdivision, the peaks were finally assigned using single-frequency off-resonance proton-decoupling experiments and by the effect of lanthanide shift reagents (column 4 in Table II).

Carbon-3 is readily identified by its unique chemical shift and by its multiplicity in the coupled spectrum and by its large LIS. The rest of the ring A carbon atoms were assigned by their LIS, and the characteristic α, β, γ, and δ shifts caused by esterification at position 3 (column 5 in Table II).[15,16] The assignments were tested by comparing spectra of epimeric pairs and by comparison with calculated shifts (column 6, in Table II) based on ^{13}C chemical-shift additivity parameters.[17] Good agreement was obtained for the alkane carbon atoms (standard deviation of 1.7 ppm), although the agreement for the olefinic carbon atoms proved less satisfactory (standard deviation 3.0 ppm). Similar analysis, although less extensive,

Table I. ^{13}C NMR Data for the Vitamins D and Analogues[a,b]

C no.	1 (1a)	2 (2a)	3 (3a)	4 (4a)	5 (5a)	6 (6a)	7	8	9 (9a)	10 (10a)	11
1	32.05	32.40	31.20	31.15	33.20	31.30	30.90	30.95	37.35	33.30	32.00
	(−0.05)[c]	(−0.35)[c]	(−0.35)	(−0.25)[c]	(0.65)	(0.75)			(−0.3)	(0.75)	
2	35.25	35.60	34.80	34.75	34.95	32.05	35.30[c]	35.35[c]	31.70	28.95	35.25
	(−3.15)[c]	(−3.25)[c]	(−3.8)	(−3.65)[c]	(−4.6)	(−2.95)			(−3.85)	(−2.6)	
3	69.20	69.70	69.00	68.95	70.90	69.65	66.55	66.65	71.75	67.15	69.20
	(4.35)	(4.15)	(4.0)	(4.05)	(3.8)	(4.5)			(4.1)	(5.4)	
4	46.00	46.25	37.25	37.10	38.30	35.65	35.65[c]	35.65[c]	42.35	39.95	46.00
	(−3.85)	(−3.95)	(−4.05)	(−3.85)	(−4.75)	(−3.2)			(−4.2)	(−3.4)	
5	145.20	145.05	149.25	149.20	139.75	139.30	128.80	178.80	140.85	138.60	145.15
	(−0.8)	(−0.75)	(−0.85)	(−0.8)	(−1.6)	(−0.8)			(−1.55)	(−0.04)	
6	122.40	122.25	121.05	121.05	117.05	119.15	133.15	133.15	121.65	124.05	122.45
	(0.55)	(0.7)	(0.55)	(0.5)	(1.25)	(−0.5)			(1.55)	(−1.37)	
7	117.65	117.65	116.0	115.9	115.75	115.60	115.65	115.65	31.95	32.05[c]	117.60
	(−0.2)	(−0.25)	(−0.4)	(−0.35)	(−0.2)	(−0.05)			(0.0)	(0.1)	
8	142.10	142.15	144.55	144.65	142.15	142.20	156.45	156.45	31.95	31.95[c]	142.10
	(0.7)	(0.8)	(0.65)	(0.6)	(0.6)	(0.0)			(0.0)	(0.0)	
9	29.10	29.10	29.15	29.10	29.00	28.95	29.85	29.85	50.25	50.45	29.05
10	135.15	135.40	134.95	134.80	37.80	38.40	199.35	199.50	36.55	37.40	135.20
	(−1.35)	(−1.45)	(−1.3)	(−1.45)	(0.2)	(−0.05)			(0.15)	(−0.2)	
11	22.30	22.35	22.40	22.35	22.40	22.35	22.20	22.20	21.15	20.85	22.25
12	40.65	40.65	40.70	40.60	40.55	40.45	40.45	40.45	39.90	39.85	40.50
13	45.90	45.95	46.00	46.00	45.70	45.65	47.10	47.10	42.35	42.40	45.80
14	56.40	56.45	56.70	56.60	56.60	56.55	57.30	57.35	56.30[d]	56.25[d]	56.50
15	23.60	23.70	23.65	23.65	23.60	23.50	23.95	24.00	24.30	24.30	23.60
16	27.70	27.65	27.70	27.70	27.80	27.80	27.60	27.65	28.25	28.25	27.80
17	56.75	56.80	56.85	56.75	56.60	56.55	56.90	56.95	56.85[d]	56.85[d]	56.60
18	12.00	12.00	12.20	12.15	12.40	12.40	12.15	12.20	11.90	11.85	12.30
	(0.05)	(−0.05)	(−0.25)		(−0.2)	(−0.1)				(−0.05)	
19	112.35	112.50	108.15	108.2	17.85	(18.70	(—)	(—)	19.40	18.70[e]	112.35
	(0.7)	(0.6)	(0.3)	(0.4)	(0.0)	(−0.2)			(0.05)	(0.25)	

[a] Shifts are given relative to Me_4Si and are accurate within ±0.05 ppm. The side-chain carbon resonances not listed in the table for compounds 1 to 4, 7 to 10 and their esters are: C_{20}, 36.20; C_{21}, 18.90; C_{22}, 36.20; C_{23}, 23.95; C_{24}, 39.60; C_{25}, 28.05; C_{26}, 22.60; C_{27}, 22.80; and for compounds 5, 6 and 11: C_{20}, 40.35; C_{21}, 19.70; C_{22}, 135.65; C_{23}, 132.05; C_{24}, 42.90; C_{25}, 33.15; C_{26}, 19.95; C_{27}, 21.15; C_{28}, 17.65. [b] The values in parentheses are $\Delta\delta = \delta_{ester} - \delta_{OH}$; estimated error ± 0.07 ppm; any $\Delta\delta < 0.1$ was neglected altogether for all carbons other than ring A and B carbon atoms. [c] Assignment may be reversed down any column. [d] Original assignments have been reversed. [e] Appears as a shoulder on the C_{21} resonance peak.

Table II. ^{13}C-Chemical Shift Assignments of Carbons 1 to 19 for Vitamin D_3

C no.	Vit D_3(1) shifts, ±0.05 ppm	Multiplicity[a]	LIS ($\Delta\delta$),[b] ±0.15 ppm	$\delta_{ester} - \delta_{OH}$[c] ppm ± 0.08 ppm	Calcd[d] shifts, ppm	Ergosterol,[e] 0.1 ± ppm
1	32.05	t	2.9	−0.0[5]	33.1	38.4
2	35.25	t	4.2	−3.5	35.7	32.0
3	69.20	d	24.4	4.3[5]	71.1	69.5
4	46.00	t	2.8	−3.8[5]	43.6	40.5
5	145.20	s	2.6	−0.8	144.9	140.5
6	122.40	d	3.0	0.5[5]	122.6	119.5
7	117.65	d	0.9	−0.2	122.6	116.5
8	142.10	s	1.2	0.7	143.2	140.4
9	29.10	t	0.3	—[f]	31.4	46.4
10	135.25	s	2.1	−1.3[5]	142.3	37.0
11	22.30	t	0.3	—	22.0	21.0
12	40.65	t	—[f]	—	39.8	39.2
13	45.90	s	—	—	46.0	42.8
14	56.40	d	0.5	—	52.6	54.4
15	23.60	t	0.2	—	23.0	22.9
16	27.70	t	—	—	26.4	28.1
17	56.75	d	—	—	52.7	55.8
18	12.05	q	0.2	—	13.9	11.6
19	112.35	t	1.7	0.7	112.0	15.8

[a] The multiplicity was determined from off-resonance measurements at various offsets. [b] Gradual increase of the concentration of Eu(fod)$_3$ up to ca. 1:1 molar ratio. [c] Negative sign indicates an upfield shift. [d] Calculated from ref 15, using $\delta = B + \sum_i A_{ij}\eta_i$ for $j = \alpha, \beta$, and γ carbons where B(alkyl) = −2.5 ppm and B(alkene) = 122.1 ppm relative to Me_4Si. [e] Taken from ref 16. [f] Bars indicate that observed differences are within the experimental error.

were made for the rest of the compounds studied and the results are given in Table I.

For those compounds which were also studied by Tsukida et al.[12] there is complete agreement in the assignment of the carbon resonances except for the reversal of the resonances due to C_5 and C_{10}. Our assignment is mainly based on the LIS effect. We performed careful shift measurements on these two signals as a function of added Eu(fod)$_3$[14] and have assigned

Table III. ^{1}H NMR Results

Compd[a]	H(6), ppm	H(7), ppm	$^3J_{H6,H7}$, Hz	$H(19)_Z$, ppm	$H(19)_E$, ppm	H(3), ppm	$^3J_{H(3)}$, Hz	H(18), ppm
1[c]	6.2 (6)	6.0 (6)	11.2	4.9 (6)	4.7 (3)	3.9 (6)	3.8	0.5 (5)
2	6.2 (1)	6.0 (1)	11.2	5.0 (1)	4.8 (0)	3.9 (6)	4.1	0.5 (5)
3[c]	6.5 (7)	5.8 (8)	11.1	4.9 (8)	4.6 (9)	3.8 (8)	4.3	0.5 (6)
4	6.5 (6)	5.8 (7)	11.1	4.9 (7)	4.6 (8)	3.8 (8)	4.2	0.5 (6)
5[c]	6.1 (5)	5.9 (0)	11.1			3.6 (0)	4.8	0.5 (6)
6	6.2 (8)	5.8 (6)	11.2			3.8 (5)	3.7	0.5 (6)
7	8.4 (4)[d]	4.9 (9)	12.0			4.1 (9)	3.8	0.5 (4)
8	8.4 (4)[d]	5.0 (0)	12.1			4.1 (8)	3.8	0.5 (4)
1a	6.2 (5)	6.0 (6)	11.1	5.1 (2)	4.9 (0)	5.2 (6)	3.8	0.5 (5)
2a	6.2 (7)	6.0 (8)	11.3	5.1 (2)	4.9 (2)	5.1 (6)	4.1	0.5 (5)
3a	6.5 (7)	5.7 (9)	11.1	5.0 (0)	4.7 (1)	5.2 (3)	(—)[b]	0.5 (6)
4a	6.5 (9)	5.8 (0)	11.0	3.0 (3)	4.7 (3)	5.2 (8)	4.2	0.5 (6)
5a	6.2 (1)	5.8 (0)	11.0			4.9 (3)	4.8	0.5 (7)
6a	6.2 (0)	5.7 (0)	11.0			5.1 (7)	(—)[b]	0.5 (4)

[a] Chemical shifts are given in ppm downfield from Me_4Si as an internal standard, SD = ±0.03 ppm; the coupling constants are given in Hz and believed to be accurate to ±0.2 Hz. [b] The fine structure of the multiplet was too distorted to permit analysis. [c] See also ref 3. [d] This part of the multiplet seemed to have a secondary splitting to a triplet probably arising from the H(4) protons.

Table IV. The Trans Vicinal Coupling Constants of H at C_3, $^{13}C_3$ Chemical Shift Differences, and the Relative Excess of the Equatorial Chair Conformers at Room Temperature[a]

Compd	^3J_t,[b] Hz	N_q, %[c]	ΔN(H), %[d]	$\Delta\delta$ (^{13}C), ppm[e]	ΔN (^{13}C), %[d]
1 (1a)	7.6 (7.6)	57	−8 ± 12	−0.48 (−0.27)	−10 (−8) ± 2
2 (2a)	8.2 (8.2)	65			
3 (3a)	8.6	70	1 ± 14	0.07 (0.01)	1 (0) ± 1
4 (4a)	8.5 (8.5)	69			
5 (5a)	9.7 (9.3)	84	26 ± 15	1.29 (0.56)	27 (17) ± 3
6 (6a)	7.7 (7.7)	58			
7	7.6	57	−2 ± 11	−0.07	−2 ± 1

[a] Values in parentheses are for the corresponding *p*-nitrobenzoate esters. [b] Trans vicinal proton spin–spin coupling constant at C_3. [c] Percentage of the OH-equatorial conformer calculated using the Karplus relation with $J_{ax,ax}$ = 11.1 ± 0.2 Hz and $J_{eq,eq}$ = 2.7 ± 0.2 Hz; errors estimated to be ca. ±10% of the value quoted. [d] Difference between the percentages of the equatorial conformer in the C_3-epimeric pairs. [e] Difference in the $^{13}C_3$ chemical shifts of the epimeric pairs.

the resonance that was more affected by the shift reagent to C_5, since this carbon is closer to the hydroxyl group which is expected to be the binding site for the LIS reagent.

(b) Conformational Analysis. In addition to the ^{13}C NMR measurements, we have also studied the proton spectra of all compounds, some of which (**1, 3, 5**) have been previously analyzed.[3,5] The chemical shift of the protons bonded to C_3, C_{18}, C_6, and C_7, as well as the proton–proton spin–spin couplings of the C_3 multiplet, $^3J_{H(3)}$, and the vicinal couplings, $^3J_{H(6),H(7)}$, are summarized in Table III. In all spectra, the C_3 protons exhibited a heptet indicating fast dynamic equilibrium between the two possible ring A conformers. We have employed these coupling constants to determine the equilibrium population of the conformers using the Karplus equation, as was done by La Mar et al. for vitamin D_2.[3] The results are summarized in column 2 of Table IV.

We attempted a similar conformational analysis on the ^{13}C NMR data. The analysis of ^{13}C NMR data (Table I) shows that the resonance shifts of ring D and the side-chain carbon atoms are insensitive to changes in the structure of ring A, unlike those of ring C and the butadiene bridge. It also appears that all these resonances are similar in the C_3-epimeric pairs (**1,2; 3,4; 5,6; 7,8**). In contrast, the resonances of the ring A carbon atoms differ significantly, not only among the compounds having dissimilar ring A structure but also between the pairs of epimers (e.g., C_3 shifts in the pairs **1,2**; or **3,4**). These differences are attributed to the chair–chair conformational equilibrium of ring A,[18] in which one conformer has an equatorial and the other an axial OH group at C_3 (Figure 1).

In principle, these differences can be used to determine the equilibrium constants between the two conformers, provided the chemical shifts δ^{eq} and δ^{ax} of the OH-equatorial and OH-axial conformers were known for a given atom. The observed shift δ is then given by:

$$\delta = \delta_0 + (\Delta/2)(N_{eq} - N_{ax}) \quad (1)$$

$$N_{eq} + N_{ax} = 1 \quad (2)$$

where $\delta_0 = \frac{1}{2}(\delta^{eq} + \delta^{ax})$ is the average of δ^{eq} and δ^{ax}, $\Delta = \delta^{eq} - \delta^{ax}$, and N_{eq}, N_{ax} are the fractional populations of the OH-equatorial and OH-axial conformers, respectively. This approach cannot be utilized directly, since the values of δ_0 are unknown and cannot be ascertained.

We may, however, obtain more reliable information on the relative ratios of conformers within epimeric pairs. Corresponding conformers in C_3 epimeric pairs have their ring A in a similar conformational relationship with respect to the rest of the molecule and are thus expected to show identical shifts (Figure 2). In particular, we may assume that $\Delta = \delta^{eq} - \delta^{ax}$ is identical for an epimeric pair and interpret the ^{13}C shift between the C_3 epimers as solely reflecting the different populations of the two conformers. Thus, from eq 1 and 2

$$(\delta^{epi} - \delta)/\Delta = N_{eq}{}^{epi} - N_{eq} = \Delta N \quad (3)$$

where the superscript epi refers to the epimeric compound.

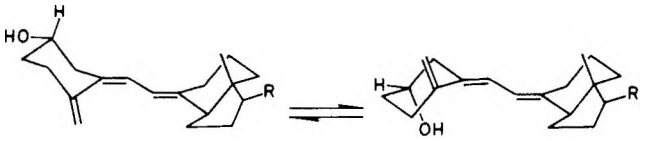


Figure 1. Conformational equilibria in vitamin D_3.

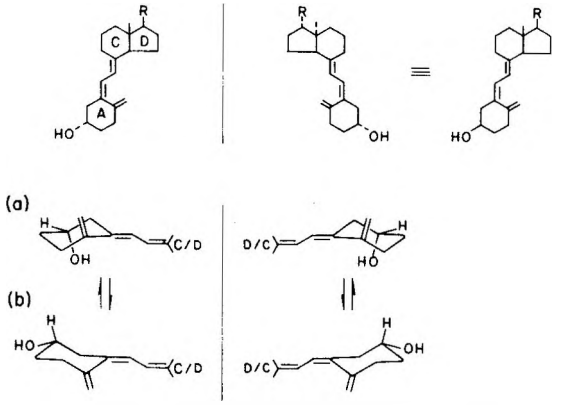


Figure 2. Conformational equilibria in vitamin D_3 and epivitamin D_3. (a) OH-axial conformers; (b) OH-equatorial conformers. Epivitamin D_3 formulas are drawn inverted in the middle row to show the pseudoenantiomeric relationship of rings A in vitamin D_3 and epivitamin D_3.

Consequently, if Δ is known, we may determine the excess of one of the conformers in the epimeric compound from the relative shift ($\delta^{epi} - \delta$).

For the structures under consideration, we have chosen Δ = 4.62 ppm for the C_3 resonances, which was calculated from the C_3 shift of cholesterol (**9**) and epicholesterol (**10**). These two compounds have the C_3 carbon with an equatorial-OH and an axial-OH conformation, respectively, and resemble the structure of the vitamin systems. Similar Δ values may be derived from compounds having analogous substitution patterns as the ring B secosteroids. For example, we calculate Δ = 4.9, 4.6, and 4.4 ppm for the carbinol carbon in cholestanol,[19] androstanol,[19] and 10-methyl-*trans*-decal-3-ol,[20] respectively.[21] For the ester derivatives, we use Δ = 3.27 ppm which was derived from the *p*-nitrobenzoic esters of cholesterol and epicholesterol.

Discussion

In this work we have determined the equilibrium population of the ring A conformers of vitamin D analogues using both ^1H and ^{13}C NMR spectra. The first method relies on the spin–spin coupling of the protons at C_3 using the Karplus relation,[3,4] while the second approach uses the ^{13}C chemical shift differences between an axial and equatorial carbinol groups.

The conformational analysis using ^{13}C NMR data as utilized by us is based on the γ-shift effect. This γ effect is mainly a steric effect and is directly involved with the carbon under consideration (C_3). This method does not give the absolute equilibrium ratios, but, nevertheless, provides reliable information about the conformational equilibria.

In Table IV we have summarized the pertinent results used for the conformational analysis. The first column shows the vicinal coupling constants for the protons at C_3, and the second the calculated populations of the OH-equatorial conformers, using these values. In the fourth column are listed the differences between ^{13}C chemical shifts of the C_3 atoms in the C_3-epimeric pairs. The third and the fifth columns show the differences between the percentage of the equatorial conformers of these epimeric pairs, calculated from the ^1H and ^{13}C NMR data, respectively.

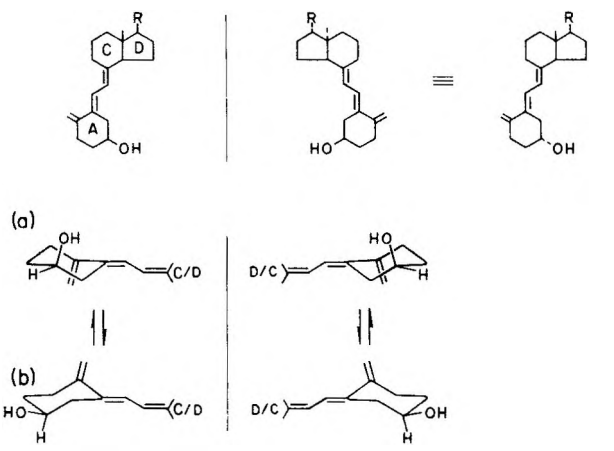


Figure 3. Conformational equilibria in *trans*-vitamin D_3 and epi-*trans*-vitamin D_3. (a) OH-axial conformers; (b) OH-equatorial conformers. Epi-*trans*-vitamin D_3 formulas are drawn inverted in the middle row to show the pseudoenantiomeric relationship of rings A in *trans*-vitamin D_3 and epi-*trans*-vitamin D_3.

As may be seen from Table IV, similar results are obtained for the relative excess of the equatorial conformers in the epimeric pairs (ΔN) using both the ^{13}C and ^1H NMR methods. However, the errors in the calculation of the ΔNs using the ^1H NMR method are of the same order of magnitude as the ΔNs themselves. On the other hand, the ^{13}C results are of much higher accuracy.

In the following, we discuss the four pairs of C_3-epimeric compounds in order to determine the various factors that influence the conformational equilibrium in the vitamin D system.

Dihydrotachysterol$_2$ (5). The population ratios of conformers in dihydrotachysterol$_2$ (**5**) and its epimer **6**, obtained from the coupling constants analysis of the C_3 proton, were found to be 84:16 and 58:42, respectively. Accordingly, **5** possesses 26% more of the equatorial conformer than its epimer **6**. A similar value was calculated from the corresponding ^{13}C NMR data (Table IV).

Dihydrotachysterol$_2$ (**5**) and its epimer **6** may be regarded as analogues of *trans*- and *cis*-4-methylcyclohexanol, respectively. However, it was found that **5** and **6** have a higher proportion of the conformer with an axial CH_3 group than the corresponding 4-methylcyclohexanols (16 and 58% in **5** and **6** vs. <2 and 10% *trans*- and *cis*-4-methylcyclohexanol,[22] respectively). This difference in population ratios is due to the 1:3 peri interaction between the C_6–H and C_{10}–CH_3 groups, which destabilizes the conformers having an equatorial CH_3 group by about 1 kcal/mol.[8a]

The same ratios of conformers were found from the coupling-constant analysis of the C_3 protons of the corresponding *p*-nitrobenzoate esters **5a** and **6a**. However, the relative excess of the OH-equatorial conformer, as calculated from the ^{13}C spectra of **5a** and **6a**, was found to be lower than the corresponding excess in the alcohols (17 vs. 27%).[23]

***trans*-Vitamin D_3 (3) and its Keto Analogue 7.** In both epimeric pairs the coupling constant of the C_3 protons as well as the ^{13}C chemical shifts of epimers were similar (see Tables IV and I). This similarity indicates that the OH-equatorial and OH-axial conformers in these pairs are not only magnetically equivalent, but are also in the pseudoenantiomeric relationship in respect to their ring A and C_6 atoms (Figure 3). However, we attribute the difference of 11% in the population ratios between the *trans*-vitamin D_3 and its keto analogue (69 vs. 58%) to the change in ring A geometry caused by substituting the methylene by a carbonyl group.

The *p*-nitrobenzoate esters **3a** and **4a** have identical ^1H and

^{13}C NMR spectra and a similar ratio of the conformers as the corresponding alcohols **3** and **4**.

Vitamin D_3 (1). The ^1H NMR spectra of **1** and **2** are similar and the only observable difference lies in their C_3-proton spin–spin coupling constants (7.6 vs. 8.2 Hz).[9b] The calculated ratio of the conformers in **1** was 57:43 and in **2** was 65:35, i.e., an excess of 8% of the OH-axial conformer in vitamin D_3 (**1**). Similar results were obtained from the analysis of their ^{13}C NMR spectra. The corresponding *p*-nitrobenzoate esters **1a** and **2a** have almost the same population ratios as their parent alcohols.

The difference in the population ratio of the OH-equatorial and OH-axial conformers in **1** and **2**, respectively, is surprising as they are expected to be identical due to the pseudoenantiomeric relationship of their rings A and C_6 [as found in *trans*-vitamin D_3 (**3**) and the keto analogue **7** systems (Figure 2)]. Therefore, it must be assumed that there are different steric interactions between ring A and C_6 and rings C/D in the respective conformers of **1** and **2**. These interactions are responsible for the predominance of the β conformation[2] in which the methylene group lies above the plane of the butadiene bridge.

X-ray single crystal-structure determination of vitamin D_2 (**11**)[24] and D_3(**14**)[25] have shown that two types of molecules, each with a different ring A chair conformation, are present in a unit cell. One molecule has the OH group in an equatorial orientation and the methylene group below the plane of the butadiene bridge (α conformation), while the other has the OH group in an axial orientation and the methylene group above the plane of the butadiene bridge (β conformation). It was also found that in the vitamin D_2 the two molecules differ not only in the ring A conformations but also in their C_6–C_7 torsional angle, this angle being +175° for the α conformation and −164° for the β conformation.

Similar differences may also exist in the solution conformations of vitamin D_3 (**1**) and its epimer **2**. Thus, respective ring A conformers in the two epimers do not have a pseudoenantiomeric relationship, as the butadiene bridge is more distorted in the β than in the α conformation.

A different approach to the conformational analysis of vitamin D analogues, using ^{13}C NMR spectroscopy, was recently described by Tsukida et al.[12] These authors have derived the C_3 chemical shifts of the OH-equatorial and the OH-axial conformers using the respective chemical in shifts of the *cis*- and *trans*-4-*tert*-butylcyclohexanol and correcting for the substituent effects. In order to test this approach we have calculated the equilibrium populations in the compounds investigated by us, using our experimental data for the $^{13}C_3$ chemical shifts.[26] However, these calculations resulted in population ratios which sometimes differed significantly from the respective ratios derived from the $^3J_{H(3)}$ data. Thus, the OH-equatorial conformer populations found in *trans*-vitamin D_3 (**3**) and its C_3 epimer **4** were 46 and 44% as compared with 70 and 69%, respectively, as established from the proton spin–spin coupling-constant values.

Registry No.—**1**, 67-97-0; **1a**, 6183-79-5; **2**, 57651-82-8; **2a**, 60413-84-5; **3**, 22350-41-0; **3a**, 62743-69-5; **4**, 57651-83-9; **4a**, 60413-85-6; **5**, 67-96-9; **5a**, 62743-70-8; **6**, 62777-58-6; **6a**, 60503-42-6; **7**, 62743-71-9; **8**, 62743-72-0; **9**, 57-88-5; **9a**, 23838-12-2; **10**, 474-77-1; **10a**, 62743-73-1; **11**, 50-14-6; *p*-nitrobenzoic acid, 62-23-7.

References and Notes

(1) A. W. Norman, H. Henry, *Recent Prog. Hormone Res.*, **30**, 431–480 (1974); J. L. Omdahl, H. F. DeLuca, *Physiol. Rev.* **53**, 327–372 (1973).
(2) E. Havinga, *Experientia*, **29**, 1181 (1973).
(3) G. N. La Mar and D. L. Budd, *J. Am. Chem. Soc.*, **96**, 7317 (1974).
(4) F. A. L. Anet, *J. Am. Chem. Soc.*, **84**, 1053 (1962).
(5) R. M. Wing, W. H. Okamura, A. Rego, M. R. Pirio, and A. W. Norman, *J. Am. Chem. Soc.*, **97**, 4980 (1975).
(6) R. M. Wing, W. H. Okamura, M. R. Pirio, S. M. Sine, and A. W. Norman, *Science*, **186**, 939 (1974).
(7) M. L. Hammond, M. R. Pirio, R. M. Wing, A. Rego, N. N. Mitra, W. H. Okamura, and A. W. Norman, "Vitamin D and Problems Related to Uremic Bone Disease", A. W. Norman et al., Ed., W. de Gruyter Co., Berlin, 1975, pp 259–279.
(8) (a) W. H. Okamura, M. L. Hammond, A. Rego, A. W. Norman, and R. M. Wing, in press. We thank the authors for this manuscript; (b) A. G. M. Barrett, D. H. R. Barton, R. A. Russel, and D. A. Widdowson, *J. Chem. Soc., Perkin Trans. 1*, in press (1977).
(9) (a) M. Sheves, E. Berman, D. Freeman, and Y. Mazur, *J. Chem. Soc., Chem. Commun.*, 643 (1975); (b) M. Sheves and Y. Mazur, *Tetrahedron Lett.*, 1913 (1976); (c) *J. Chem. Soc., Chem. Commun.*, 21 (1977); (d) E. Berman, N. Friedman, Y. Mazur, and M. Sheves, submitted for publication.
(10) J. B. Stothers, "^{13}C-NMR Spectroscopy", Academic Press, New York, N.Y. 1972.
(11) (a) H. J. Reich, M. Jautelat, M. R. Messe, F. T. Weigert, and J. D. Roberts, *J. Am. Chem. Soc.*, **91**, 7445 (1969); (b) ref 10, p 440.
(12) K. Tsukida, K. Akutsu, and K. Saiki, *J. Nutr. Sci. Vitaminol.*, **21**, 411 (1975).
(13) (a) I. T. Harrison, R. A. A. Hurst, B. Lythgoe, and D. H. Williams, *J. Chem. Soc.*, 5176 (1960); (b) H. H. Inhoffen, K. Irmscher, H. Hirschfeld, U. Stache, and A. Kreutzer, *Chem. Ber.*, **91**, 2309 (1958).
(14) fod = 1,1,2,2,3,3,-heptafluoro-7,7-dimethyl-1,6-octanedionato chelate.
(15) Reference 10, p 168.
(16) Reference 10, p 440.
(17) Reference 10, pp 58 and 75.
(18) Reference 10, Chapter 11B, p 420.
(19) H. Eggert, C. L. Van Antwerp, N. S. Bhacca, and C. Djerassi, *J. Org. Chem.*, **41**, 73 (1976).
(20) S. H. Gorver and J. B. Stothers, *Can. J. Chem.*, **52**, 870 (1974).
(21) It is interesting to note that in a recently published communication by O. A. Subbotin and N. M. Sergeyer in *J. Chem. Soc., Chem. Commun.*, 141 (1976), it was shown that the corresponding Δ ($=\delta^{eq} - \delta^{ax}$) value obtained for the cyclohexanol conformers, at low temperature, was found to be 4.67 ppm.
(22) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience, New York, N.Y., 1967, Chapter 2.
(23) The value of 17% was derived from the difference in the C_3 chemical shifts of the corresponding *p*-nitrobenzoate esters of **9a** and **10a** (Δ = 3.27 ppm). The different rotameric conformations adopted by the *p*-nitrobenzoate group in secosteroids as compared to rigid steroids may be responsible for the lower value in the former compounds.
(24) S. E. Holl, I. Leban, P. Main, P. S. White, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, **32**, 2374 (1976).
(25) Trinh-Taon, H. F. Deluca, and L. F. Dahl, submitted for publication.
(26) These ^{13}C data were used in conjunction with the appropriate substituent effects: for compounds **1–4** these are given in ref 12; for compounds **5,6** and **7,8** we have used in addition the values −0.7 ppm for the methyl derivative (see ref 10, p 64) and −3.6 ppm for the ketone derivative (see ref 10, p 174), respectively.

Photorearrangement of 10-Methyloctalone in Concentrated Acid Solution[1]

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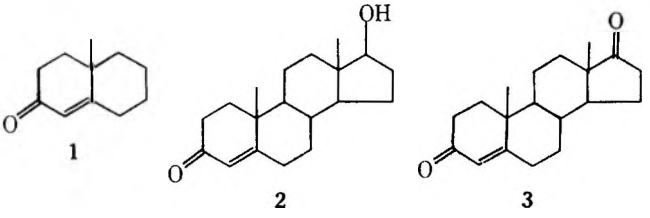
Received January 31, 1977

When dissolved in concentrated sulfuric acid, 10-methyloctalone undergoes only complete protonation. It can be recovered unchanged after long periods of storage in the dark and subsequent hydrolysis of the acid solution. Irradiation of the hydroxycarbocation generated by the octalone in acid with ultraviolet light of 300 nm caused an efficient rearrangement to 1-hydroxy-3-(1-methylcyclopentyl)cyclopenten-2-yl cation. Time-lapse spectrometry experiments showed this first transformation to be virtually free of any side reactions. Further photolysis of the resulting solutions with light of 254 nm, where the first photoproduct exhibited strong absorption, caused a second rearrangement to a tricyclic hydroxycarbocation. The identity of the photoproducts was established from the spectral data of their neutral derivatives and their deuterated analogues. A reaction mechanism is proposed.

The photochemistry of unsaturated cyclic ketones has received much attention because these structures offer interesting interactions between the carbonyl and alkene π systems within the steric constraints of the cyclic configuration. Numerous photorearrangements of cyclohexenone incorporated in polycyclic configurations have been reported.[3] Several interesting rearrangements have been uncovered on photolysis of 10-methyloctalone in organic solvents.[4-6]

This paper describes our results obtained by irradiating $\Delta^{1,9}$-10-methyl-2-octalone 1 in concentrated sulfuric acid. The methyl group is not only a useful analytical "label" in the complex problem of elucidating the structure of rearranged photoproducts, but also the natural angular substituent at the 10 position of many steroid hormones. In fact, methyloctalone 1 represents the common "half-molecule" of androgens testosterone 2 and androstenedione 3, without the C and D rings.



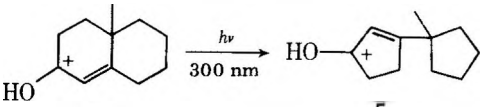
1 2 3

Since the classical method of assay of these hormones in biological fluids involves measurement of fluorescence excited by ultraviolet light in concentrated sulfuric acid, the results outlined in this study are also relevant to the complicated and poorly-understood behavior of natural steroids in strongly acidic solutions.[7]

Results and Discussion

When dissolved in concentrated sulfuric acid, methyloctalone 1 formed stable solutions of hydroxycarbocation 4. The UV spectrum of these solutions remained unchanged for many months. The absence of any dark reaction was also demonstrated by recovery of only the starting octalone 1 from acid solutions stored for a long time.

Time-Lapse Spectrometry (TLS).[8] Figure 1 shows the consecutive changes in the UV spectrum of a dilute solution of 1 in concentrated acid on successive short irradiations at 300 nm. The absorption band centered at 290 nm, characteristic of protonated 1, decreased progressively during the photolysis. The formation of photoproduct 5 was demonstrated by the appearance and corresponding increase in a new absorption band with λ_{max} 265 nm. The UV spectra of 4 and 5 are consistent with α,β-unsaturated alicyclic ketones in sulfuric acid.[9] After a total irradiation time of 6 min there was no residual reactant, as shown by scan 8. The absorption curves in Figure 1 pass through three well-defined isosbestic points at 210, 277, and 318 nm. This isosbestic behavior testifies that the phototransformation is free of significant side or consecutive reactions.[8] The existence of only two components, reactant ion 4 and photoproduct 5, was confirmed by the gas chromatographic analysis of extracted hydrolysates form preparative-scale photoreactions.



4 5

Further irradiation at 300 mm of the solution shown in Figure 1 after the completion of the 4 → 5 step caused only a very slow decrease in absorbance at 265 nm. However, photolysis with light of 254 nm, where photoproduct 5 exhibited intense absorption, caused a rapid change in the absorption spectrum as shown in Figure 2. The peak at 265 nm in the last spectrum of Figure 1 decreased gradually with the simultaneous appearance of a new maximum at 340 nm. This indicated that the first photoproduct 5 underwent photolysis to a second product. The isosbestic point formed at about 285 nm by the first seven scans in Figure 2 is less well defined than the isosbestic points in the TLS diagram of Figure 1, with some intersections occurring in the 284–288-nm spectral region. This suggests either the occurrence of minor consecutive or side reactions, or the presence of some residual protonated octalone. Since curves 15 and 16, corresponding to 10 and 12 min total irradiation, did not pass through the isosbestic point, and the scans in 230–240-nm region did not cross at a clearly defined point, some further breakdown of the second photoproduct seems likely.

Preparative-Scale Irradiation of 1 in Sulfuric Acid. For small scale preparative purposes, a 3×10^{-3} M solution of 1 in sulfuric acid was photolyzed at 300 nm in a Vycor preparatory cell. The progress of the photoreaction was evaluated by monitoring the UV spectra of diluted aliquots. At the end of the first 2 h of irradiation, the 4 → 5 conversion was essentially complete with little, if any, other product being formed. Quenching of the photolyzed solution on ice and ether extraction of the hydrolysate followed by solvent evaporation yielded an oil with a faint yellow tint. No degradation products could be identified in the aqueous phase. GLC analysis of the extract indicated the presence of only one volatile component. The UV spectrum of this component, isolated by GLC and redissolved in sulfuric acid, was identical with that of photoproduct 5 shown in scan 8 of Figures 1 and 2. This shows that product 6 was recuperated from concentrated acid solutions without irreversible change.

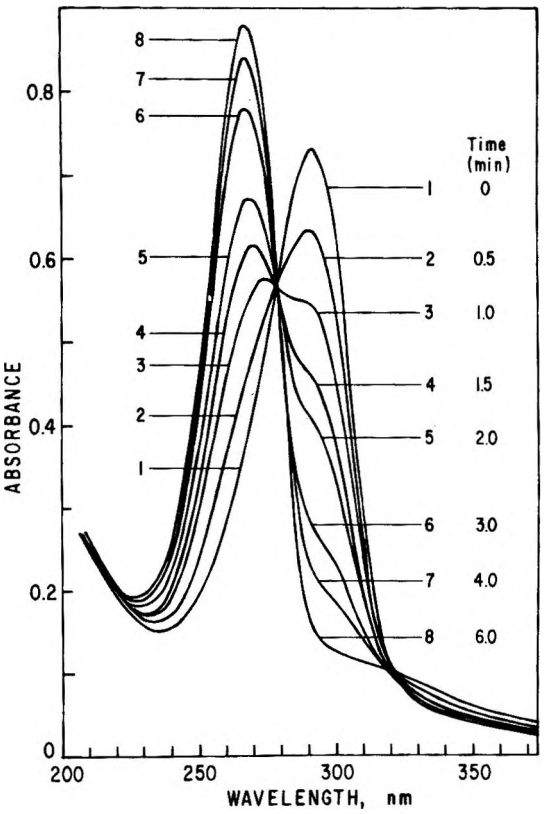


Figure 1. Changes in the UV spectrum of a 6×10^{-5} M solution of 10-methyloctalone in sulfuric acid, when irradiated at 300 nm. Total photolysis time indicated in the diagram to the right of the corresponding scan.

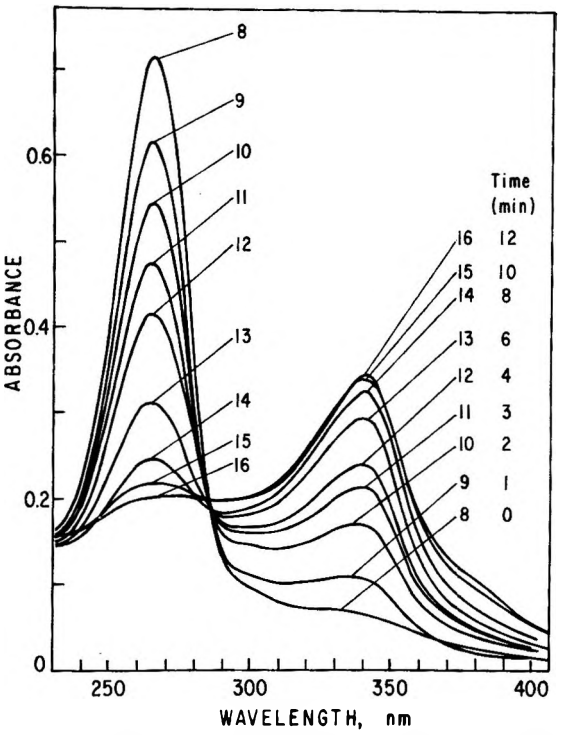


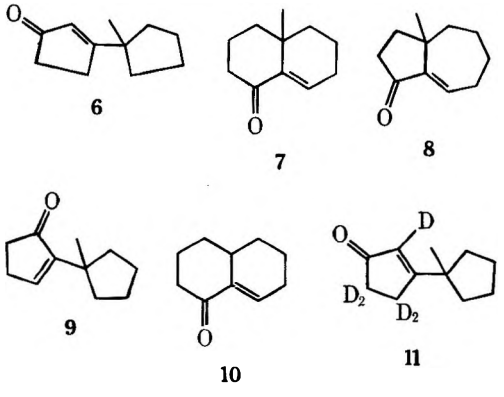
Figure 2. Further changes in the UV spectrum of the same solution shown in Figure 1 on photolysis at 254 nm.

Identification of First Photoproduct. Analytically pure photoproduct by GLC of ether extracted hydrolysate was a clear light-yellow liquid. Its mass spectrum, like that of **1**, showed a prominent molecular ion peak at *m/e* 164. There is little doubt that the overall **1** → **6** reaction represents an isomerization.

The IR spectrum of **6** exhibited peaks at 1713 and 1683 cm^{-1} characteristic of a carbonyl group which is either unconjugated, out-of-plane with respect to an adjacent alkene group, or part of a cyclopentenone ring.[10] The relatively intense IR peak at 1605 cm^{-1} is usually associated with a conjugated alkene group.

The UV spectrum of **6** in methanol showed a moderately intense band centered at 228 nm with $\epsilon = 1.1 \times 10^4$ L mol^{-1} cm^{-1} consistent with the absorption of a conjugated carbonyl group.

The NMR spectrum showed the presence of a vinyl proton (triplet centered at 5.87 ppm vs. Me_4Si $J = 1.8$ Hz) coupled to two equivalent protons. Multiplets centered at approximately 2.6 and 2.3 ppm, each equivalent to two protons, suggested the presence of methylene groups adjacent to C=O and/or C=C.[11] The rest of the spectrum displayed a broad unresolved band from about 1.3 to 1.9 ppm, with integration equivalent to 8 saturated protons, and a 3 hydrogen singlet at 1.20 ppm.



Structures **6**, **7**, **8**, and **9** at first sight seemed to satisfy the above analytical data. They all have one vinyl proton, a tertiary methyl group, 8 "high-field" methylene protons, C=O and C=C chromophores, and an appropriate number of methylene groups α to each of the two unsaturated groups. However, only **6** is consistent with a 1.8-Hz coupling constant observed for the vinyl proton of our photoproduct. All other structures contain methylene groups adjacent to the vinyl hydrogen which would be expected to give coupling constants of 6–7 Hz.[14,15] Also the chemical shifts for the vinyl protons of **8** and **9** would be expected to be close to the 6.57 ppm reported by House and Thompson[13] for **10**. We observed an absorption signal attributed to a vinyl hydrogen at 5.87 ppm in the NMR spectrum of **6** in agreement with the resonance observed at 5.81 ppm for 3-*tert*-butylcyclopentenone.[16] Furthermore, the UV and IR data of Djerassi and Marshall[12] for an authentic sample of **7** are incompatible with the data for our photoproduct.

Effects of Deuteration. Following deuterium exchange, **6** had an average of 2.5 deuterium atoms per molecule as determined by mass spectrometry and confirmed by its NMR spectrum. The corresponding methylene and vinyl hydrogen signals were reduced in intensity and showed quadrupole broadening without splitting. Complete exchange of the hydrogens α to the carbonyl and the allyl hydrogens would generate molecule **11** with five deuterium atoms per molecule. Hence, only about 50% exchange was effected. The vinyl hydrogen was replaced by deuterium in 80% of the molecules while only 30% exchange occurred at the high-field methylene group adjacent to the carbonyl group and 60% at the allylic low-field methylene protons. The exchange of the vinyl hydrogen, which appears to be nonreplaceable, has been reported by other investigators.[17] This seemingly unusual isotopic exchange pattern was determined by the stereoelectronic control of the relative rates of exchange. The orienting influ-

ence depends on the degree of delocalization of electrons in perturbed axial and equatorial bonds α to the exocyclic π orbital.[18]

Since the transition state for enolization–ketonization type processes is stabilized by bonding between the α carbon and the carbonyl carbon involving δ–π delocalization, an axial δ substituent is lost or gained preferentially over an equatorial δ substituent. In flexible systems such as cyclohexanone, all α hydrogens eventually assume an axial orientation and are subject to facile exchange. In more rigid ring systems such as cyclopentanone and especially cyclopentenone, however, the hydrogens are fixed in an intermediate position midway between the axial and equatorial orientations. Furthermore, the transition state for the allylic hydrogen exchange is stabilized by bond delocalization over the 5 atoms of the enone system. It is reasonable, therefore, that in photoproduct **6** the exchange of hydrogens α to the carbonyl group is less favorable than that of the allylic hydrogens.

Base-catalyzed exchange of **6** over two days in deuteriomethanol yielded a product with an average of 3.6 deuterium atoms per molecule or about 70% replacement of exchangeable hydrogens. The distribution was d_1 3%, d_2 11%, d_3 26%, d_4 44%, and d_5 16%. The main peaks in the mass spectrum of the deuterated **6** were found at *m/e* 153, 136, and 124 corresponding to loss of CH_3, C_2D_4, and CD_2CO, respectively. The analogous peaks in nondeuterated **6** were at *m/e* 149 ($M^+ - CH_3$), *m/e* 136 ($M^+ - C_2H_4$), and *m/e* 122 ($M^+ - CH_2CO$, base peak).

NMR Spectroscopy in Sulfuric Acid. The species responsible for light absorption and subsequent rearrangement is undoubtedly hydroxycarbocation **4** formed by protonation of **1** in concentrated sulfuric acid solution. Its NMR spectrum in D_2SO_4 correlates well with that of unprotonated **1** in CD_2Cl_2. The signal for the vinyl proton found at 5.64 ppm in CD_2Cl_2 was shifted to lower field by 0.8 ppm in D_2SO_4. The multiplet between 2.2 and 2.5 ppm in CD_2Cl_2 due to the methylene protons adjacent to C=O and C=C was separated into two broad unresolved bands at 2.6 and 2.9 ppm in D_2SO_4. Except for some loss of resolution, the saturated methylene groups appeared in the same spectral range from 1 to 2 ppm in both solvents. Similarly, the chemical shift of the methyl group remained unchanged. The downfield shift exhibited by protons adjacent to the α,β-unsaturated carbonyl group in sulfuric acid is undoubtedly due to the electron withdrawing or deshielding effect of protonation on the carbonyl group. It is thus apparent that **1** undergoes complete protonation but maintains its structural integrity when dissolved in sulfuric acid solution.

In separate experiments, 10-methyloctalone **1** was photolyzed in D_2SO_4 at 300 nm directly in the NMR tube. The extent of photoconversion was monitored by recording ultraviolet absorption spectra of aliquots diluted with sulfuric acid. After 4 h of total irradiation the **4** → **5** photoreaction was complete. The NMR spectrum of the irradiated solution was remarkably clean and consistent with photonated photoproduct structure **5**.

The Second Photochemical Rearrangement. Solutions (3×10^{-3} M) of 10-methyloctalone in sulfuric acid were first photolyzed at 300 nm until the first step was complete, as determined by recording the UV absorption of diluted aliquots. The photolysis was then continued with a UV source of 254 nm. This second irradiation was terminated before all the first product **5** was reacted in order to minimize the complicating side or consecutive reactions which tended to give more complex reaction mixtures. Usually the first **4** → **5** step required about 4 h for completion. The subsequent photolysis at 254 nm was stopped after another 4 h.

The final solution was hydrolyzed over ice and extracted with methylene chloride. GLC analysis of the extract revealed the presence of one major product representing about 50% of all components, eight other minor products, and unreacted cyclopentenone **6**. When the residue of the evaporated methylene chloride was redissolved in acid, it gave the same UV–visible absorption as the acid solution before hydrolysis, and the same as that prepared from dissolving the GLC-trapped components in acid. These findings show that no essential change occurred during hydrolysis, that virtually all the products are volatile, and that they do not exhibit sensitivity to atmospheric oxygen during processing.

Characterization of Second Photoproduct. Analytical samples of the major product from the photolysis of **5** were obtained by repeated collection of GLC fractions from the mixture of hydrolyzed and extracted products. The mass spectrum exhibited a relatively weak molecular ion peak at *m/e* 164, the same as that of **1** and its first photoproduct **6**. Therefore, it seems that the second photochemical reaction represents another isomerization. Base-catalyzed deuterium exchange of the second product gave a species with molecular ion at *m/e* 168, a gain of four mass units, suggestive of four exchangeable hydrogen atoms.

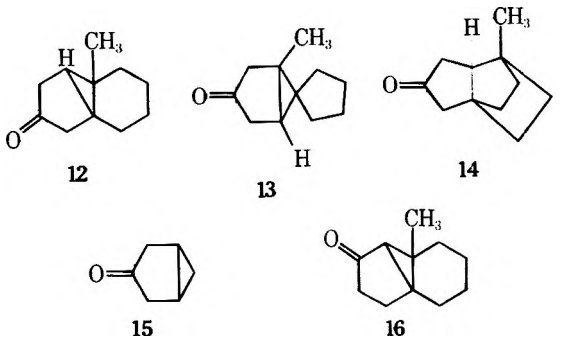
The UV absorption spectrum of an ethanolic solution showed only a low intensity peak (ϵ = 24 L mol^{-1} cm^{-1}) around 280 nm with no other absorption band above 220 nm. The UV spectrum of an alcohol solution of the unresolved reaction mixture showed a broad relatively strong absorption band around 260–280 nm suggesting conjugated chromophores in the minor photoproducts. This could be the source of the 340-nm peak in the TLS diagram of the second photochemical conversion in sulfuric acid. The IR spectrum of the major product showed a peak at 1742 cm^{-1}, consistent with an unconjugated carbonyl group in a five-membered ring.[10]

The ^{1}H NMR spectrum showed the presence of a methyl singlet at 1.02 ppm, eight methylene protons between 1.4 and 1.8 ppm, a partially resolved multiplet equivalent to three protons between 2.0 and 2.3 ppm, and a singlet equivalent to two protons at 2.4 ppm. There was no signal attributable to vinyl protons.

Several noise-decoupled ^{13}C magnetic resonance spectra were recorded with a different number of scans, different angles of pulsation, and different time intervals between pulses. Analysis of these spectra revealed the presence of two quaternary carbon atoms at 50.2 and 54.1 ppm, a carbonyl carbon part of a cyclopentanone ring at 219.2 ppm,[19] and eight carbons bearing hydrogen atoms between 14.4 and 43.6 ppm. Again, no absorption signals appeared in the spectral range between 120 and 170 ppm, usually associated with alkene carbon atoms. The ^{13}C atoms with chemical shifts of 54.1 and 50.2 ppm and the carbonyl carbon gave resonance signals of lower intensity than the rest of the carbon atoms by a factor of about 2–2.4, as expected for ^{13}C atoms not bonded to hydrogens. The two quaternary carbons and the non-aldehydic carbonyl carbon require longer relaxation times and a slower scan rate than the proton-bearing carbons.[20]

The above analytical data have established that the second photoproduct must have a molecular weight of 164, a cyclopentanone ring, four exchangeable hydrogen atoms, five low-field protons, two of which give rise to an NMR singlet, eight protons in the methylene region between 1 and 2 ppm, a methyl group giving a singlet NMR peak, two quaternary carbon atoms, and no alkene group. There are three structures satisfying these requirements, namely **12**, **13**, and **14**.

Both configurations **12** and **13** contain the bicyclo[3.1.0]-hexan-3-one moiety. Strong support for the existence of such a group in the structure of the second photoproduct was provided by the similarity of its infrared spectrum with that of bicyclo ketone **15** synthesized by Winstein and Sonnensberg.[21] The resemblance is strong enough to exclude possibility **14** from consideration.[22]

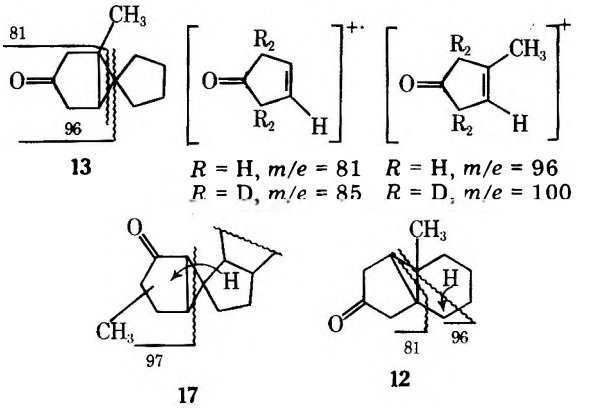


The selection of structure **13** over **12** was more subtle. A singlet corresponding to the angular methyl group was reported[5] at 1.20 ppm in the ^1H NMR spectrum of **16** which has marked structural similarity to **12**. In contrast, the methyl signal of our second photoproduct was found at 1.02 ppm. Molecular models showed that the hydrogens of the freely rotating methyl groups of **12** and **16** have very similar orientations with respect to the carbonyl groups. Therefore, one would expect almost identical chemical shifts in their signal. On the other hand, the methyl group in **13** is oriented directly away from the carbonyl group and would be expected to absorb at higher field than in **16**. This also agrees with the reported signals at 1.1 ppm for methyl groups located at the bridgehead carbon in bicyclopropanes.[23]

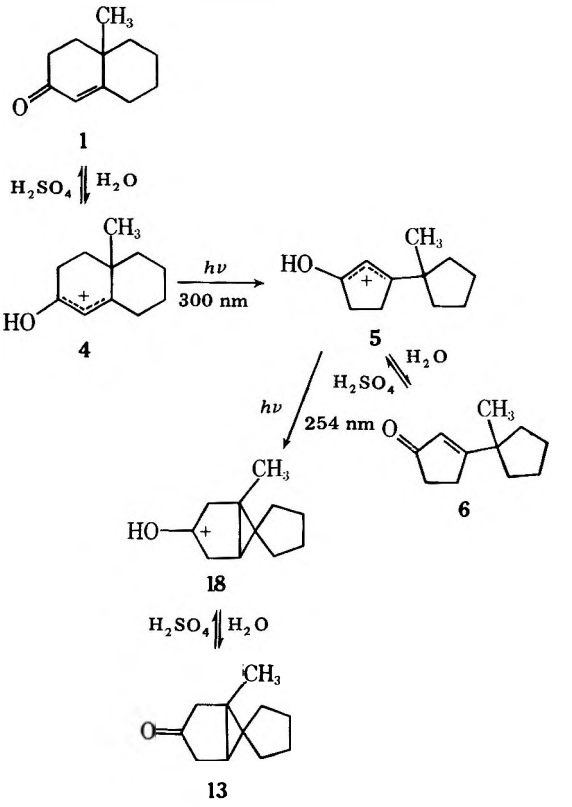
The mass spectra of our last photoproduct and its deuterated analog are also more consistent with configuration **13** than with **12**. The base peak in the second photoproduct was found at *m/e* 81. The analogous peak in its deutero derivative is also at *m/e* 81 but relatively less abundant. This suggests that the peak at *m/e* 81 is caused by different fragments, one of which contains no exchangeable hydrogen atoms. When the fragment containing exchangeable hydrogens is "subtracted out" by deuteration, the base at *m/e* = 81 becomes relatively less abundant. The presence of such a fragment was confirmed by the appearance of a prominent new peak at *m/e* 85 in the deuterated analog. Another significant difference between the two spectra consists of the changing of the prominent peak at *m/e* 96 in the product to *m/e* 100 in the deuterated product. This fragmentation pattern is easier to rationalize with structure **13** than **12** as shown in Scheme I. Loss of exocyclic methyl group is expected to occur readily. The double fission of the three-member ring suggested above is not unique. In fact,[24] cleavage of the two bonds of the cyclopropane ring lead to the base peak at *m/e* 97 in the mass spectrum of **17**. The formation of fragments at *m/e* 81 and 96 in the spectrum of **12** would require cleavage of two cyclopropane bonds (one of which is part of a cyclohexane ring) and cyclohexane bond adjacent to the quaternary C_9 (*m/e* 81) or to C_9 (*m/e* 96) as shown in Scheme I. Such events, requiring a two-ring opening step, seem substantially less probable than the fragmentation shown for **13** in the same scheme.

Reaction Mechanism. The overall photochemical transformation of **1** in sulfuric acid is summarized is Scheme II. The outcome is quite different from the reactions reported for the photolysis of 10-methyloctalone in various neutral organic solvents.[4-6] The absence of dimerization and reduction-dimerization combinations is not surprising, since, in acid, such reactions would require collisional interaction of two cations, an electrostatically unfavorable event. That α,β to β,γ double bond photoisomerization does not occur in acid is understandable since it also involves a collision between two cationic solute molecules and since it seems to originate in an n,Π^* rather than a Π,Π^* excited triplet state. Since in sulfuric acid the nonbonding electrons of the carbonyl oxygen are subject to protonation, a n,Π^* reactive level excitable with light of 300 nm is extremely unlikely.

Scheme I



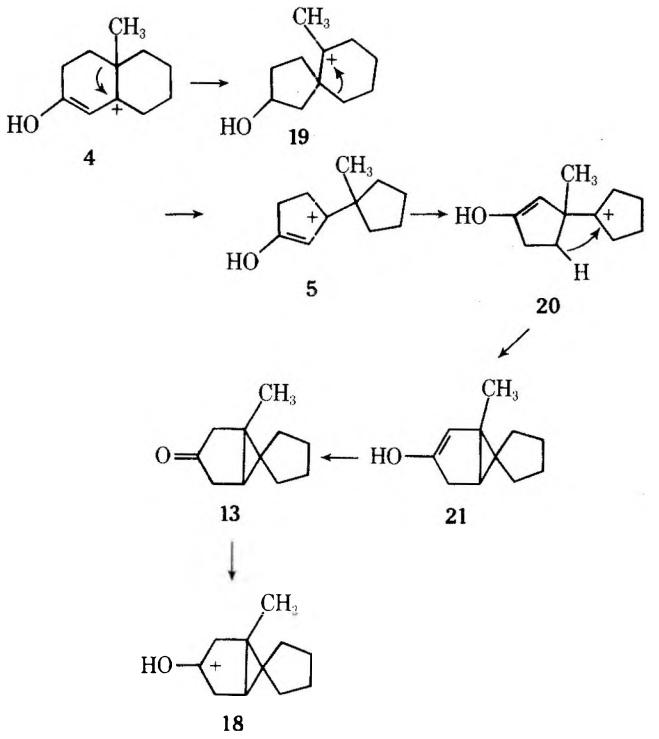
Scheme II



The formation of hydroxycarbocation **5** from protonated bicyclic cyclohexenone **4** is readily visualized in terms of two 1,2 shifts with the intermediate formation of tertiary cation **19**, as shown in Scheme III. Actually only the first 1,2 migration needs to be photochemically induced since the second **19** → **5** step could well take place after demotion to the ground state. The latter involves an energetically favorable transformation to a more stable allylic cation with further delocalization on the hydroxyl oxygen.

The hydrolysis product **6** was isolated in 2–5% during the photolysis of **1** in alcohol.[5] It was shown to be a side product from the photoreaction of tricyclic ketone **16** and not directly from **1**. The photochemical **16** → **6** rearrangement was reversible. To explain retention of chirality at C_1 and inversion at C_{10} on going from **16** to **6**, the authors had to postulate a diradical intermediate formed by initial homolytic cleavage of the C_4–C_{10} bond, an unusual step in both ground and photochemical reactions.[5] We feel that the two 1,2-shifts mechanism from **4** to **5** is reasonable. Furthermore, no hydroxycarbocation corresponding to **16** could be detected during the **4** → **5** reaction. If an intermediate similar to the diradical proposed for **16** → **6** reaction were formed in the acid reaction,

Scheme III



some protonated **16** should have been detectable. There is one more basic difference between the photochemical reaction of **1** in alcoholic solution and in concentrated acid. The former gave side-product cyclopentenone **6** in less than 5% whereas the **4** → **5** reaction was essentially quantitative.

The mechanism of the second photorearrangement in acid solution from **5** to **18** is alsc reasonably explained by a sequence of a 1,2-shift, γ-proton elimination, tautomerization, and reprotonation, as shown in Scheme III. In terms of ground-state reactions, the 1,2 shift of a methyl group in the **5** → **20** initial step is apparently endothermic, as it converts an allylic cation with further stabilization from delocalization over the hydroxylic oxygen, to a simple tertiary carbocation. This undoubtedly is an excited-state reaction. Elimination of a proton with cyclopropane ring formation, as shown for the **20** → **21** step, is a well established pathway for carbocation stabilization.[25] The remaining enol → ketone tautomerization from **21** to **13** and reprotonation to homoaromatic[26] carbocation **18** are readily acceptable steps. Again, only the initial 1,2 shift requires an electronically excited state, while all the subsequent steps of the **5** → **18** rearrangement are well understood in terms of ground-state reactions.

Experimental Section

General. Ultraviolet spectra were recorded with a Cary 14 spectrophotometer.[27] Infrared spectra (IR) were obtained on a Perkin-Elmer 467 grating spectrophotometer with CCl_4 as solvent. Nuclear magnetic resonance (NMR) spectra were recorded with a Brucker WH-90 Fourier-transform spectrometer in CD_2Cl_2 or $CDCl_3$, and chemical shifts are reported in parts per million (δ) from tetramethylsilane. Gas–liquid chromatographic (GLC) analyses were performed with a Hewlett-Packard 5750B gas chromatograph with flame ionization detector and helium carrier gas. Columns were: column A, 6 ft × 0.125 in., 5% Triton X-305 on Chromasorb W; column B, 10 ft × 0.125 in., 3% JXR on Gas Chrom Q; column C, 4 ft × 0.125 in., 3% JXR on Gas Chrom Q; column D, 17 × 0.25 in., 5% Triton X-305 on Chromasorb W. Mass spectra were obtained with an LKB-9000 combined gas chromatograph–mass spectrometer at an ionization potential of 70 eV employing either columns A or C.

The photolysis apparatus consisted of five low-pressure lamps, either 1.3-W type RPR-3000A or 1.8-W type RPR-2537A (The Southern New England Ultraviolet Co., Middletown, Conn.) arranged in a circle with a 30-mm core. Photolysis of dilute solutions was carried out in a 1-cm ground glass stoppered quartz cuvette polished on four sides, with magnetic stirring and cooling by forced air draft. Preparatory reactions on more concentrated solutions were carried out in a Vycor cylindrical cell (22-mm i.d. × 33-cm length) cooled with a 16-mm o.d. cold-finger condenser with nitrogen bubbling for agitation.

Synthesis of $\Delta^{1,9}$-10-Methyl-2-octalone. The procedure of Hussey[28] was followed except that the mole ratio of methiodide to ketone was 2:1, essentially as recommended by Dauben.[29] A solution of 9 g each of 2-methylcyclohexanone and potassium *tert*-butoxide in 100 mL of anhydrous *tert*-butyl alcohol was refluxed for 1 h. A solution of 46 g of 4-diethylamino-2-butanone methiodide (from 23 g each of 4-diethylamino-2-butanone and methyl iodide mixed slowly in 100 mL of anhydrous *tert*-butyl alcohol) was added slowly with good cooling. After 16 h at room temperature, the mixture was heated to reflux for 1 h, and then acidified with ice cold hydrochloric acid. Solvent was removed under vacuum and the residue extracted with ether. Removal of the ether solvent and vacuum distillation of the remaining liquid gave 2.2 g of the crude octalone, bp 114–127 °C (4 mm), which proved to be 75% 10-methyloctalone by GLC analysis (13% yield). Further purification was by GLC fractionation using column D.

Preparation of Deuterated Species. Exchange deuteration was carried out on milligram amounts of photoproduct dissolved in a few tenths of a milliliter of deuteriomethanol to which a catalytic amount of sodium methoxide was added. The temperature of the solution was maintained at 50 °C for several hours after which the solvent was removed under a stream of nitrogen. The residue was dissolved in methylene chloride for injection into the gas chromatograph–mass spectrometer.

Time-Lapse Spectrometry. Changes in the UV spectrum of a 6×10^{-5} M solution of 10-methyloctalone in concentrated sulfuric acid were recorded upon successive short intervals of irradiation with light of 300-nm wavelength (RPR-3000A source). Upon disappearance of the last traces of the starting octalone, 254-nm wavelength source lamps (RPR-2537A) were installed in the photochemical reactor and further changes in the UV spectrum were recorded upon continued photolysis.

Photoproduct 6. Forty milliliters of a 0.003 M solution of 10-methyloctalone in concentrated sulfuric acid was irradiated for 2 h with light of 300-nm wavelength. Monitoring of the photolysis was by UV spectroscopy on diluted aliquots. Upon disappearance of the last trace of starting material, the sulfuric acid solution was quenched in 250 g of ice and extracted with ether. Analysis of the extract showed the presence of a single photoproduct **6**. Isolation of **6** was by GLC employing column B; spectral data: UV_{max} (MeOH) 228 nm, log ε 4.04; IR (CCl_4) 3080, 2875, 1713, 1683, 1605, 1184, 990, 866, and 847 cm^{-1}; ^1H NMR (CD_2Cl_2, 90 MHz) δ 5.87 (*t*, 1 H, *J* = 1.8 Hz vinylic H), 2.6, 2.3 (m, 2H ea, cyclopentenone CH_2), 1.9-1.3 (unresolved m, 8H cyclopentane CH_2), 1.20 (s, 3H, CH_3). Mass spectrum *m/e* (rel. intensity): perhydro species 164 (M^+, 33), 149 (22), 136 (47), 122 (100); deuterated species 168 (M^+, 45), 153 (16), 136 (43), 124 (100).

Photoproduct 13. Forty milliliters of a 0.05 M solution of 10-methyloctalone in concentrated sulfuric acid was irradiated for 24 h with light of 300-nm wavelength. Conversion of the protonated octalone to protonated photoproduct **6** was complete as shown by UV scans of diluted aliquots. The source lamps were changed to 254-nm wavelength (RPR-2537A) and

irradiation continued for an additional 48 h. The sulfuric acid solution was quenched in 250 g of ice and extracted with ether. Analysis of the extract and isolation of the principal photoproduct **13** was by GLC using column A.

Spectral data: IR (CCl_4) 3470, 2990 (v w sh) 2952, 2920 (sh), 2887, 2860 (sh), 1742, 1715 (sh), 1480, 1452, 1402, 1380, 1261, 1177, 1160, 1130, 1103, 1062, 1025, 955, 910, and 840 cm^{-1}. ^1H NMR ($CDCl_3$, 90 M Hz) δ 2.40 (s, 2H); 2.3–2.0 (m, 3H); 1.7–1.4 (unresolved m, 8H cyclopentane CH_2); 1.02 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 22.6 M Hz) δ (rel. intensity) 219.2 (45), 54.1 (47), 50.2 (42), 43.6 (81), 41.9 (70), 40.4 (88), 37.8 (82), 31.5 (83), 25.5 (83), 24.8 (100), 14.4 (74). Mass spectrum *m/e* (rel. intensity): perhydro species 164 (M^+, 5), 149 (13), 136 (10), 123 (14), 122 (18), 109 (30), 107 (20), 96 (42) 93 (30), 91 (22), 81 (100), 67 (68); deuterated species 168 (M^+, 8), 153 (16), 140 (15), 127 (22), 124 (18), 113 (22), 112 (26), 110 (20), 109 (22), 100 (58), 95 (32), 93 (28), 85 (72), 81 (100), 69 (52).

Acknowledgment. This work was supported in part by the Energy Research and Development Administration on Contract E-(40-1)-3797 and by the Research Committee of The George Washington University.

Registry No.—**1**, 826-56-2; **6**, 22960-97-0; **13**, 63076-57-3.

References and Notes

(1) Taken from the doctoral dissertation of Donald G. Cornell at George Washington University, 1976.
(2) Agriculture Research Service, U.S. Department of Agriculture.
(3) See, for example, P. J. Kropp in "Organic Photochemistry", O. L. Chapman Ed., Marcel Dekker, New York, N.Y., Vol. 1, 1967; K. Schaffner in "Advances in Photochemistry", W. A. Noyes, G. S. Hammond, and J. N. Pitts, Ed., Vol. 4, Interscience, New York, N.Y., 1966, p 81, and in *Tetrahedron* **30**, 1891 (1974); O. L. Chapman in "Advances in Photochemistry", W. A. Noyes, Ed., Vol. I, Interscience, New York, N.Y., 1963, p 323.
(4) H. E. Zimmermann, R. G. Lewis, J. J. McCullough, A. Padwa, S. W. Staley, and M. Semmelback, *J. Am. Chem. Soc.*, **88**, 1965 (1966).
(5) D. Bellus, D. R. Kearns, and K. Schaffner, *Helv. Chim. Acta*, **52**, 971 (1969).
(6) P. Margaretha and K. Schaffner, *Helv. Chim. Acta*, **56**, 2884 (1973).
(7) H. A. Jones and R. Hahnel, *Steroids*, **13**, 693 (1969); H. A. Jones, *Can. Spect.*, 10 (Jan 1971).
(8) N. Filipescu, F. L. Minn, and J. W. Pavlik, *Anal. Chem.*, **43**, 83 (1971); N. Filipescu and J. W. Pavlik, *J. Am. Chem. Soc.*, **92**, 6062 (1970).
(9) R. I. Zalewski and G. E. Dunn, *Can. J. Chem.*, **47**, 2263 (1969).
(10) K. Nakanishi, "Infrared Absorption Spectroscopy", Holden-Day, San Francisco, Calif., 1962.
(11) C. F. Hammer, "NMR Chemical Shifts", 3rd ed, Georgetown University, Washington, D.C., 1966.
(12) C. Djerassi and D. Marshall, *J. Am. Chem. Soc.*, **80**, 3986 (1958).
(13) H. O. House and H. W. Thompson, *J. Org. Chem.*, **26**, 3729 (1961).
(14) R. R. Fraser and D. E. McGreer, *Can. J. Chem.*, **39**, 505 (1961).
(15) N. Heap and G. H. Whitham, *J. Chem. Soc. B*, 164 (1966).
(16) H. N. A. Al-Jallo and E. S. Waight, *J. Chem. Soc. B*, 73 (1966).
(17) R. H. Shapero, J. M. Wilson and C. Djerassi, *Steroids*, **1**, 1 (1963); B. W. Rockett, T. M. Harris and C. R. Hauser, *J. Am. Chem. Soc.*, **85**, 3491 (1963); M. F. Zinn, T. M. Harris, D. G. Hill, and C. R. Hauser, *J. Am. Chem. Soc.*, **85**, 71 (1963).
(18) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 6269 (1956).
(19) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley, New York, N.Y., 1972. See spectra no. 113 and 180.
(20) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemistry," Wiley, New York, N.Y., 1972.
(21) S. Winstein and J. Sonnenberg, *J. Am. Chem. Soc.*, **83**, 3235 (1961).
(22) Most of the discrepancies between the IR spectra of the second photoproduct and that of bicyclic ketone **15** can be accounted for by the presence of a methyl substituent in the former.
(23) W. G. Dauben, L. Schutte, R. E. Wolf, and E. J. Deviny, *J. Org. Chem.*, **34**, 2512 (1969).
(24) J. Frei, C. Ganter, D. Kogi, K. Kocsis, M. Milijkovic, A. Siewsinski, R. Wenger, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **49**, 1049 (1966); L. Lorenc, M. Milijkovic, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **49**, 1183 (1966).
(25) See, for example, J. March in "Advanced Organic Chemistry," McGraw-Hill New York, N.Y., 1968, p 141.
(26) S. Winstein and J. Sonnenberg, *J. Am. Chem. Soc.*, **83**, 3235, 3244 (1961).
(27) Reference to brand or firm name does not constitute endorsement by the U.S. Department of Agriculture over others of a similar nature not mentioned.
(28) A. S. Hussey, H. P. Liao, and R. H. Baker, *J. Am. Chem. Soc.*, **75**, 4727 (1953).
(29) W. G. Dauben, J. B. Rogan, and E. J. Blanz, *J. Am. Chem. Soc.*, **76**, 6384 (1954).

Stereoselectivity of the Retro-Ene Reaction of 2-Vinylcyclohexanols[1]

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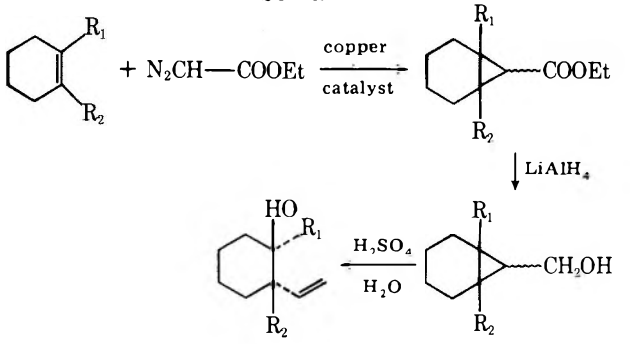
Received April 11, 1977

The retro-ene reaction of a 2-vinylcyclohexanol occurs readily in the vapor phase at 400–450 °C giving an unsaturated carbonyl compound in good yield. For the reactant the terms cis and trans refer to the hydroxyl and vinyl groups, R_1 refers to the other group on C_1, and R_2 to that at C_2. The numbers listed refer to percent *E*, percent *Z*, percent unidentified materials, and overall yield of product. Vapor phase reaction of the following examples was carried out: trans, 1 H, 2 H, 96, 0, 4, 95; cis, 1 H, 2 H, 59, 36, 5, 97; trans, 1 Me, 2 H, 92, 0, 8, 98; cis, 1 Me, 2 H, 52, 44, 4, 93; mixture trans (53), cis (47), 1 H, 2 Me, 81, 14, 5, 92; mixture trans (90) cis (10), 1 Me, 2 Me, 92, 0, 8, 96. The results suggest that the reaction is concerted and the products are kinetically determined. The reaction constitutes a useful stereoselective procedure for the synthesis of trisubstituted olefins.

The last decade has seen a great enhancement of interest in the stereoselective syntheses of double bonds of known configuration. Problems associated with the widespread dispersal of persistent insecticides in the environment and the discovery of insect pheremones have focussed attention particularly on the preparation of trisubstituted double bonds.[3] Many concerted thermal rearrangements exhibit a high degree of stereoselectivity, and numerous examples of their use for the synthesis of such alkenes have been reported.[4] Though the retro-ene reaction has not been used for this purpose, Arnold and Smolinsky[5] have established that rearrangement of *trans*-2-(alk-1-enyl)cycloalkanols leads to unsaturated aldehydes in high yield and apparently with high stereoselectivity. They examined cycloalkanols of varying ring size from cyclopentanols to cycloheptanols. In all cases the double bonds formed were disubstituted, and only the trans isomers were found. These results suggested that the retro-ene reaction might be useful for the stereoselective synthesis of more highly substituted alkenes. However, in view of the known sensitivity of the ene reaction to steric effects,[6] the stereoselectivity observed for disubstituted alkenes cannot a priori be extrapolated to more hindered systems. Therefore to ascertain the

Scheme I



1t, $R_1 = R_2 = H$
2t, $R_1 = Me$; $R_2 = H$
4t, $R_1 = R_2 = Me$

potential of the retro-ene reaction for the synthesis of alkenes of known configuration we have prepared and pyrolyzed a series of stereoisomeric 2-vinylcyclohexanols.

Reactants, Synthesis, and Stereochemistry

Arnold[5] prepared *trans*-2-alkenylcyclohexanols by treating cyclohexene oxide with an acetylide. This method suffers from poor yields and cannot be applied in general to substituted oxides. Both *cis*- and *trans*-2-vinylcyclohexanols have been prepared by Crandall.[7] He based his configurational assignment on the reasonable assumption that vinyllithium reacts with cyclohexene oxide to open the ring in the *trans* manner. For our studies it was advantageous to use a route with greater general utility for the preparation of substituted vinylcyclohexanols. This route is shown in Scheme I. In the first step the use of an activated copper catalyst rather than a soluble ionic copper coordination compound[8] gave better yields and no C–H insertion products. Reduction of the ester and formation of the homoallylic alcohol proceeded routinely. Though formation of the homoallylic product from a cyclopropylcarbinyl reactant is attributed to thermodynamic control, the homoallylic cation apparently reacts with water almost exclusively on the axial side. We obtained appreciable amounts of cis isomers only when the alcohol formed was tertiary. It is not clear whether the cis isomer[9] arises by ring inversion at the cation stage or via equilibration of the tertiary alcohol after its formation. It is obvious, however, that the major product results from kinetic control in the trapping step.

Acid catalyzed reaction of 7-hydroxymethylbicyclo[4.1.0]heptane gave only **1t**, with no discernible **1c** present. Collins' oxidation of **1t** gave 2-vinylcyclohexanone,[10] and reduction of this ketone with lithium aluminum hydride permitted a correlation between our assignments and those of Crandall.[7] When 2-vinylcyclohexanone was reduced with lithium tri-*s*-butylborohydride, **1c** was obtained in better than 95% purity. Reaction of 1-methyl-7-hydroxymethylbicyclo[4.1.0]heptane gave a mixture of two isomeric tertiary alcohols in 83:17 ratio. The major product was assigned the structure **2t** with vinyl and hydroxyl groups trans,[9] partially

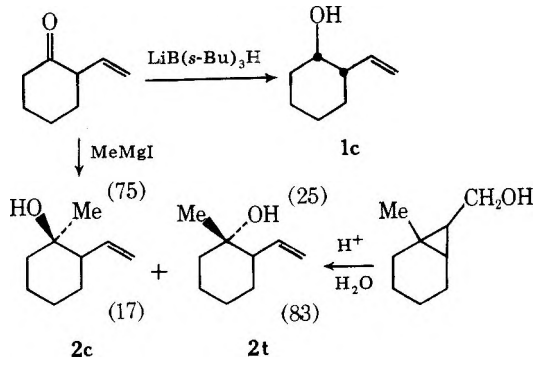


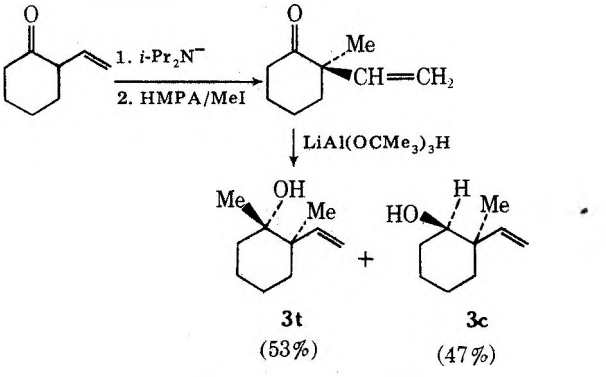
Table I. Stereoselectivity of the Retro-Ene Reaction of Substituted Vinylcyclohexanols

Reactant	% *E*	% *Z*	Yield[a]	% Other products
1t	100	0	95	4
1c	62	38	97	5
2t	100	0	98	8
2c	54	46	93	4
3t + **3c** (53:47)	85	15	92	5
4t + **4c** (90:10)	100 (−5 + 0)	0 (+5 − 0)	96	8

[a] Yields given are of total isolated material including by-products.

by analogy with the first example. This assignment was confirmed by a study of the reaction between 2-vinylcyclohexanone and methylmagnesium iodide. Two products were obtained in a 75:25 ratio. In this case the major isomer should be the cis product **2c** because the Grignard reagents generally enter equatorially.[11] As expected the major product of the ring opening corresponds to the minor isomer from the Grignard reaction. Opening of the cyclopropane ring of 1,6-dimethyl-7-hydroxymethylbicyclo[4.1.0]heptane produced a mixture of **4t** and **4c** in 86:14 ratio. Thus both reactions which lead to tertiary alcohols give very similar ratios of isomers. Assignment in this last case was based purely on analogy with the earlier reactions.

The final pair of isomers, **3t** and **3c**, was obtained by methylation of 2-vinylcyclohexanone followed by reduction of the methylation product. Alkylation caused unexpected problems, principally because we failed to recognize just how lethargic the S_N2 reaction of this enolate is. Reaction of the carbanion with methyl iodide must be carried out at elevated temperatures, even in the presence of HMPA. Reduction of 2-methyl-2-vinylcyclohexanone is not expected to show any great degree of selectivity because the methyl and vinyl groups have similar size requirements. This expectation was borne out since a mixture containing 53% of **3t** and 47% of **3c** was



obtained. Separation of the mixture was not attempted, and the more abundant isomer was assigned the **3t** structure, primarily because the resonance of methyl group in that isomer was further downfield (1.13 ppm) than that of the other isomer (0.98 ppm).[12]

Results and Discussion

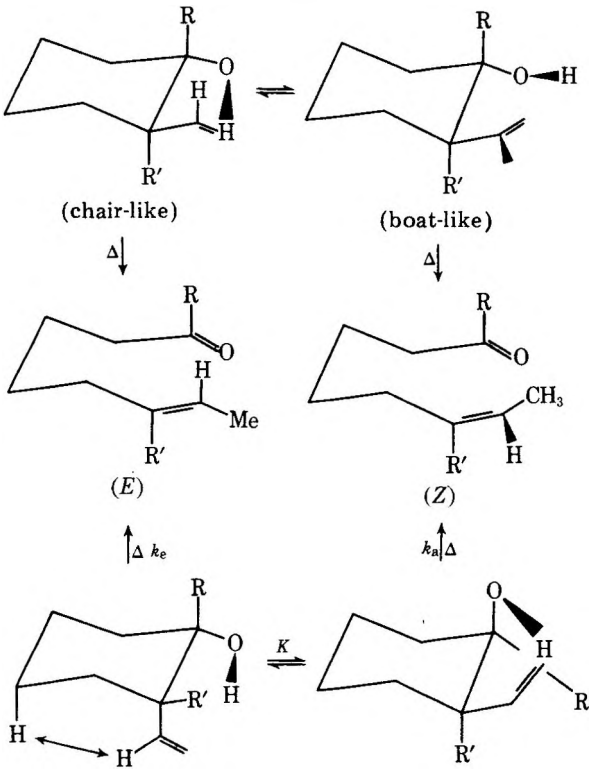
The vinylcyclohexanols were pyrolyzed in a flow reactor using nitrogen as a carrier gas. No attempt was made to optimize contact times or temperatures, but recovery was excellent in all cases, and the reaction was extremely clean. Aside from the retro-ene product only traces (4–8%) of other products were found, and no attempt was made to separate and identify these minor products. The results are listed in Table I. Before considering the significance of these data, we will discuss the structural assignments for the products. Products from both

isomers of **1** and **2** have disubstituted double bonds, and the presence or absence of the out-of-plane C–H bending band at 970 ± 5 cm^{-1} was used to determine the double bond geometry. Coupling constants for the olefinic protons could not be obtained from the NMR spectra. Interestingly, this assignment was supported in both cases by the appearance of virtual coupling[13] in the resonance of the allylic methyl groups of both trans isomers, and its absence in the cis isomers.

The initial product from **3t** + **3c** was inseparable on all GLC columns we tried, but the NMR spectrum showed that it was a mixture since two cleanly separated resonances appeared for the aldehydic proton with an intensity ratio ca. 5:1. The aldehyde was reduced to an alcohol, and the alcohols were separated by GLC giving a ratio of the two isomers of 85:15. The assignment of configurations to the stereoisomers of trisubstituted double bonds of the general type RC(Me)=CHR′ has generally been based on the chemical shift of the methyl group and the coupling constant between the methyl and the olefinic proton.[14] Two problems complicated application of this procedure to the products from **3t** + **3c**. First the difference between the chemical shifts for the methyl groups was smaller than normal, thus lending a measure of uncertainty to the assignment. Second the R′ group in our case is a methyl, and its doublet pattern could not be cleanly identified. As a result the apparent splitting of the internal methyl resonance in the spectrum of the isomer assigned the *E* configuration could not be attributed with confidence to that coupling. Both indicators, however, lead to the same assignment for the *E* isomer, and this assignment is in agreement with expections based on the first four examples and on theory. This internal consistency engenders confidence in the assignment. The final example **4t** + **4c** gave a product which was not separable on any column we tried; however, the NMR spectrum of the product showed one sharp singlet at 2.02. Since the aldehydic proton of 6-methyl-6-octenal showed peaks for the *E* and *Z* isomers separated by 15 Hz, we expected some small separation of the methyl resonances for the *E* and *Z* isomers of 7-methyl-7-nonen-2-one. However, even if some separation were present, about 5% of a second isomer would not be identified. The *E* assignment in this case was based purely on analogy.

The most obvious conclusion reached from our data is that the reaction of the trans isomers **1t** and **2t** (presumably also **3t** and **4t**) is highly stereoselective. Tests using mixtures of *E* and *Z* products from **1t** and **1c** showed that 0.1% of the *Z* isomer could be identified in the *E*. Thus stereoselectivity is at least 99.9% for **1t**. From this we conclude that the product is kinetically determined, and that stereomutation of the double bond does not occur. The stereoelectronic requirements for the ene reaction demand a parallel alignment of the O–H and C–C σ bond orbitals with the p orbitals of the π bond.[6] As Scheme II shows, this requirement can be quite adequately met by a chair-like arrangement in the (ee) conformer of the trans isomer. This gives the *E* isomer in the product. A boat-like arrangement which would give the *Z* isomer cannot meet the stereoelectronic requirement, and our results indicate this transition state must be at least 10 kcal/mol above the chair-like state. It is also very clear from our results that the cis reactant is much less stereoselective. To treat this case we assume that conformational interconversions of the cyclohexane ring are fast compared to the retro-ene reaction, and the Curtin–Hammett principle applies. Transition states of the chair-like type having the OH either equatorial or axial (k_e and k_a of Scheme II, respectively) are attainable. The k_e state meets the stereoelectronic requirement better than the k_a state, but the k_e state introduces some steric interaction between the vinyl hydrogen and an axial hydrogen on the ring. While it is difficult to make any clear predictions, one certainly expects that (a) stereoselectivity will be reduced in comparison with trans reactants, and (b) stereoselectivity will be a function of the substituents R and R′.

Scheme II. Conformational Effects on the Retro-Ene Reaction of 2-Vinylcyclohexanols



These ideas can be compared with our experimental results if we assume that the trans reactants are 100% stereoselective in all cases, and that the cis isomers with the equatorial hydroxyl give exclusively *E* products while those with axial hydroxyls lead only to *Z* products. Thus for **1c** k_e/k_a = 1.6; for **2c**, 1.2; for **3c**, 2.2; and no information can be obtained for **4c**. The values for k_e/k_a obtained seem quite reasonable in terms of the transition states. Clearly, addition of a methyl at C_1(R = Me) should increase the energy of the transition state for k_e (Me is axial), but the full 1.7 kcal/mol of the $\Delta G_{conf.}$ for methyl is not effective. The vinyl–methyl skew interaction in the k_a transition state could account for some increase in energy in that state. A $\Delta\Delta G^{\ddagger}$ of ca. 0.5 kcal/mol favoring k_a would account for the effect of changing R = H to R = Me. For the change R′ = H to R′ = Me, i.e., **1c** to **3c**, the methyl should show the opposite effect and a $\Delta\Delta G^{\ddagger}$ of 0.5 kcal/mol favoring k_e would give k_e/k_a = 2.2 for **3c**. The agreement is better than this simplistic approach deserves.

Experimental Section

7-Carbethoxybicyclo[4.1.0]heptane. A mixture of 82.0 g (1.0 mol) of cyclohexene, 2.9 g of benzoyl peroxide, and 222 mg of (trimethyl phosphite)copper(I) chloride[8] was heated until a green solution was obtained. To this was added a mixture containing 82 g of cyclohexene and 23 g (0.2 mol) of ethyl diazoacetate. The solution was heated to reflux overnight, and the cold mixture was filtered. Excess cyclohexene was removed by distillation, and the residual product was distilled with a 45-cm spinning band column giving 26 g (77%) of 7-carbethyoxybicyclo[4.1.0]heptane: bp 41 °C (1.9 mm) [lit.[15] bp 110 °C (18 mm)]; NMR (CCl_4) δ 1.13 (t, 3H, *J* = 7 Hz), 1.1–1.5 (broad m, 6H), 1.8 (broad m, 4H), 4.04 (q, 2H, *J* = 7 Hz).

1-Methyl-7-carbethoxybicyclo[4.1.0]heptane. A 13 g sample (0.14 mol) of 1-methylcyclohexene was treated with 6.9 g (0.06 mol) of ethyl diazoacetate according to the procedure described above. Distillation gave 4.4 g (40%) of 1-methyl-7-carbethoxybicyclo[4.1.0]-heptane: bp 125–130 °C (25 mm); NMR (CCl_4) δ 1.05 (s, 3H), 1.15 (t, 3H, *J* = 7 Hz), 1.1–1.3 (broad m, 5H), 1.6 (broad m, 4H), 4.04 (q, 2H, *J* = 7 Hz) [lit.[17] bp 110 °C (18 mm)].

Copper Catalyst. A solution containing 60 g of copper sulfate in 400 mL of water was mixed with 10 g of 20 mesh zinc, and the mixture was stirred for 2 h at 100 °C. The precipitate was removed by filtration and was treated for 30 min with 100 mL of a solution containing 2 g of iodine in 100 mL of acetone. The catalyst was isolated by filtration and was washed with a 1:1 mixture of acetone and hydrochloric acid. After having been dried in vacuo at 66 °C for 2 h, 6.6 g of catalyst was obtained.

1,6-Dimethyl-7-carbethoxybicyclo[4.1.0]heptane. A mixture containing 300 mg of the copper catalyst and 6.0 g (55 mmol) of 1,2-dimethylcyclohexene was heated to reflux and 6.3 g (55 mmol) of ethyl diazoacetate was added dropwise. The mixture was heated at reflux overnight, and the product was isolated as described above. Distillation gave 3.6 g (51%) of 1,6-dimethyl-7-carbethoxybicyclo[4.1.0]heptane: bp 133–135 °C (13 mm); NMR (CCl_4) δ 1.17 (t, 3H, J = 7 Hz), 1.1–1.3 (broad m, 4H), 1.23 (s, 6H), 1.6 (broad m, 4H), 4.02 (q, 2H, J = 7 Hz) [lit.[18] bp 105–125 °C (20 mm)].

7-Hydroxymethylbicyclo[4.1.0]heptane. A solution containing 5.6 g (33 mmoles) of 7-carbethoxybicyclo[4.1.0]heptane in 25 mL of anhydrous ether was added dropwise to a mixture of 1.25 g (32 mmol) of lithium aluminum hydride and 25 mL of ether. The reaction mixture was treated cautiously with 1 mL of water followed by 40 mL of 10% sulfuric acid. The product was taken up in ether and dried ($MgSO_4$), and the ether was removed giving 3.8 g (90%) of 7-hydroxymethylbicyclo[4.1.0]heptane: NMR (CCl_4) δ 0.70 (broad s, 2H), 1.1–1.2 (broad m, 5H), 1.73 (broad s, 4H), 3.33 (d, 3/2 H, J = 6 Hz), 3.59 (d, 1/2 H, J = 6 Hz) 4.4 (OH). This spectrum matches that of an authentic sample.[16]

1-Methyl-7-hydroxymethylbicyclo[4.1.0]heptane. A 4.4 g sample (24 mmol) of 1-methyl-7-carbethoxybicyclo[4.1.0]heptane was reduced as described above. There was obtained 3.3 g (97%) of a liquid: NMR (CCl_4) δ 0.70 (m, 1H), 1.11 (s, 3H), 1.1–1.3 (broad m, 5H), 1.7 (broad m, 4H), 3.59 (m, 2H), 3.97 (OH). This crude material was not purified but was used directly in the next step.

1,6-Dimethyl-7-hydroxymethylbicyclo[4.1.0]heptane. A sample of 1,6-dimethyl-7-carbethoxybicyclo[4.1.0]heptane was reduced as above, and the crude alcohol was isolated in 85% yield, 2.1 g: NMR (CCl_4) δ 1.04 (s, 3H), 1.16 (s, 3H), 1.1–1.3 (broad m, 5H), 1.6 (broad m, 4H), 3.54 and 3.68 (two d, 2H, J = 7 Hz), 4.08 (OH). The crude product was used directly in the next step.

***trans*-2-Vinylcyclohexanol (1t).** A mixture of 3.4 g (26 mmol) of 7-hydroxymethylbicyclo[4.1.0]heptane and 25 mL of 10% sulfuric acid was stirred at room temperature overnight. The product was taken up in ether, and the ether solution was washed with sodium bicarbonate solution and then with saturated sodium chloride solution. The solution was dried (Na_2SO_4), the ether was evaporated and the crude product, 3.2 g (94%), was distilled giving 1.2 g, bp 41 °C (1.9 mm) [lit.[7] bp 44 °C (2 mm)]. GLC analysis on a 5% FFAP column at 150 °C showed the product was a single substance: NMR (CCl_4) δ 1.2 (m, 4H), 1.78 (m, 5H), 2.42 (OH), 3.18 (apparent sextet, spacing 4 Hz, probable d of t, J_{aa} ~8, J_{ae} ~ 4 Hz), 5.05, 5.75 (ABM part of ABMX, 3H, J_{AB} ~ 2, $J_{AM} + J_{BM}$ = 28, J_{MX} = 6 Hz); IR (neat) 3400, 1640, 995, 910 cm^{-1}.

***trans*-1-Methyl-2-vinylcyclohexanol (2t).** Reaction of 1-methyl-7-hydroxymethylbicyclo[4.1.0]heptane, 3.1 g (22 mmol), with 25 mL of 10% sulfuric acid and isolation of the product as described above gave 1.0 g (32%) of a mixture of isomers after distillation. GLC analysis on a 5% FFAP column at 155 °C showed the mixture to contain 83% **2t** and 17% **2c**. Preparative GLC separation permitted isolation of 300 mg of pure **2t**: NMR (CCl_4) δ 1.02 (s, 3H), 1.0–2.2 (broad m, 9H), 2.3 (OH), 5.05, 5.88 (ABM of ABMX, 3H, J_{MX} = 7.5, $J_{AM} + J_{BM}$ = 27 Hz); IR (neat) 3500, 1640, 970, 910 cm^{-1}. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.82; H, 11.49.

***trans*-1,2-Dimethyl-2-vinylcyclohexanol (4t).** A 2.1 g (13.6 mmol) sample of 1,6-dimethyl-7-hydroxymethylbicyclo[4.1.0]heptane was stirred with 25 mL of 10% sulfuric acid and worked up according to the procedure above. The distilled product was obtained in 76% yield (1.6 g) and GLC analysis on a 5% FFAP column at 160 °C showed the product contained 86% **4t** and 14% **4c**: NMR (CCl_4) δ 1.02 (s, 3H), 1.08 (s, 3H), 1.5 (m, 8H), 4.92, 5.04, 6.12 (ABX, J_{AB} = 1.8, J_{AX} = 18, J_{BX} = 10 Hz). Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.97; H, 11.83.

2-Vinylcyclohexanone. A solution containing 2.0 g (16 mmol) of 2-vinylcyclohexanol was added in one portion to a solution containing 24 g (0.10 mol) of Collin's reagent[12] in 315 mL of methylene chloride. This mixture was stirred at room temperature for 2 h, and the solution was decanted from a gummy precipitate. The precipitate was extracted with methylene chloride and the combined extracts and supernatent solution was washed with 5% sodium hydroxide, then 5% hydrochloric acid. The solution was concentrated to ca. 50 mL, dried ($MgSO_4$), and the solvent removed, giving 1.82 g (92%) of crude ketone. Distillation, bp 95–96 °C (35 mm) [lit.[7] bp 35 °C (0.3 mm)], gave 1.67 g (85%) of 2-vinylcyclohexanone: NMR (CCl_4) δ 1.5–2.1 (broad m, 6H), 2.2–2.5 (m, 2H), 2.95 (m, 1H), 5.1 and 6.0 (ABM of ABMX, J_{AB} ~ 1.5, $J_{AM} + J_{BM}$ = 28, J_{MX} = 6.5).

***cis*-2-Vinylcyclohexanol (1c).** A solution of 1.08 g (8.7 mmol) of 2-vinylcyclohexanone in 25 mL of anhydrous THF was cooled in an ice bath under nitrogen, and 8.9 mL (8.9 mmol) of a 1 M solution of lithium tri-*s*-butylborohydride in THF was added dropwise. The solution was stirred at 0 °C for 6 h, and then 1 mL of water was added to the mixture. After 25 mL of ether had been added the solution was extracted with saturated ammonium chloride, water, and saturated sodium chloride. The ether solution was dried ($MgSO_4$) and the ether was removed by evaporation. The residue was mixed with 5 mL of acetic acid, the acid was neutralized with dilute sodium hydroxide, and the organic material was taken up in 10 mL of ether. To this was added 10 mL of 1.5 N sodium hydroxide and the mixture was cooled in an ice bath while 4 mL of 50% hydrogen peroxide was added. This mixture was stirred at room temperature for 12 h, and the layers were separated. The aqueous layer was extracted with ether; the ether solutions were combined and dried ($MgSO_4$). The ether was removed and the residue distilled giving 0.66 g (60%) of a liquid which GLC analysis showed was at least 95% **1c**, bp 68–70 °C (4 mm). Preparative GLC on a 3% DEGS column at 165 °C gave 200 mg of pure **1c**: NMR (CCl_4) δ 1.1–2.0 (broad m, 9H), 2.18 (b, OH), 3.80 (broad s, $W_{1/2}$ = 11 Hz, 1H), 5.1 and 5.9 (ABM of ABMX, J_{MX} = 6.5, $J_{AM} + J_{BM}$ = 28, J_{AB} ~1.5 Hz); IR (CCl_4) 3650, 3100, 1640, 1010, 920 cm^{-1}.

***cis*-1-Methyl-2-vinylcyclohexanol (2c).** A Grignard reagent was prepared from 15.6 mmol of methyl iodide, and a solution containing 1.8 g (14.5 mmol) of 2-vinylcyclohexanone in 20 mL of anhydrous ether was added dropwise. The reaction mixture was treated with saturated ammonium chloride solution and the ether layer was separated and dried ($MgSO_4$). The ether was evaporated and 2.0 g (93%) of crude alcohol was obtained. GLC analysis showed this contained 75% **2c** and 25% **2t**. A sample of **2c** was separated by preparative GLC on a 5% FFAP column at 135 °C: NMR (CCl_4) δ 1.13 (s, 3H), 1.2–2.0 (broad m, 10H), 5.0 and 5.9 (ABM of ABMX, J_{AB} = 2, J_{MX} = 8, $J_{AM} + J_{BM}$ = 27 Hz); IR (neat) 3500, 1640, 1000, 910 cm^{-1}. Anal. Calcd for $C_9H_{16}O$: C, 77.09, H, 11.50. Found: C, 76.97, H, 11.51.

2-Methyl-2-vinylcyclohexanone. A solution containing 1 mmol of lithium diisopropylamide in 25 mL of THF was prepared at −60 °C under nitrogen using butyllithium as a base. To this solution at −60 °C was added a solution of 11 mg (0.89 mmol) of 2-vinylcyclohexanone in 2 mL of THF. This solution was allowed to warm to room temperature and it was heated then to 30 °C for 30 min. After 0.2 mL of HMPT had been added, 0.3 g (2.1 mmol) of methyl iodide was added and the solution was heated at 40 °C for 2 h. The solution was mixed with 25 mL of ether, and the mixture was washed with saturated ammonium chloride, water, and then saturated sodium chloride. The ether layer was dried ($MgSO_4$) and the solvent was removed, giving 110 mg (90%) of 2-methyl-2-vinylcyclohexanone: NMR (CCl_4) δ 1.09 (s, 3H), 1.5–2.1 (broad m, 6H), 2.32 (m, 2H), 5.0 and 5.95 (ABX, 3H, J_{AB} ~1.5, $J_{AX} + J_{BX}$ = 27 Hz); IR (CCl_4) 1725, 1000, 910 cm^{-1}.

***cis*- and *trans*-2-Methyl-2-vinylcyclohexanols (3t and 3c).** Lithium tri-*tert*-butoxyaluminum hydride[13] was prepared under nitrogen in THF from 1.22 g (33 mmol) of lithium aluminum hydride and 7.26 g (98 mmol) of *tert*-butyl alcohol. A solution containing 946 mg (6.9 mmol) of 2-methyl-2-vinylcyclohexanol in 6 mL of THF was added dropwise at 0 °C. The mixture was stirred 22 h at room temperature, and then 10 mL of a 1:1 mixture of THF/H_2O was added, followed by 30 mL of 10% sulfuric acid and 50 mL of ether. The ether layer was washed with water, saturated sodium bicarbonate, and finally saturated sodium chloride solution. The ether solution was dried ($MgSO_4$), and the ether was evaporated to give 782 mg (75%) of product. GLC analysis on a 5% FFAP column at 150 °C showed 53% of **3t** and 47% of **3c**: NMR (CCl_4) δ 0.98 and 1.13 (2s, 3H), 1.2–2.0 (broad m, 8H and OH), 3.24 (broad m, 1H), 5.1 and 5.9 (two overlapping ABX, $J_{AX} + J_{BX}$ = 28 for both); IR (neat) 3400, 1640, 990, 915 cm^{-1}.

Thermolysis Apparatus. All thermolyses described below were carried out in a vertical quartz column packed with cut pieces of quartz tubing and heated externally by a electric oven. Temperatures were monitored continuously near the top, at the center and near the bottom of the column. The column was surmounted by a short preheater section wrapped with heating tape and equipped with a nitrogen inlet and a septum for injection of the sample. The preheater was kept at 200–215 °C, while the column was maintained at 440 °C. The nitrogen flow rate was about 50–75 mL/min, which equates to contact times between 1.5 and 2.2 min. Products were collected in a

series of three traps cooled in dry ice–acetone.

***trans*-6-Octenal.** A total of 78 mg (0.62 mmol) of **1t** was pyrolyzed with a contact time of 1.46 min, and 74.2 mg of product (95%) was collected. The product was separated on a 5% FFAP column, and it contained 96% *trans*-6-octenal: NMR (CCl_4) δ 1.65 (m, 3H), 1.2–1.8 (broad m, 4H), 2.0 (m, 2H), 2.36 (d of t, J = 6.8, J = 1.8, 2H), 5.38 (m, 2H), 9.13 (t, 1H, J = 1.8 Hz); IR (neat) 2725, 1725 (s), 965 (s) cm^{-1}. Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.72; H, 11.23.

***cis*-6-Octenal.** Pure *cis*-2-vinylcyclohexanol, 80 mg (0.64 mmole), was pyrolyzed with a contact time of 1.41 min, and 78 mg (97%) of crude product was collected. GLC analysis on a 5% OV-17 column at 150 °C showed the product contained 59% *trans*-6-octenal, 36% *cis*-6-octenal, and 5% unidentified material. A sample of *cis*-6-octenal was collected from the GLC column: NMR (CCl_4) δ, 1 62 (d, 3H, J = 5 Hz), 1.2–1.9 (broad m, 4H), 2.0 (m, 2H), 2.35 (m, 2H), 5.38 (m, 2H), 9.15 (t, 1H, J = 1.8 Hz); IR (CCl_4), 1715, 905, 670 cm^{-1}.

***trans*-2-Nonen-8-one.** A 72 mg (0.52 mmol) sample of **2t** was pyrolyzed with a contact time of 1.5 min, and 70 mg (98%) of crude product was collected. GLC analysis on a column at 150 °C showed that the product contained 92% *trans*-2-nonen-8-one and 8% of unidentified products. A sample of *trans*-2-nonen-8-one collected from GLC showed an NMR spectrum (CCl_4) δ 1.65 (m, 3H), 1.2–1.8 (m, 4H), 1.95 (m, 2H), 2.04 (s, 3H), 2.33 (t, 2H, J = 7 Hz), 5.38 (m, 2H); IR (neat) 1730, 1360, 970 (s); mol wt 140, mass spectrum m/e (rel intens) 140 (2), 125 (4.4), 122 (3.6), 111 (7.5), 97 (9.4), 82 (29.7), 81 (11.0), 71 (35.3), 67 (39.6), 58 (20.9), 55 (34.2), 43 (100), 41 (23.4).

***cis*-2-Nonen-8-one.** A sample of **2c** (45 mg, 0.33 mmol) was pyrolyzed with contact time of 1.98 min, and 42 mg (93%) was recovered. The crude product was analyzed on a 3% DEGS column at 150 °C, and it contained 52% *trans*-2-nonen-8-one (GLC internal comparison), 44% *cis*-2-nonen-8-one and 4% by-products. Separation on a 16 ft × 1/4 in. 3% DEGS column gave pure *cis*-2-nonen-8-one: NMR (CCl_4) δ 1.62 (d, 3H, J = 5 Hz), 1.2–1.85 (broad m, 4H), 1.98 (broad m, 2H), 2.05 (s, 3H), 2.35 (t, 2H, J = 7 Hz), 5.38 (m, 2H); IR (CCl_4) 1730 (s), 1340, 860 cm^{-1}; mol wt 140, mass spectrum m/e (rel intens) 140 (3.4), 125 (4.7), 122 (5.0), 111 (7.7), 97 (9.7), 82 (29.3), 81 (13.5), 71 (37.3), 67 (40.7), 58 (21.1), 55 (40.1), 43 (100), 41 (24.5).

Thermolysis of a Mixture of 3t and 3c. A mixture containing 53% of **3t** and 47% of **3c** (244 mg, 2.6 mmol) was pyrolyzed with 2 min contact time. The recovered material amounted to 205 mg (92%), but the mixture which contained 5% by-products could not be separated successfully with 5% FFAP, 3% DEGS, or 5% OV-17 columns. The crude mixture showed NMR (CCl_4) δ 1.55 (m), 1.60 (s, 3H), 1.98 (apparent t, 2H, $J \sim 7$ Hz), 2.48 (d of t, 2H, J = 7 Hz, J = 1 Hz), 5.2 (m, 1H), 9.56 and 9.70 (2t, 1H, $J \sim 1$ Hz); IR (CCl_4) 1730 (s), 1370 cm^{-1}. Anal. Calcd for $C_9H_{16}O$: C, 77.09, H, 11.50. Found: C, 77.20, H, 11.49.

***(E)*- and *(Z)*-6-Methyl-6-octen-1-ols.** The mixture of 6-methyl-6-octenals above (66.8 mg, 0.48 mmol) was added dropwise to 20 mg (0.52 mmol) of lithium aluminum hydride in 20 mL of ether. The mixture was stirred for 2 h and was then hydrolyzed with 10% sulfuric acid. The ether layer was separated and the aqueous layer was extracted with ether. The ether solutions were combined and dried ($MgSO_4$), and the ether was evaporated giving 65.5 mg (97%) of a mixture of 6-methyl-6-octen-1-ols. GLC analysis on a 3% DEGS column at 140 °C showed the mixture contained 85% of the *E* isomer and 15% of the *Z* isomer. The isomers were separated on the DEGS column: *E* isomer, NMR (CCl_4) δ 1.2–1.8 (broad m), 1.55 (partly resolved d, $J \sim 1$ Hz), 1.8–2.2 (m), 3.50 (m), 5.0–5.3 (broad m); *Z* isomer, NMR (CCl_4) δ 1.2–1.8 (broad m), 1.56 (s), 1.8–2.2 (m), 2.85 (s, OH), 3.2–3.7 (broad m), 5.0–5.3 (broad m).

***(E)*-7-Methyl-7-nonen-2-one.** Three separate runs on mixtures containing respectively 88% **4t**/12% **4c**, 86% **4t**/14% **4c**, and 90% **4t**/10% **4c** were carried out under the same conditions, and the products were the same in all cases. Thus 75.3 mg (0.50 mmol) of the 86/14 mixture was pyrolyzed with a contact time of 2.2 min, and 72.1 mg (96%) was recovered. This product contained 92% of 7-methyl-7-nonen-2-one and 8% of unidentified material. No GLC evidence for separation of the ketone was found, and a pure sample showed NMR (CCl_4) δ 1.2–1.7 (broad m), 1.55 (s, CH_3), 1.8–2.1 (m), 2.02 (s, 3H), 2.32 (clean t, 2H, J = 6.5 Hz), 5.17 (m, 1H); IR (neat) 1730 s, 1380, 1372, 1360, 805 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.65, H, 11.80.

Registry No.—**1c**, 17807-20-4; **1t**, 6376-95-0; **2c**, 63196-52-1; **2t**, 63196-53-2; **3c**, 63196-54-3; **3t**, 63196-55-4; **4c**, 63196-56-5; **4t**, 63196-57-6; cyclohexene, 110-83-8; ethyl diazoacetate, 623-73-4; 7-carbethoxybicyclo[4.1.0]heptane, 52917-64-3; 1-methycyclohexane, 591-49-1; 1-methyl-7-carbethoxybicyclo[4.1.0]heptane, 63196-58-7; 1,6-dimethyl-7-carbethoxybicyclo[4.1.0]heptane, 63196-59-8; 7-hydroxymethylbiocyclo[4.1.0]heptane, 6226-39-7; 1-methyl-7-hydroxymethylbicyclo[4.1.0]heptane, 63196-60-1; 1,6-dimethyl-7-hydroxymethylbicyclo[4.1.0]heptane, 63196-61-2; 2-vinylcyclohexanone, 1122-24-3; 2-vinylcyclohexanol, 29108-24-5; methyl iodide, 74-88-4; 2-methyl-2-vinylcyclohexanone, 63196-62-3; *trans*-6-octenal, 63196-63-4; *cis*-6-octenal, 63196-64-5; *trans*-2-nonen-8-one, 25143-93-5; *cis*-2-nonen-8-one, 63196-65-6; (*E*)-6-methyl-6-octen-1-ol, 63196-66-7; (*Z*)-6-methyl-6-octen-1-ol, 63196-67-8; (*E*)-7-methyl-7-nonen-2-one, 63230-66-0.

References and Notes

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.
(2) American Chemical Society–Petroleum Research Fellow, Sept 1974–July 1976.
(3) See, for example, B. M. Trost, T. J. Dietsche, and T. J. Fullerton, *J. Org. Chem.*, **39**, 737 (1974); R. S. Lenox and J. A. Katzenellenbogen, *J. Am. Chem. Soc.*, **95**, 957 (1973); B. M. Trost and T. J. Fullerton, *ibid.*, **95**, 292 (1973); S. B. Bowles, and J. A. Katzenellenbogen, *J. Org. Chem.*, **38**, 2733 (1973); M. P. Cooke, Jr., *Tetrahedron Lett.*, 1983 (1973); P. Grieco and R. S. Finkelhor, *J. Org. Chem.*, **38**, 2245 (1973).
(4) See J. A. Katzenellenbogen and K. J. Christy, *J. Org. Chem.*, **39**, 3315 (1974); D. A. Evans, G. C. Andres, T. T. Fujimoto, and D. Wells, *Tetrahedron Lett.*, 1389 (1973); P. A. Griecw, *Chem. Commun.*, 702 (1972); E. J. Corey, H. Yamamoto, D. K. Herron, and K. Achiwa, *J. Am. Chem. Soc.*, **92**, 6635 (1970); D. J. Faulkner and M. R. Petersen, *ibid.*, **95**, 553 (1973).
(5) R. T. Arnold and G. Smokinsky, *J. Org. Chem.*, **25**, 129 (1960).
(6) For a review of the ene reaction see H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969).
(7) J. K. Crandall, J. P. Arrington, and J. Hen, *J. Am. Chem. Soc.*, **89**, 6208 (1967).
(8) B. W. Peace, F. Carman, and D. S. Wulfman, *Synthesis*, 658 (1971).
(9) Throughout this paper the designations cis and trans as applied to the variously substituted vinylcyclohexanols always refer to the relative positions of the vinyl and hydroxyl groups.
(10) We are indebted to Mr. William Whalley for this procedure. The use of Jones' oxidation as described by Crandall[7] was exceedingly sensitive and mixtures containing α-ethylidenecyclohexanone were invariably obtained by us.
(11) G. F. Hennion and F. X. O'Shea, *J. Am. Chem. Soc.*, **80**, 614 (1958); A. V. Kamernitzky and A. A. Akhrene, *Tetrahedron*, **18**, 705 (1962).
(12) L. M. Jackman and S. Sternhell, "Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, London, 1969, p 225.
(13) J. L. Lambert, H. F. Shurvell, L. Verbit, R. G. Cooks, and G. H. Stout, "Organic Structural Analysis", Macmillan, New York, N.Y., 1976, p 87.
(14) M. Julia, C. Descoins, M. Baillarge, B. Jacquet, and D. Uguen, *Tetrahedron*, **31**, 1737 (1975); B. M. Trost, *Acc. Chem. Res.*, **3**, 120 (1970); J. A. Katzenellenbogen and K. J. Christy, *J. Org. Chem.*, **39**, 3315 (1974).
(15) M. Mousseron, R. Jacquier, and R. Fraisse, *C. R. Hebd. Seances Acad Sci.*, **243**, 1880 (1956).
(16) We thank Mr. William Whalley for an authentic sample of this compound.
(17) R. Jacquier and P. Bésinct, *Bull. Soc. Chim. Fr.*, 749 (1956).
(18) P. S. Wharton and T. I. Bair, *J. Org. Chem.*, **31**, 2480 (1966).

Synthesis of 31- and 35-Amino Acid Carboxyl Terminal Fragments of the β Subunit of the Human Chorionic Gonadotropin

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Received June 2, 1976

The 31- and 35-amino acid carboxyl terminal fragments (hCG 117–147 and hCG 111–145) based on two sequences for the β subunit of human chorionic gonadotropin have been synthesized using the solid-phase technique. N^{α}-Boc, protected L amino acids were automatically coupled on the chloromethylated Merrifield resin by the DCC method, with the exception of Boc-Gln, which was incorporated by the ONP active ester method. The completed peptides were cleaved from the resins, deprotected with anhydrous liquid HF, and purified by a series of gel filtration, partition and ion-exchange chromatography columns, and preparative thin layer electrophoresis. The purity of the two hCG fragments was shown by thin layer chromatography, electrophoresis, and amino acid analyses.

Human chorionic gonadotropin (hCG) is a glycoprotein hormone of the placenta. It is composed of 2 subunits, α and β.[1] The β subunit is hormone specific, while the α subunit is common to other pituitary glycoprotein hormones such as luteinizing hormone, thyroid stimulating hormone, and follicle stimulating hormone (LH, TSH, and FSH).[2,3] The β subunit of hCG also has approximately 30 additional amino acids at its carboxyl terminus which are not present in the β subunits of other glycoprotein hormones. Consequently, this additional carboxyl terminal fragment is of interest from a biological standpoint as to its function in the activity and potency of hCG.

Two slightly differing structures for the β subunit of hCG have been proposed, one by Carlsen, Bahl, and Swaminathan[4] and the other by Morgan, Birken, and Canfield.[6] The structure of Morgan et al. contains 145 amino acid residues. The structure of Carlsen et al. has 147 residues, namely an additional Ser-Leu-Pro sequence at the carboxyl terminus and no Ser^{121} (Scheme I).

It is of interest to synthesize specifically selected fragments of the β subunit of hCG. Such synthetic peptides will then be coupled to one or more suitable protein carriers which will then be used to achieve antibodies in vivo. It is desirable to achieve antibodies against hCG, but not against LH, FSH, and TSH. Since there is no established basis to indicate which sequences of the β subunit of hCG of the additional carboxyl terminal fragment which might provide immunological differentiation, a priority of peptide sequences based on this β subunit are being synthesized to support the biological research to achieve such specific antibodies against hCG. We now describe the synthesis of a 31- and a 35-amino acid peptide fragment of this subunit. A total of five samples of the two synthetic peptides have been provided to Dr. Sheldon Segal and Dr. Harold A. Nash of the Population Council, the Rockefeller University, New York. Antibody titers produced in rabbits by the 31-unit peptide were lower than those produced by the β subunit of hCG. Both were injected as "tetramers" with Freund's Complete Adjuvant. The antibodies were assayed by measuring the binding of I^{125}hCG. Less than 1% binding of the labeled hCG was observed with a 1:250 dilution of antisera from rabbits injected with the "tetramer" of the 31-unit peptide. Approximately 50% binding with a 1:250000 dilution of antisera from rabbits injected with the tetramer of the β subunit was observed.[6]

Syntheses

The peptides were synthesized by the solid phase technique[7,8] using the chloromethylated Merrifield resin. The starting resins were prepared by esterification with the appropriate Boc-amino acid, namely Boc-Pro for hCG (117–147)C and Boc-Gln for hCG (111–145)M, and the resin in refluxing ethanol and triethylamine. Amino acid analyses gave a content of 0.68 mM Pro/g for the Boc-Pro resin and 0.39 mM Gln/g for the Boc-Gln resin.

Scheme I

(hCG 117–147)C (Carlsen et al.[4]): hentriacosapeptide Asp^{117}-Ser-Ser-Ser-Lys-Ala-Pro-Pro-Pro-Ser-Leu-Pro-Ser-Pro-Ser-Arg-Leu-Pro-Gly-Pro-Pro-Asp-Thr-Pro-Ile-Leu-Pro-Gln-Ser-Leu-Pro-^{145}-OH

(hCG 111–145)M (Morgan et al.[6]): pentatriacosapeptide Asp^{111}-Asp-Pro-Arg-Phe-Gln-Asp-Ser-Ser-Ser-Ser-Lys-Ala-Pro-Pro-Pro-Ser-Leu-Pro-Ser-Pro-Ser-Arg-Leu-Pro-Gly-Pro-Ser-Asp-Thr-Pro-Ile-Leu-Pro-Gln^{145}-OH

Since the Boc-Pro resin had a high amino acid content, Boc-Leu was coupled to the Pro resin in the limited ratio of 0.80 Lue to 1.0 Pro, in order to limit the resin content to allow sufficient space for the growing peptide chain. After acetylation of unreacted amino groups, the Leu content of the Boc-Leu-Pro resin was 0.32 mM/g. The couplings for the remainder of the syntheses of both peptides were done on a Beckman 990 automatic synthesizer.

α-Amino functions were protected by the *tert*-butyloxycarbonyl (Boc) group, except for arginine which was protected by the amyloxycarbonyl (Aoc) group which is more soluble in methylene chloride. Side chain protecting groups were benzyl (Bzl) for serine, threonine, and aspartic acid; tosyl (Tos) for aginine; and 2-chlorocarbobenzoxy (2-Cl-Z) for lysine. Deprotection of the amino-protected intermediates on the resin was accomplished with 30% trifluoroacetic acid (TFA) in methylene chloride, with neutralization on the resulting TFA salt by 10% triethylamine in methylene chloride to give the free amino group. Each amino acid was coupled by the dicyclohexylcarbodiimide (DCC) method[9] in methylene chloride or dimethylformamide, with the exception of Boc-Gln which was incorporated by the nitrophenyl active ester method[10] in dimethylformamide. Completeness of coupling was monitored by the ninhydrin color test procedure of Kaiser et al.[11] and when doubtful, the resin was double-coupled or acetylated with acetic anydride.

Double coupling was employed throughout the synthesis of hCG (117–147)C, the first coupling for 3–5 h, and the second coupling, with fresh Boc-amino acid, for 4–6 h, while the Boc-Gln^{144}-ONP active ester was incorporated once as a 5-fold excess for about 12 h. Ser^{145} and Pro^{143} through Pro^{140} were incorporated as 2.5-fold excesses for the first coupling and 1.5-fold excesses for the double coupling; the next ten amino acids, Thr^{139} through Pro^{128} as 4.0 and 2.5-fold excesses; and the last eleven amino acids, Leu^{127} through Asp^{117} as 5.0- and 3.0-fold excesses. The color tests were doubtful after coupling Ile^{141}, Pro^{140}, and Arg^{132}, and the resin was acetylated. From 3.0 g of Boc-Pro-CH_2-resin, there was obtained 5.145 g of the protected hentriacosa peptide resin.

Table I. Amino Acid Analyses[a] of hCG (117–147)C

Theory	Found: Sample 4B	Found: Sample 5B
2 Asp	2.13	1.89
1 Thr	0.73	0.79
7 Ser	7.22	7.65
1 Glu	0.85	0.95
11 Pro	11.56	11.78
1 Gly	0.91	0.80
1 Ala	0.95	0.86
1 Ile	0.67	0.52
4 Leu	4.06	3.82
1 Lys	0.95	1.06
1 Arg	1.02	0.91

[a] Amino acid analyses were done on a Beckman Model 119 amino acid analyzer set up for a single column methodology after hydrolysis of the peptide with 6 N HCl at 110 or 130 °C overnight.

Table II. Amino Acid Analyses[a] of hCG (111–145)M

Theory	Found: Sample 6B	Found: Sample 9A	Found: Sample 10A	Found: Sample 10B	Found: Sample 10C
4 Asp	3.59	4.32	3.77	3.77	4.32
1 Thr	0.87	0.53	0.59	0.65	0.45
8 Ser	8.84	9.79	6.44	7.48	8.16
2 Glu	1.86	1.52	1.77	1.84	1.64
10 Pro	10.58	10.32	11.95	11.68	11.9
1 Gly	1.16	0.88	1.59	1.15	0.86
1 Ala	0.80	0.92	1.10	1.06	0.88
1 Ile	0.69	0.31	0.49	0.45	0.45
3 Leu	2.73	2.20	2.28	2.23	1.89
1 Phe	1.10	1.00	1.79	1.52	0.97
1 Lys	0.81	1.18	1.59	1.03	0.85
2 Arg	1.92	2.00	1.92	2.02	1.64

[a] Amino acid analyses were done on a Beckman Model 119 amino acid analyzer set up for a single column methodology after hydrolysis of the peptide with 6 N HCl at 110 or 130 °C overnight.

Double couplings were not used in the synthesis of hCG (111–145)M. Instead the molar excess of each Boc-amino acid was increased with an average coupling time of 3–6 h. Pro^{144} through Gly^{136} were incorporated as 3.0-fold excesses; Pro^{135} and Leu^{134} as 3.22-fold excesses; Arg^{133} through Pro^{126} as 4.0-fold excesses; Pro^{125} through ASP^{117} as 5.0-fold excesses; Gln^{116} as a 12-fold excess for 12 h; and Phe^{115} through Asp^{111} as 6.0-fold excesses. Using these higher molar excesses, all the couplings appeared complete by the color tests, making double couplings unnecessary. However, Ile^{142} was double-coupled to Leu^{143} since this is known to be a difficult coupling; 3.18 g of Boc-Gln-CH_2-resin yielded 7.05 g of the protected pentatriacosa peptide resin.

Cleavage of the completed protected peptides from the resins, with simultaneous removal of the protecting groups and formation of the carboxyl terminal acid, was effected with anhydrous, liquid hydrogen fluoride in the presence of 10% anisole for 1 h at 0 °C.[12,13] The crude, deprotected peptides were extracted from the resin with diluted acetic acid, lyophilized, and purified as follows.

Experimental Section

Purification. hCG (117–147)C. The crude peptide (737 mg from 3.0 g of the hentriacosa resin) after HF was first desalted by gelfiltration on a 112 × 2.5 cm column of Bio-Gel P-4 eluted with 1 N HOAc in 15-mL fraction. Detection of the peptide by the Folin–Lowry procedure[14] at 660 nm showed a broad multishouldered peak. Lyophilization of the fractions corresponding to the top of the peptide peak (tubes 17–22) gave 465 mg of desalted peptide. This material showed two spots on TLC.

The desalted peptide was then subjected to partition chromatography on a 59 × 2.0 cm column of Sephadex G-25, eluted first with upper-phase and then lower-phase of the system *n*-BuOH–HOAc–H_2O (4:1:5) in 6-mL fractions. Detection of the peptide by the Folin–Lowry procedure showed one peak in the first portion of the upper-phase eluent at tubes 11–12 (2A), a smaller peak near the end of the upper-phase elution at tubes 53–59 (2D), and another peak at the beginning of the lower-phase elution at tube 60 (2E).

The upper-phase peak fractions (2A) upon lyophilization gave 80.6 mg of white solid, which was further purified by ion-exchange chromatography on a 28 × 1.5 cm column of carboxymethyl cellulose (CM-52) eluted in 6-mL fractions with 1 to 100 mM ammonium acetate buffer gradient at pH 3.5 giving one peak which yielded 52.3 mg (3B) of white solide. Upon amino acid analyses, this material proved to be a mixture of by-product peptides which were missing about seven or eight amino acids (namely 4.8 serines, 1 alanine, 1 lysine and 1 argine) and showed two high R_f spots on TLC.

The desired hentriacose peptide hCG (117–147)C was found in the trailing end of the upper-phase eluent (2D, 118.4 mg) and the first part of the lower-phase eluent (2E, 29.2 mg) of the 4:1:5 system partition column. Both fractions 2D and 2E had the same TLC pattern in *n*-BuOH–HOAc–EtOAc–H_2O (1:1:1:1) and *i*-PrOH–1 N HOAc (2:1) systems consisting of major low R_f spots due to by-product peptide contaminants.

Table III. Thin Layer Chromatography R_f Values[a] of β Subunit hCG (117–147)C

	R_f^1	R_f^2	R_f^3
hCG (117–147)C (5B)	0.15	0.17	0.98

[a] TLC systems on silica gel are: R_f^1, *n*-BuOH–HOAc–EtOAc–H_2O (1:1:1:1); R_f^2, *i*-PrOH–1 N HOAc (2:1); R_f^3, $CHCl_3$–MeOH–conc NH_4OH (60:45:20).

Fraction 2E from the lower-phase eluent of the partition column was then subjected to ion-exchange chromatography on a 28 × 1.5 CM-52 column eluted in 5-mL fractions with 1 to 100 mM ammonium acetate buffer gradient at pH 5.0. Detection of the peptide by the Folin–Lowry procedure showed only one peak at tubes 6 and 7, which gave 3.5 mg (4B) of white solid upon lyophilization. This material showed only one spot, R_f = 0.15, on TLC in the *n*-BuOH–HOAc–EtOAc–H_2O (1:1:1:1) system and was not contaminated by the higher R_f by-product peptides which eluted later, mixed with some more of the hCG (117–147)C.

Since the desired hentriacose peptide was also found in the trailing end of the upper-phase eluent of the partition column (fraction 2D), it seemed appropriate to purify further this material by some technique employing an organic solvent rather than by ion exchange. Thus, fraction 2D was subjected to chromatography on a 39 × 1.0 cm column of Sephadex LH-20 eluted with *n*-BuOH–H_2O (6:100) in 4-mL fractions. Detection of the peptide by Folin–Lowry showed one sharp peak of tube 6 which upon lyophilization gave 57.0 mg (5B) of white material identical by TLC to fraction 4B. Material which eluted in the shoulder and beyond the peptide peak (5C, 36.3 mg) contained primarily the desired hCG (117–147)C contaminated by some of the higher R_f by-product peptides.

The data on amino acid analyses of fractions 4B and 5B, Table I, are consistent with the 31 amino acids of the hCG (117–147)C fragments. The low values for Thr are to be expected due to some oxidation during hydrolysis. The low values for Ile are due to incomplete hydrolysis of the Ile^{141}–Leu^{142} bond. Both samples 4B and 5B were identical by thin layer chromatography, single spot R_f's in 3 systems, Table III, and each showed the same one spot moving toward the cathode on electrophoresis.

Consequently, both ion-exchange chromatography on CM-52 and chromatography on LH-20 were successful in separating the desired hentriacosa peptide hCG (117–147)C from the failure sequence peptides.

hCG (111–145)M. The crude peptide from HF (1.56 g from 4.0 g of the protected peptide resin) was first desalted on a 118.5 × 2.5 cm column of Bio-Gel P-4, eluted with 1 N HOAc in 18-mL fractions. Detection of the peptide by Folin–Lowry showed one broad, multishouldered peak. Lyophilization of the fractions corresponding to the top of the peak (tubes 2–21) gave 367.8 mg (6B) of white solid which showed two spots on TLC in the *n*-BuOH–HOAc–EtOAc–H_2O

(1:1:1:1) system, a major low R_f spot for the desired pentatriacose hCG (111–145)M peptide and a minor mid R_f streak for impurities. Amino acid analyses of the desalted peptide (6B), listed in Table III, were almost acceptable for the pentatriacosa peptide.

The material was then chromatographed on a 58 × 2.0 cm column of Sephadex LH-20, eluted with *n*-BuOH-H_2O (6:100) in 7-mL fractions with detection of the peptide by a UV monitor at 256 nm (Phe), to give a single symmetrical peak. Lyophilization of tubes 14–16, corresponding to the top of the peptide peak, gave 225.5 mg (7B) of white solid which on TLC showed primarily the low R_f spot for the pentatriacosa peptide contaminated by only a small amount of the higher R_f impurity.

Since the hentriacosa peptide hCG (117–147)C eluted in the lower phase of the 4:1:5 system partition column, it was decided to use a different partition system for the pentatriacosa peptide hCG (111–145)M. Fraction 7B was partitioned on a 57 × 2.0 cm column of Sephadex G-25 eluted with upper and then lower phase of the system 0.1 N HOAc–*n*–BuOH–Pyr (11:5:3), in 5.5-mL fractions with detection of the peptide by Folin–Lowry. No peak appeared in the upper-phase eluent, but there was a sharp, symmetrical peak at the beginning of the lower-phase elution. Lyophilization of tubes 43 and 44, corresponding to the top of this peak, gave 74.7 mg (8B) of white solid which now showed only the one low R_f spot on TLC for the desired pentatriacosa peptide.

A further purification of 50 mg of fraction 8B was carried out by ion-exchange chromatography on a 28 × 1.5 cm -52 column eluted in 25-mL fractions with 1 to 500 mM ammonium acetate buffer gradient, pH 6.4. A single, symmetrical peak was detected by the UV monitor at 256 nm and by Folin–Lowry at 660 nm. Lyophilization of tube 2, corresponding to the top of this peak, gave 27.6 mg (9A) of purified hCG (111–145)M, which gave the amino acid analysis of ratios listed in Table II.

9A (5.76 mg) was further purified by preparative thin layer electrophoresis on cellulose plates (160 μ thick, Eastman chromagram sheet) at 500 V in pyridine acetate buffer of pH 6.5 to give 2.0 mg of pentatricosa hCG (111–145)M (10A; IBR 12755). The amino acid analytical ratios are in Table II. Two separate purifications in the same manner of 8.97 mg of (9A) and 12.87 mg of (9A) gave 3.6 mg (10B; IBR 13202) and 5.5 mg (10C, IBR 13669) of pentatriacosa hCG (111–145)M. The amino acid analytical results are in Table II.

The purified hCG (111–145)M showed one spot by electrophoresis moving toward the cathode in pyridine acetate buffers of pH 3.6 and pH 6.5.

Acknowledgment. Appreciation is expressed to the Population Council, the Robert A. Welch Foundation, and the John A. Hartford Foundation for their respective support of this research.

Registry No.—Boc-Pro, 15761-39-4; Boc-Gln, 4530-20-5; (hCG 117–147)C, 63215-95-2; (hCG 111–145)M, 63301-41-7.

References and Notes

(1) D. N. Swaminathan and O. P. Bahl, *Biochem. Biophys. Res. Commun.*, **40**, 127 (1970).
(2) J. G. Pierce, *Endocrinology*, **89**, 1331 (1971).
(3) J. G. Pierce, O. P. Bahl, J. S. Cornell, and N. Swaminathan, *J. Biol. Chem.*, **246**, 2321 (1971).
(4) R. B. Carlsen, O. P. Bahl, and N. Swaminathan, *J. Biol. Chem.*, **248**, 6810 (1973).
(5) C. C. Chang, Population Council, The Rockefeller University, New York, N.Y., personal communication.
(6) F. J. Morgan, S. Birken, and R. E. Canfield, *Mol. Cell. Biochem.*, **2**, 97 (1973).
(7) R. B. Merrifield, *Biochemistry*, **3**, 1285 (1964).
(8) R. B. Merrifield, *Adv. Enzymol.*, **32**, 221 (1969).
(9) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).
(10) M. Bodanszky, *Nature (London)*, **175**, 685 (1955).
(11) E. Kaiser, R. L. Colescott, C. D. Bossinger, and P. I. Cook, *Anal. Biochem.*, **34**, 595 (1970).
(12) S. Sakakibara, Y. Shimonishi, Y. Kishida, M. Okado, and H. Sugihara *Bull. Chem. Soc. Jpn.*, **40**, 2164 (1967)
(13) J. Lenard and A. B. Robinson, *J. Am. Chem. Soc.*, **89**, 181 (1967).
(14) D. H. Lowry, N. H. Rosenbrough, and A. L. Farr, *J. Biol. Chem.*, **193**, 261 (1951).

Metabolites of the Red Alga *Laurencia subopposita*

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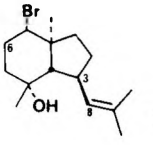
Received April 19, 1977

The red alga *Laurencia subopposita* contains a variety of secondary metabolites, some of which have previously been described from other sources. We have previously reported that the major metabolite was oppositol (1). The antibiotic activity of the alga was due to 7-hydroxylaurene (2) and 10-bromo-7-hydroxylaurene (3). Laurene (4), isoprelaurefucin (6), laurefucin (7), acetyllaurefucin (8), and oplopanone (19) have all been described previously. Two epimeric diols 13 and 14 were shown to be related to oppositol (1). A diol 21 having the germacrane skeleton rearranged on dehydration to give 8(15)-dehydrooplopanone (26). Two aromadendrene alcohols 27 and 29 were isolated. The optical enantiomer of 1-hydroxylalloaromadendrene (27) was synthesized by oxidation of alloaromadendrene (28) with selenium dioxide.

Red algae of the genus *Laurencia* have proved to be a most prolific source of halogenated metabolites of three major classes, sesquiterpenes, diterpenes, and acetylenes.[1] The halogenated sesquiterpenes may be further subdivided into three groups: the aromatic compounds, the chamigrenes and their precursors and rearrangement products, and the oppositol–eudesmane group. Although it is not uncommon to find representatives of more than one group in a *Laurenica* species, the structural elucidations have generally been described separately. In this paper we wish to present an account of the diversity of chemical structures which may be found in *Laurencia subopposita*.

We have previously reported that the major metabolite of *Laurencia subopposita* (J. G. Agardh) Setchell was oppositol (1), a sesquiterpene having a previously undescribed carbon skeleton.[2] On reinvestigation of the metabolites of *L. subopposita*, we found that oppositol (1) was not an antibiotic, as had been previously stated. The mild antibiotic activity of oppositol (1) had been due to the presence of traces of 7-hydroxylaurene (2) and/or 10-bromo-7-hydroxylaurene (3).

Hexane, ether, and acetone extracts of powdered, air-dried



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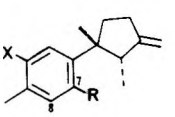
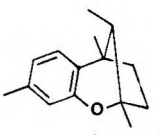




5

2 R = OH X = H

3 R = OH X = Br

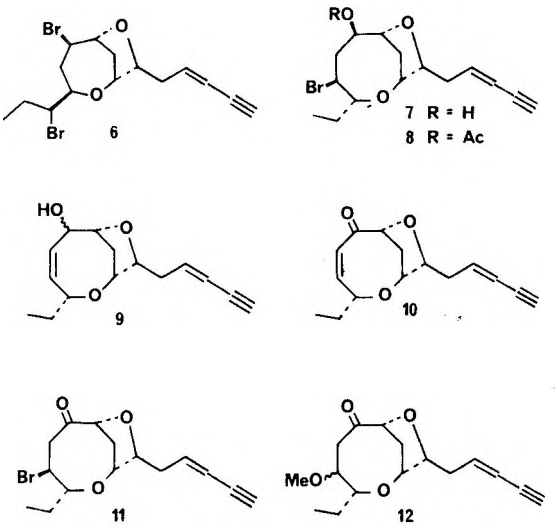
4 R = H X = H

Laurencia subopposita were combined to yield a viscous oil (2.3% dry weight) which showed antibiotic activity against *Staphylococcus aureus*. The oil was chromatographed on Florisil, using a solvent gradient of increasing polarity from petroleum ether to methanol. Selected fractions were rechromatographed to obtain individual compounds, of which oppositol (1) (0.11% dry weight) was again the major metabolite.

The least polar sesquiterpene metabolite was laurene (4), whose spectral properties were identical with those reported.[3] The antibiotic activity of *L. subopposita* was due to two phenols, 7-hydroxylaurene (2) and 10-bromo-7-hydroxylaurene (3). The spectral data of our sample of 10-bromo-7-hydroxylaurene (3) were nearly identical with those recently reported by Kazlauskas et al.[4] for allolaurinterol,[5] isolated from *Laurencia filiformis*. The major antibiotic from *L. subopposita* was 7-hydroxylaurene (2) (0.013% dry weight). The ^{1}H NMR spectrum of 7-hydroxylaurene (2) showed signals due to an aromatic methyl group at δ 2.19, three aromatic protons at 6.36 (s), 6.56 (d, J = 7 Hz) and 6.93 (d, J = 7 Hz) and a hydroxyl proton at 4.76 (s). The remaining signals, at δ 0.67 (d, 3H, J = 7 Hz) due to the secondary methyl group, 1.30 (s, 3H) due to the tertiary methyl group, 2.95 (q, J = 7 Hz), and 4.82 and 4.92 due to the exocyclic methylene protons, were remarkably similar to the signals for the nonaromatic portion of laurene (4). Irradiation of the methyl doublet at δ 0.67 caused the methine quartet at 2.95 to collapse to a singlet, indicating that the methine proton was not coupled to other protons. The chemical shift of the secondary methyl signal at δ 0.67 suggested that the methyl group was in the deshielding region of the aromatic ring and hence the two groups must be *cis* with respect to the cyclopentane ring.[3] Since 7-hydroxylaurene (2) underwent a slow isomerization to a cyclic ether 5, the phenolic hydroxyl group must be at C-7, rather than C-8. The formation of the cyclic ether 5 from the phenol 2 parallels the reported isomerization of bromophenol 3 to a cyclic ether.[4]

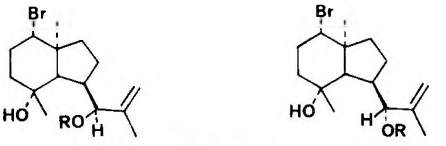
Laurencia subopposita contains eight acetylenes, which were isolated as four pairs of geometrical isomers. The geometrical isomers about the Δ^3 olefinic bond were inseparable by column chromatography but could be distinguished by the characteristic signals in the ^{1}H NMR spectra and, in some cases, could be estimated by VPC analysis. Since most of the acetylenes had been described previously, we did not attempt to separate the mixtures of geometrical isomers. The major acetylenic metabolites were a 1:2 mixture of *cis*- and *trans*-isoprelaurefucin (6) (0.1% dry weight), the trans isomer of which had previously been isolated from *L. nipponica*.[6] A 1:1 mixture of *cis*- and *trans*-acetyllaurefucin (8) (0.016% dry weight) and a 1:3 mixture of *cis*- and *trans*-laurefucin (7) (0.019% dry weight) were also obtained.[7] Each of the pairs of acetylenes had spectral characteristics appropriate for a mixture of geometrical isomers about the Δ^3 olefinic bond. Although very complex, the ^{1}H NMR spectra of the mixtures provided the most diagnostic information. In each case, the spectra were identical with those of a pure geometrical isomer except for the signals due to the acetylenic and olefinic protons. The signals due to the acetylenic proton were at δ ~2.8 in the cis isomers and at δ ~3.1 in the trans isomers. The olefinic signals for cis and trans isomers usually overlapped but could be clearly identified due to the difference between cis (J = 11 Hz) and trans (J = 16 Hz) coupling constants.

The only undescribed acetylenes were a 1:1 mixture of *cis*- and *trans*-dehydrobromolaurefucin (9) (0.03% dry weight). The GC–mass spectra of the two isomers were almost identical, as expected, each showing a molecular ion at m/e 248, corresponding to the molecular formula $C_{15}H_{20}O_3$. Examination of the ^{1}H NMR spectrum suggested that the alcohol 9 was related to laurefucin (7) by loss of hydrogen bromide.

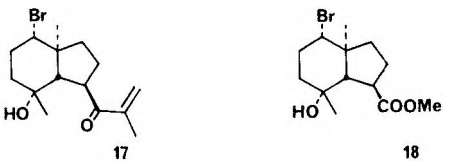


The ^{1}H NMR spectrum of 9 contained signals at δ 5.03 (bd, J = 13 Hz) due to the α-hydroxy proton, 5.59 (bt, J = 12, 13 Hz) and 5.41 (bd, J = 12 Hz) due to the olefinic protons in the ring, and four signals between 3.88 and 4.19 due to the protons adjacent to ether oxygens. The allylic alcohol 9 was oxidized with chromic oxide to an α,β-unsaturated ketone 10 (IR 1680 cm^{-1}). The ^{1}H NMR spectrum of 10 contained two signals at δ 5.81 (bd, J = 12 Hz) and 6.14 (d, J = 12 Hz) due to the olefinic protons in the ring. Oxidation of laurefucin 7 with Jones reagent gave a bromoketone 11 (IR 1720 cm^{-1}). Treatment of the bromoketone 11 with potassium hydroxide in methanol did not give the expected α,β-unsaturated ketone 10 but resulted instead in the formation of a β-methoxyketone 12. Treatment of the bromoketone 11 with stronger bases such as potassium *tert*-butoxide in *tert*-butyl alcohol resulted in decomposition of the molecule. However the α,β-unsaturated ketone 10 was converted into the same β-methoxy ketone 12 by treatment with potassium hydroxide in methanol. This sequence of reactions indicated that the allylic alcohol 9 had the gross structure shown. The stereochemistry was defined at all centers except the carbon bearing hydroxyl.

The most interesting compounds to be isolated from *L. subopposita* were oppositol (1), two related diols 13 and 14,



13 R = H 14
15 R = Ac 16
19 R = PhCO



and a series of nonhalogenated sesquiterpenes. The diols 13 and 14 were shown to be epimers, but the relative configurations at the epimeric center in the side chain could not be conclusively defined. The more polar diol 13 (0.015% dry weight), mp 123–124 °C, $[\alpha]^{20}_D$ +10°, had the molecular formula $C_{15}H_{25}O_2Br$. The ^{1}H NMR spectrum of 13 contained a signal due to an α-bromo proton at δ 3.96 (dd, 1H, J = 4, 12 Hz) and two methyl signals at 1.19 and 1.41 (CH_3-C-OH) reminiscent of signals in oppositol (1). Perhaps the most unusual and characteristic signal in the ^{1}H NMR spectra of op-

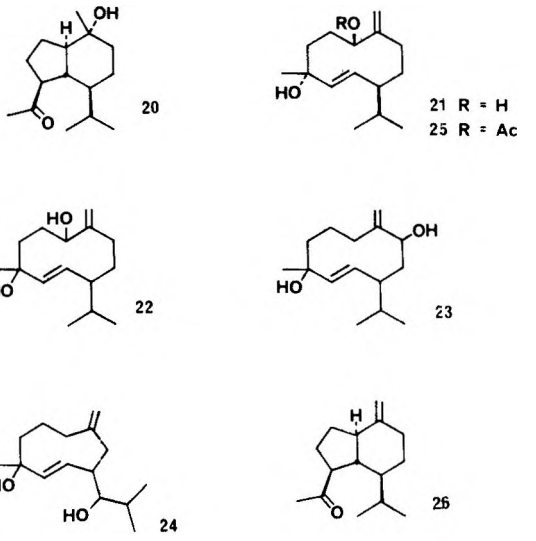
positol (1) and related compounds was a quartet of doublets (J = 12, 12, 12, 4 Hz) which was cleanly separated from all other signals. This signal, which was at δ 2.33 in the diol **13** and 2.28 in oppositol (1), was due to the axial proton at C-6, which was shifted downfield from a normal cyclohexane position by a 1,2 interaction with bromine and a 1,3-diaxial interaction with hydroxyl. The side chain of **13** gave rise to ^{1}H NMR signals at δ 1.74 (s, 3H), 4.11 (d, 1H, J = 7 Hz) and 4.86 (s, 2H). The ^{1}H NMR spectrum of the corresponding acetate **15** contained two signals at δ 4.99 and 5.04 due to the methylene protons, 5.44 (d, J = 5 Hz) due to the methine proton, 2.04 for the acetoxy protons, and 1.78 due to the vinyl methyl group. The change in chemical shift of the methine and methylene protons on acetylation implied the presence of an allylic alcohol moiety.

The less polar diol **14** (~0.008% dry weight) was isolated as an inseparable mixture with oplopanone (**20**). The two compounds were separated by acetylation of the mixture, since only the diol **14** reacted, allowing isolation of the monoacetate **16**, which was then treated with lithium aluminium hydride in ether at −78 °C to regenerate the diol. Neither the diol **14** nor the corresponding acetate **16** gave a molecular ion in the mass spectrum; the molecular formula $C_{15}H_{25}O_2Br$ was determined by high resolution mass measurement on the m/e 316 peak $(M - CH_2CO)^+$ of the monoacetate. The ^{1}H NMR spectrum of the diol **14**, with signals at δ 1.18 (s, 3H), 1.34 (s, 3H), 1.75 (s, 3H), 2.35 (qd, 1H, J = 12, 12, 12, 4 Hz), 4.06 (dd, 1H, J = 12, 4 Hz), 4.41 (bs, 1H), 4.89 (s, 1H), 5.01 (s, 1H), suggested that the diols **13** and **14** might have the same gross structure. The ^{1}H NMR spectrum of the monoacetate **16** was very similar to that of the monoacetate **15**, the major difference being that the allylic α-acetoxy proton in **16** appeared as a broad singlet at δ 5.48, while the equivalent proton in **15** appeared as a doublet at 5.44 (J = 5 Hz). These data suggested that the diols **13** and **14** were epimers at either C-3 or C-8. Oxidation of either diol with Jones reagent gave the same α,β-unsaturated ketone **17** (IR 1675 cm^{-1}). The ^{1}H NMR spectrum of **17** contained signals at δ 6.05 and 5.84 due to methylene protons β to the ketone, 1.91 due to the vinyl methyl and 3.77 (dt, 1H, J = 4, 11, 11 Hz) due to an α-keto proton which was trans to the bridgehead proton and shifted downfield by 1,3-diaxial interaction with the hydroxyl. The two diols must therefore be epimeric at C-8.

The gross structures of the epimeric diols were confirmed by ozonolysis of the ketone **17** to an acid, which was esterified with diazomethane to obtain the methyl ester **18**, identical in all respects with the methyl ester obtained from oppositol (**1**) by ozonolysis followed by methylation.

The relative configurations of the diols **13** and **14** have been determined by two methods, neither of which can be regarded as conclusive. The diol **13** was converted into the corresponding benzoate **19**. According to Brewster's rule, comparison of the optical rotation of the benzoate **19**, $[\alpha]^{20}_D$ −17°, with that of the diol **13**, $[\alpha]^{20}_D$ +10°, suggested the configuration shown.[8] The coupling constant of the α-hydroxy proton in each diol indicated that the side chain adopted a fairly rigid conformation in solution. We performed lanthanide-induced shift experiments on both acetates **15** and **16**. In each case we were able to determine a position for the europium atom in which it must be associated with the tertiary alcohol functionality. In each complex, the α-acetoxy proton was directed toward the tertiary alcohol and the "best fit" for the shifts of the acetoxy methyl signal and the signals due to the isopropylidene group occurred with the configurations shown.

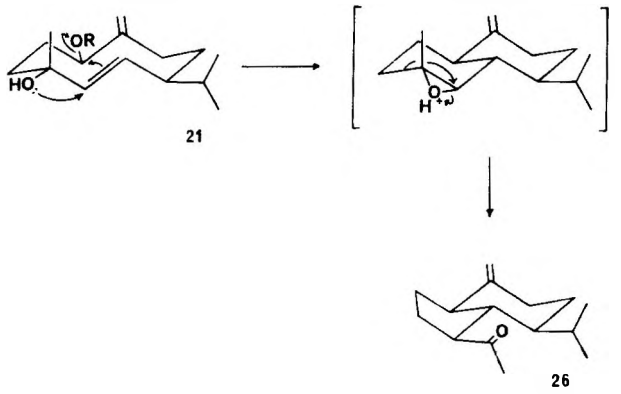
The remaining metabolites were all nonhalogenated sesquiterpenes. We identified oplopanone (**20**), previously isolated from *Oplopanax japonicus*, by comparison of physical data with literature values[9] and confirmed the assignment by showing that the melting point (93–94 °C) was undepressed on admixture with an authentic sample. The most polar metabolite that we isolated was a diol **21**, mp 118–120 °C, $[\alpha]^{20}_D$ +55°, having a molecular formula $C_{15}H_{26}O_2$. The infrared spectrum showed a strong hydroxyl band at 3600 cm^{-1} and bands at 1382 and 1367 cm^{-1} due to a gem-dimethyl group. The ^{1}H NMR spectrum contained signals at δ 0.85 (d, 3H, J = 7 Hz) and 0.91 (d, 3H, J = 7 Hz) due to an isopropyl group, 1.26 (s, 3H) due to methyl on a carbon atom bearing hydroxyl, 3.96 (dd, 1H, J = 3, 10 Hz) due to an α-hydroxy proton, 4.94 (bs, 1H) and 5.14 (bd, 1H) due to the exocyclic methylene protons, and 5.24 (d, 1H, J = 16 Hz) and 5.29 (dd, J = 16, 9 Hz) due to a trans olefinic bond which has only one proton on an adjacent carbon atom. The ^{13}C NMR spectrum confirmed the presence of a disubstituted olefin (δ 137.6 and 129.9), an exocyclic methylene (151.0 and 111.4), a secondary alcohol, (78.7), a tertiary alcohol (72.3), and no other tetrasubstituted carbons. The diol **21**, having three degrees of unsaturation, must contain a single ring. Since the UV spectrum showed only end absorption, the trans-disubstituted olefinic bond must be in a side chain or medium-sized ring and must be between the tertiary alcohol carbon and a carbon bearing only one hydrogen. Spin decoupling experiments revealed that both methyl doublets were collapsed to singlets upon irradiation at δ 1.52, while the olefinic signals were not affected, and that the secondary hydroxyl group was not on a carbon atom adjacent to the trans-disubstituted olefinic bond. Assuming that the isopropyl group must be adjacent to a chiral center for the ^{1}H NMR signals of the methyl groups to have different chemical shifts, and assuming an isoprenoid skeleton, we found only three reasonable gross structures, **22**, **23**, and **24**.



In the corresponding acetate **25**, the ^{1}H NMR signals of all the olefinic protons were shifted downfield [δ 5.00 (bs), 5.20 (bs) and 5.35 (d, 2H, J = 6 Hz)], while the isopropyl methyl signals (0.83 and 0.88) were scarcely shifted, indicating a preference for structure **22**.

Dehydration of the diol **21** with phosgene in pyridine or Moffatt oxidation conditions[10] gave a ketone **26** (IR 1710 cm^{-1}, no hydroxyl band) in quantitative yield. The ^{1}H NMR spectrum contained signals due to an exocyclic methylene (δ 4.51 and 4.61), a methyl ketone (2.09) and an isopropyl group [0.89 (d, 3H, J = 7 Hz) and 0.64 (d, 3H, J = 7 Hz)]. An identical product could be obtained by dehydration of oplopanone **20** with phosphorus oxychloride in pyridine. The formation of 8(15)-dehydrooplopanone **26** from the diol **21** can be explained only if the diol has the structure shown. Assuming a concerted reaction mechanism for dehydration and ring formation (Scheme I), we can derive the most likely relative configuration for the diol **21**. An alternative configuration at

Scheme I. Proposed Mechanism for the Conversion of Diol 21 to 8(15)-Dehydrooplopanone (26)

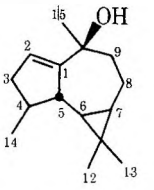


the tertiary alcohol carbon is possible, but we prefer the configuration shown.

The remaining two compounds were isomeric tertiary alcohols having the aromadendrene skeleton. 1-Hydroxyalloaromadendrene (27), isolated as an oil, had the molecular formula $C_{15}H_{24}O$. The ^1H NMR spectrum contained signals at δ 0.22 (dd, 1H, J = 9, 12 Hz) and 0.56 (m, 1H) due to two cyclopropyl protons, 0.98 (d, 3H, J = 6 Hz), 0.99 (s, 3H) and 1.02 (s, 3H) due to methyl groups, and 4.89 and 5.03 due to methylene protons. This ^1H NMR spectrum closely resembles that expected from a sesquiterpene of the aromadendrene group. The infrared spectrum indicated the presence of a hydroxyl group (3420 cm^{-1}) which must be tertiary and which must be adjacent to the exocyclic methylene group, since in the ^1H NMR spectrum neither of the cyclopropane protons appeared as a doublet and the exocyclic methylene protons were well separated in chemical shift. Treatment of an authentic sample of alloaromadendrene (28) with selenium dioxide in aqueous ethanol at 70 °C yielded a mixture of products from which was isolated a single tertiary alcohol, 1-hydroxyalloaromadendrene (27), identical with the natural product in all respects except that the optical rotations were of opposite signs. An LIS study of 1-hydroxyalloaromadendrene (27) showed that the proton experiencing the greatest induced shift was coupled to the high-field cyclopropane proton, which appeared as a double doublet, and to a proton which was, in turn, coupled to the secondary methyl group. These data indicated a cis-fused bicyclic ring system for 1-hydroxyalloaromadendrene (27).

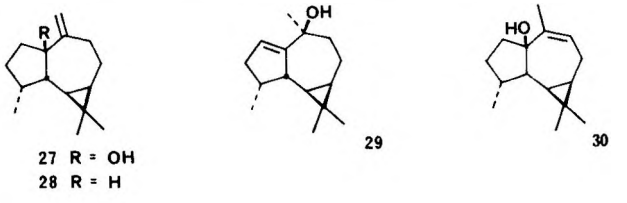
The second aromadendrene alcohol (29) (IR 3460 cm^{-1}) was isolated as an oil of molecular formula $C_{15}H_{24}O$.[11] The ^1H NMR spectrum contained signals at δ 0.44 (t, 1H, J = 9 Hz) and 0.53 (m, (m, 1H) due to the cyclopropyl protons, 1.02 (s, 3H), 1.06 (s, 3H), 1.07 (d, 3H, J = 7 Hz) and 1.45 (s, 3H) due to methyl groups and at 5.52 (bs, 1H) due to a vinyl proton. Assuming the aromadendrene skeleton, both the isomers 29 and 30 were compatible with the spectral data. The observation that the vinyl proton appeared as a broad singlet strongly suggested that the double bond was in a five-membered ring. In addition, the chemical shift of the methyl singlet at δ 1.45 was outside the normal range for a vinyl methyl. An LIS study of the alcohol 29 indicated that the alcohol had the gross structure and stereochemistry shown. After addition of 0.6 equivalents of $Eu(fod)_3$, each proton was observed as a separate signal and the coupling constants were measured (Table I). We were able to find a position for the europium ion such that a graph of log $\Delta\delta$ against log r_{meas} gave a line of slope −3 (r_{meas} is the distance between the europium ion and a proton measured using a Dreiding model; $\Delta\delta$ is the shift induced by 1 equiv of $Eu(fod)_3$ obtained by graphical extrapolation.) The structural assignment can be explained on the basis of two observations: the second largest induced shift was experienced by the methyl singlet originally at δ 1.45 and the next largest

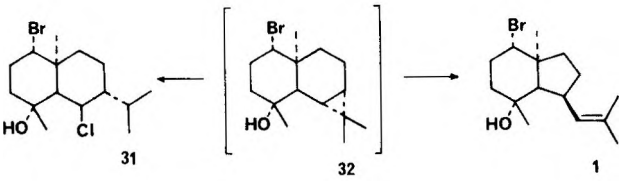
Table I. ^1H NMR Data for the Alcohol 29. Chemical Shifts (δ), Induced Shifts ($\Delta\delta$), Multiplicities, and Coupling Constants



H at C-	δ, ppm	$\Delta\delta$, ppm	Multiplicity and coupling constants, Hz	
2	5.52	2.91	bs(dd)	J = 3, 1
3(α)	2.24	0.95	ddd	J = 15, 8, 3
3(β)	2.02	1.36	ddd	J = 15, 9, 1
4	2.32	1.73	m	J = 9, 8, 8, 7, 7, 7
5	2.47	4.64	t	J = 8, 8
6	0.44	2.50	t	J = 9, 8
7	0.53	2.05	m	J = 11, 9, 5
8(α)	1.88	1.91	dt	J = 13, 6, 5
8(β)	1.55	4.59	m	J = 13, 12, 11
9(α)	1.72	3.41	t	J = 14, 12
9(β)	1.72	5.91	dd	J = 14, 6
12	1.02	0.64	s	
13	1.06	0.64	s	
14	1.07	0.73	d	J = 7
15	1.45	5.23	s	

induced shift was recorded for a proton originally at 2.47 (t, J = 8 Hz) which was coupled to a proton at 0.44 (dd, J = 8, 9 Hz) and a proton at 2.32 which was, in turn, coupled to the





methyl doublet at 1.07. Thus the hydroxyl group must be on the same face as the bridgehead proton and on the carbon bearing methyl. The small induced shifts of the cyclopropyl protons suggest that they are on the opposite face of the seven-membered ring to the hydroxyl.

We have described the major compounds from our collection of *L. subopposita*. Analysis of a second sample of *L. subopposita* by thin layer chromatography suggested a very similar composition. We have found that it was well worth the effort to examine the minor constituents and particularly the nonhalogenated sesquiterpenes. Kazlauskas et al.[4] have

speculated that oppositol (1) might be formed in vivo from a eudesmane precursor such as heterocladol (31). We believe that the coexistence of cyclopropane-containing sesquiterpenes with oppositol (1) suggests a cyclopropane-containing precursor (32) for both heterocladol (31) and oppositol (1). It is interesting to note that the only other compound having the oppositol skeleton, axionitrile-1 (33), was found together with an aromadendrane derivative, axisonitrile-2 (34), in *Axinella cannabina*,[12] suggesting a similar biogenetic relationship.

Experimental Section

^{1}H NMR spectra were recorded on a Varian HR-220 spectrometer, ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer, infrared spectra were recorded on a Perkin-Elmer Model 700 spectrophotometer, and optical rotations were measured on a Perkin-Elmer Model 141 polarimeter, using a 10-cm microcell. Low resolution mass spectra were recorded on a Hewlett-Packard 5930A mass spectrometer. High resolution mass measurements were supplied by the Analytical Facility at California Institute of Technology. Melting points were measured on a Fisher-Johns apparatus and are reported uncorrected. All solvents used were either spectral grade or distilled from glass prior to use.

Collection, Extraction, and Chromatographic Separation. *Laurencia subopposita* was collected at low tide in La Jolla in May 1975, air-dried, and ground in a Wiley mill to a 1 mm particle size. The dried alga (1 kg) was extracted in a Soxhlet apparatus for 24 h each with hexane (2 L), diethyl ether (2 L), and acetone (2 L). The combined extracts were evaporated to leave a dark green viscous oil (22.5 g, 2.3% dry weight). When assayed for antimicrobial activity, the crude extract inhibited the growth of *Staphylococcus aureus*.

The crude extract (22.5 g) was added as a concentrated petroleum ether solution to a column (75 × 5 cm) containing Florisil (750 g) in petroleum ether. Elution with a solvent gradient of increasing polarity from petroleum ether through benzene, ethyl acetate, acetone, and methanol led to 36 fractions (500 mL). Antimicrobial screening of the individual fractions indicated that only fraction 13 was active against *S. aureus*.

Laurene (4). Fractions 3 and 4 were combined (500 mg) and rechromatographed on a column (20 × 2 cm) containing 10% $AgNO_3$ on silica gel (40 g) in hexane. Elution with hexane allowed isolation of a mobile oil (110 mg, 0.011% dry weight) having spectral properties identical to those reported[3] for laurene (4).

7-Hydroxylaurene (2) and 10-Bromo-7-hydroxylaurene (3). Fraction 13 (625 mg) was rechromatographed on a column (30 × 1.5 cm) of silica gel (25 g) in 10% benzene in petroleum ether, yielding a mixture of phenols (160 mg) which was separated by HPLC on a Porasil A column (4 ft × 3/8 in.) using 15% diethyl ether in petroleum ether as an eluent to obtain 7-hydroxylaurene (2) (125 mg, 0.013%) and 10-bromo-7-hydroxylaurene (3) (25 mg, 0.0025%). Antimicrobial testing showed that each of these two substances (100 μg) inhibited the growth of *S. aureus*.

7-Hydroxylaurene (2). $[\alpha]^{20}_D$ + 45° (2.5, $CHCl_3$); IR ($CHCl_3$) 3650, 2990, 1660, 1620, 1575 cm^{-1}; NMR (CCl_4) δ 6.93 (d, 1H, J = 7 Hz), 6.56 (d, 1H, J = 7 Hz), 6.36 (s, 1H), 4.92 (s, 1H), 4.82 (s, 1H), 4.76 (s, 1H), 2.95 (q, 1H, J = 7 Hz), 2.19 (s, 3H), 1.30 (s, 3H), 0.67 (d, 3H, J = 7 Hz); mass spectrum *m/e* (relative intensity) 216 (26), 201 (74), 187 (26) 159 (38), 145, (20), 121 (40), 69 (55), 57 (60), 55 (70), 43 (92), 41 (100); high resolution mass measurement, observed 216.152, $C_{15}H_{20}O$ requires 216.151.

10-Bromo-7-hydroxylaurene (3). IR ($CHCl_3$) 3690, 2990, 1660, 1610 cm^{-1}; NMR (CCl_4) δ 7.27 (s, 1H), 6.60 (s, 1H), 5.00 (s, 1H), 4.98 (s, 1H), 4.90 (s, 1H), 2.99 (q, 1H, J = Hz), 2.28 (s, 3H), 1.21 (s, 3H), 0.73 (d, 3H, J = 7 Hz); mass spectrum *m/e* (relative intensity) 294, 296 (1:1) (10), 279, 281 (26), 237,239 (9) 201 (24), 159 (21), 69 (80), 57 (65), 55 (70), 43 (90), 41 (100).

Isoprelaurefucin (6). Fractions 14 and 15 were combined (2.0 g) and rechromatographed on a column (40 × 2.5 cm) containing silica gel (100 g) in 10% benzene in petroleum ether. Elution with a solvent gradient of increasing polarity from 10% benzene in petroleum ether to dichloromethane allowed isolation of an oil (1.04 g) with spectral characteristics appropriate for a mixture (1:2) of *cis:trans*-isoprelaurefucin (6).

Oppositol (1). Fraction 16 (1.40 g) was rechromatographed on a column (30 × 1.5 cm) containing silica gel (25 g) in 15% diethyl ether in petroleum ether, which allowed isolation of oppositol (1) (1.14 g, 0.11%) identical in every respect with an authentic sample. ^{13}C NMR ($CDCl_3$) 132.0 (d), 128.7 (s), 71.6 (s), 63.3 (d), 60.7 (d), 47.7 (s), 42.0 (t), 40.4 (t), 36.4 (d), 31.2 (t), 30.6 (q), 28.5 (t), 25.7 (q), 18.0 (q), 16.3 (q) ppm.

1-Hydroxyalloaromedendrene (27) and 10β-hydroxy-Δ$^{1(2)}$-aromadendrene (29). Fractions 17 and 18 were combined (1.02 g) and rechromatographed on a column of silica gel (50 g) in 15% diethyl ether in petroleum ether. Elution allowed isolation of an oil (530 mg) which was purified further by HPLC on a μ-C18 column (2 ft × 1/4 in.) using 30% water in acetonitrile as an eluent. This yielded an oil (95 mg) which was rechromatographed on a column (20 × 1 cm) containing 10% $AgNO_3$ on silica gel (15 g) in 30% diethyl ether in hexane to yield 1-hydroxyalloaromadendrene (27) (35 mg, 0.0035%) and 10β-hydroxy-Δ$^{1(2)}$-aromadendrene (29) (25 mg, 0.0025%).

1-Hydroxyalloaromadendrene (27). $[\alpha]^{20}_D$ +99° (1.0, $CHCl_3$); IR (neat) 3410, 2960, 1460, 1390 cm^{-1}; NMR ($CDCl_3$) δ 5.03 (s, 1H), 4.89 (s, 1H), 2.63 (m, 2H), 2.34 (m, 2H), 1.02 (s, 3H), 0.99 (s, 3H), 0.98 (d, 3H, J = 6 Hz), 0.56 (m, 1H), 0.22 (dd, 1H, J = 9, 12 Hz); mass spectrum *m/e* (relative intensity) 220 (1), 205 (1), 202 (1), 191 (1), 187 (2), 177 (3), 163 (4), 159 (4), 107 (15), 91 (20), 79 (30), 67 (32), 55 (42), 43 (48), 41 (100); high resolution mass measurement, observed 220.181, $C_{15}H_{24}O$ requires 220.183.

10β-Hydroxy-Δ$^{1(2)}$-aromadendrene (29). $[\alpha]^{20}_D$ −46° (1.0, $CHCl_3$); IR (neat) 3460, 2950, 1460, 1390 cm^{-1}; NMR ($CDCl_3$) δ 5.52 (bs, 1H), 1.45 (s, 3H), 1.07 (d, 3H, J = 7 Hz), 1.06 (s, 3H), 1.02 (s, 3H), 0.53 (m, 1H), 0.44 (t, 1H, J = 9 Hz); NMR ($CDCl_3$, 0.6 equivalent Eu(fod)$_3$) δ 7.24 (bs, 1H), 5.32 (dd, 1H, J = 14, 6 Hz), 5.06 (t, 1H, J = 8 Hz), 4.46 (s, 3H), 4.33 (ddd = 1H, J = 11, 12, 13, Hz), 3.52 (dd, 1H, J = 12, 14 Hz), 3.30 (m, 1H, J = 7, 7, 7, 8, 8, 9 Hz), 2.78 (m, 3H), 1.60 (d, 3H, J = 7 Hz), 1.50 (m, 2H), 1.40 (s, 6H); mass spectrum *m/e* (relative intensity) 220 (2), 205 (1), 202 (2), 187 (2), 177 (2), 159 (20), 105 (30), 91 (45), 81 (35), 79 (40), 77 (40), 67 (40), 55 (60), 43 (100); high resolution mass measurement, observed 220.181, $C_{15}H_{24}O$ requires 220.183.

Acetyllaurefucin (8). Fractions 21, 22, and 23 were combined (1.42 g) and rechromatographed on a column (40 × 2.5 cm) containing silica gel (100 g) in 25% diethyl ether in petroleum ether. Elution led to an oil (530 mg) which was purified further on a column (30 × 1.5 cm) containing silica gel (25 g) in chloroform, which allowed isolation of an oil (160 mg) having spectral characteristics appropriate for a mixture (1:1) of *cis:trans*-acetyllaurefucin (8). A mixture of sterols (750 mg) was also isolated from these fractions.

Diol Acetate 16 and Oplopanone (20). Fractions 24, 25, and 26 were combined (1350 mg) and rechromatographed on a column (40 × 2 cm) containing silica gel (60 g) in 1:1 diethyl ether–petroleum ether, which led to two interesting components. The least polar (410 mg) was further purified on a column (30 × 1 cm) containing silica gel (20 g) in 25% diethyl ether in petroleum ether to yield an oil (270 mg). This material was treated with acetic anhydride (2 mL) and pyridine (2 mL) at 25 °C for 16 h, and the volatile liquids were evaporated to leave an oil (300 mg) which was chromatographed by preparative tlc on three silica gel plates (20 × 20 × 0.15 cm) using 25% ethyl acetate in chloroform as an eluent to yield the diol acetate 16 (120 mg, 0.012%) as an oil. The more polar component (100 mg) was purified by preparative tlc on a silica gel plate (20 × 20 × 0.15 cm) using diethyl ether as an eluent. Isolation of a band (R_F = 0.4) led to a solid (35 mg, 0.0035%) which was recrystallized from 25% diethyl ether in hexane to yield oplopanone (20): mp 93–94 °C, $[\alpha]^{20}_D$ +13° (1.0, $CHCl_3$), which proved to be identical in all respects with an authentic sample.

Diol Acetate 16. IR ($CHCl_3$) 3700, 3000, 1738, 1460, 1380 cm^{-1}; NMR ($CDCl_3$) δ 5.48 (s, 1H), 4.84 (s, 1H), 4.81 (s, 1H), 3.97 (dd, 1H, J = 4, 13 Hz), 2.59 (m, 1H), 2.35 (m, 1H), 2.10 (s, 3H), 1.76 (s, 3H), 1.27 (s, 3H), 1.18 (s, 3H); mass spectrum *m/e* (relative intensity) 316,318 (1:1) (1), 298,300 (25), 265,267 (7), 257,259 (16), 219 (35), 201 (48), 177 (68), 159 (65), 147 (25), 145 (50), 135 (100), 119 (60), 107 (85), 105 (65), 97 (55), 95 (60), 81 (62), 71 (50), 69 (45), 57 (30), 55 (37); high resolution mass measurement, observed 316.102, $C_{15}H_{25}O_2Br$ requires 316.104.

Diol 13 and Laurefucin (7). Fractions 27 and 28 were combined (1200 mg) and rechromatographed on a column (30 × 2 cm) containing silica gel (50 g) in 25% diethyl ether in chloroform, which allowed isolation of two components. The least polar had spectral characteristics appropriate for a mixture (1:3) of *cis:trans*-laurefucin (190 mg, 0.019%). The more polar component (150 mg) was recrystallized from 20% diethyl ether in hexane to yield the diol 13, mp 123–124 °C, $[\alpha]^{20}_D$ +10° (2.5, $CHCl_3$); IR ($CHCl_3$) 3630, 3450, 2960, 1650, 1460, 1375 cm^{-1}; NMR ($CDCl_3$) δ 4.86 (s, 2H), 4.11 (d, 1H, J = 7 Hz), 3.96 (dd, 1H, J = 4, 12 Hz), 2.33 (m, 1H), 1.74 (s, 3H), 1.41 (s, 3H), 1.19 (s, 3H); mass spectrum *m/e* (relative intensity) 301,303 (1:1) (2), 283,285 (3), 245, 247 (2), 228 (4), 219 (3), 203 (4), 201 (2), 185 (6), 177 (8), 165 (13), 159 (13), 147 (48), 135 (27), 121 (27), 119 (34), 107 (96), 105 (66), 93

(81), 91 (75), 81 (99), 79 (74), 71 (100), 69 (95), 57 (50), 55 (80), 43 (95). Anal. Found: C, 56.51; H, 7.88; Br, 24.96; $C_{15}H_{25}O_2Br$ requires C, 56.78; H, 7.94; Br, 25.19.

Dehydrobromolaurefucin (9) and 7β,10α-Dihydroxy-3β-isopropyl-10-methyl-6-methylene-*trans*-cyclodecene (21). Fractions 29 and 30 were combined (1.64 g) and rechromatographed on a column (30 × 2.5 cm) containing silica gel (80 g) in 30% diethyl ether in chloroform. Elution with a solvent gradient of increasing polarity from 30% diethyl ether in chloroform to diethyl ether led to two interesting components. The least polar (670 mg) was rechromatographed on a column (20 × 2 cm) containing silica gel (30 g) in diethyl ether, which allowed isolation of an oil (300 mg, 0.03%) containing a mixture (1:1) of *cis*:*trans* dehydrobromolaurefucin (**9**):λ_{max} (MeOH) 224 nm; IR ($CHCl_3$) 3500, 3350, 2960, 1660 cm^{-1}; NMR ($CDCl_3$) δ 6.29 (m, 0.5 H), 6.15 (m, 0.5 H), 5.64 (m, 1H), 5.59 (m, 1H), 5.41 (bd, 1H, J = 12 Hz), 5.03 (bd, 1H, J = 13 Hz), 4.19 (m, 1H), 4.03 (bs, 1H), 3.90 (m, 2H), 3.13 (d, 0.5 H, J = 2 Hz), 2.83 (d, 0.5 H, J = 2 Hz), 0.95 (t, 3H, J = 7 Hz); mass spectrum m/e (relative intensity) 248 (1), 233 (0.5), 230 (0.5), 219 (4), 201 (3), 191 (6), 133 (25), 105 (90), 83 (100), 79 (95), 77 (90), 65 (90); high resolution mass measurement, observed 248.140, $C_{15}H_{20}O_3$ requires 248.141. The more polar solid component was recrystallized from diethyl ether to yield **7β,10α-dihydroxy-3β-isopropyl-10β-methyl-6-methylene-*trans*-cyclodecene (21)** (220 mg, 0.022%): mp 118–120 °C; $[\alpha]^{20}_D$ +55° (2.5, $CHCl_3$); IR ($CHCl_3$) 3600, 3430, 2950, 1530, 1440, 1382, 1367 cm^{-1}; NMR ($CDCl_3$) δ 5.27 (m, 2H), 5.14 (s, 1H), 4.94 (s, 1H), 3.96 (dd, 1H, J = 3, 10 Hz), 2.27 (m, 1H), 1.26 (s, 3H), 0.91 (d, 3H, J = 7 Hz), 0.85 (d, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) 151.0 (s), 137.6 (d), 129.9 (d), 111.4 (t), 78.7 (d), 72.3 (s), 49.9 (d), 38.6 (d), 32.4 (t), 29.9 (t), 29.5 (q), 28.3 (t, 2C) 20.6 (q, 2C); mass spectrum m/e (relative intensity) 238 (1), 220 (7), 205 (5), 202 (6), 177 (35), 135 (35), 119 (40), 109 (53), 107 (68), 97 (73), 81 (100), 41 (53). Anal. Found: C, 75.75; H, 11.18; $C_{15}H_{26}O_2$ requires C, 75.63; H, 10.92.

Isomerization of 7-Hydroxylaurene (2) to the Cyclic Ether 5. Storage of 7-hydroxylaurene (**2**) (125 mg) in diethyl ether solution (3 mL) at −20 °C for 12 months followed by preparative TLC on a silica gel plate (20 × 20 × 0.15 cm) using hexane as an eluent yielded a cyclic ether **5** (85 mg); IR (neat) 2850, 1516, 1570, 1170, 1110 cm^{-1}; NMR ($CDCl_3$) δ 7.00 (d, 1H, J = 7 Hz), 6.65 (d, 1H, J = 7 Hz), 6.55 (s, 1H), 2.24 (s, 3H), 2.1–1.5 (m, 4H), 1.49 (q, 1H, J = 7 Hz), 1.39 (s, 3H), 1.34 (s, 3H), 0.76 (d, 3H, J = 7 Hz); mass spectrum m/e (relative intensity) 216 (40), 201 (100), 187 (25), 173 (30), 159 (50), 145 (20), 115 (23), 93 (30), 91 (35), 79 (25), 77 (30), 69 (20), 67 (15), 65 (15), 57 (20), 55 (30). When tested for antimicrobial activity against *S. aureus*, this material showed no inhibitory capability.

Oxidation of Dehydrobromolaurefucin (9) to Ketone 10. Dehydrobromolaurefucin (**9**) (cis:trans, 1:1, 15 mg, 0.06 mmol) was dissolved in dichloromethane (4 mL) and stirred at 25 °C. A solution of the pyridine complex of chromic oxide (0.36 mmol) in dichloromethane (0.9 mL) was added dropwise, and the resulting mixture was stirred for 15 min at 25 °C. Water (5 mL) was added, and the organic material was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried over sodium sulfate and the solvent evaporated to leave a brown oil (18 mg) which was purified by preparative tlc on silica gel (20 × 20 × 0.025 cm) using diethyl ether as an eluent to obtain the ketone **10** (mixture of cis:trans 1:1, 12 mg) as an oil: λ_{max} (MeOH) 223 nm; IR (neat) 3180, 2860, 1680, 1450, 1370, 1320 cm^{-1}; NMR ($CDCl_3$) δ 6.26 (m, 0.5 H), 6.14 (m, 0.5 H), 6.14 (d, 1H, J = 12 Hz), 5.81 (bd, 1H, J = 12 Hz), 5.65 (d, 0.5 H, J = 16 Hz), 5.57 (d, 0.5 H, J = 9 Hz), 4.27 (m, 2H), 3.98 (m, 2H), 3.12 (d, 0.5 H, J = 2 Hz), 2.95 (d, 0.5 H, J = 2 Hz), 2.0–2.5 (m, 3h), 2.02 (m, 1H), 1.66 (m, 2H), 0.97 (t, 3H, J = 7 Hz); mass spectrum m/e (relative intensity) 246 (1), 228 (1), 217 (3), 189 (3), 173 (4), 171 (4), 150 (6), 145 (9), 143 (10), 129 (30), 105 (90), 103 (40), 95 (60), 91 (55), 81 (100), 65 (45); high resolution mass measurement, observed 246.1258, $C_{15}H_{18}O_3$ requires 246.1251.

Oxidation of Laurefucin (7) to the Ketone 11. Laurefucin (**7**) (mixture cis:trans, 1:3, 15 mg, 0.05 mmol) was dissolved in dichloromethane (1 mL) and stirred at 25 °C. A solution of the pyridine complex of chromic oxide (0.3 mmol) in dichloromethane (0.8 mL) was added dropwise, and the resulting mixture was stirred for 30 min at 25 °C. Water (5 mL) was added, and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic extract was dried over magnesium sulfate and the solvent evaporated to obtain an oil (18 mg) which was purified by preparative tlc on a silica gel plate (20 × 20 × 0.025 cm) using diethyl ether as an eluent to yield the ketone **11** (mixture cis:trans, 1:3, 12 mg) as an oil: λ_{max} (MeOH) 224 nm; IR ($CHCl_3$) 3110, 2850, 1720, 1460, 1385; NMR ($CDCl_3$) δ 6.19 (m, 0.8 H), 6.05 (m, 0.2 H), 5.57 (d, 0.8 H, J = 16 Hz), 5.50 (bd, 0.2 H, J = 9 Hz), 4.28 (d, 1H, J = 8 Hz), 4.20 (bs, 1H), 3.95 (m, 2H), 3.61 (t, 1H, J = 9 Hz), 311 (d, 0.2 H, J = 2 Hz), 2.98 (m, 2H), 2.82 (d, 0.8 H, J = 2 Hz), 2.51 (m, 1H), 2.12 (m, 2H), 1.64 (m, 2H), 1.27 (m, 1H), 0.98 (t, 3H, J = 7 Hz); mass spectrum m/e (relative intensity) 326,328 (1:1) (0.1), 246 (1), 228 (2), 218 (1), 179 (3), 177 (3), 151 (10), 149 (11), 131 (20), 107 (30), 105 (40), 97 (15), 95 (15), 91 (30), 79 (35), 77 (35), 69 (100), 65 (30), 57 (20), 55 (50).

Treatment of Ketone 11 with Methanolic Potassium Hydroxide Solution. The ketone **11** (4 mg, 0.01 mmol, cis:trans, 1:3) was dissolved in methanolic potassium hydroxide solution (0.5 N, 1.0 mL) and the solution was stirred for 1 h at 25 °C. The solution was neutralized with 0.5 N hydrochloric acid solution and the product extracted with diethyl ether (3 × 10 mL). The combined extracts were dried over magnesium sulfate and the solvent evaporated to obtain an oil (3 mg) which was purified on preparative silica gel TLC using diethyl ether as eluent to give the ketone **12** (2 mg, cis:trans, 1:3): λ_{max} (MeOH) 224 nm; IR (neat) 3150, 2820, 1715; NMR ($CDCl_3$) δ 6.16 (m, 0.5 H), 6.04 (m, 0.5 H), 5.57 (d, 0.5 H, J = 15 Hz), 5.50 (d, 0.5 H, J = 9 Hz), 4.23 (m, 1H), 4.14 (bs, 1H), 3.93 (m, 1H), 3.36 (s, 3H), 3.30 (m, 2H), 3.08 (d, 0.5 H, J = 2 Hz), 2.91 (d, 0.5 H, J = 2 Hz), 2.9–2.5 (m, 4H), 2.06 (m, 1H), 1.82 (m, 2H), 1.44 (m, 1H), 0.95 (t, 1.5 H, J = 7 Hz), 0.94 (t, 1.5 H, J = 7 Hz); mass spectrum m/e (relative intensity) 278 (1), 260 (1), 246 (4), 231 (1), 217 (2), 213 (2), 202 (5), 191 (5), 145 (21), 133 (47), 131 (45), 105 (100), 91 (58), 79 (47), 77 (43), 71 (52), 69 (47), 65 (53); high resolution mass measurement, observed 278.1521, $C_{16}H_{22}O_4$ requires 278.1521.

Treatment of Ketone 10 with Methanolic Potassium Hydroxide Solution. The ketone **10** (10 mg, 0.04 mmol, cis:trans, 1:1) was dissolved in methanolic potassium hydroxide solution (0.5 N, 2.0 mL) and the solution was stirred for 1 h at 25 °C. The reaction was worked up according to the procedure above to obtain the ketone **12** (7 mg, cis:trans, 1:1), identical except for the cis:trans olefin ratios with the compound obtained above.

Acetylation of the Diol 13. The diol **13** (20 mg, 0.06 mmol) was dissolved in a mixture of acetic anhydride (1 mL) and pyridine (2 mL), and the resulting solution was stirred for 16 h at room temperature. The reagents were removed in vacuo, and the residue was purified on a silica gel plate (20 × 20 × 0.025 cm) using diethyl ether as eluent to obtain the acetate **15** (17 mg, 75% theoretical) as an oil: IR ($CHCl_3$) 2980, 1710, 1660, 1530, 1430, 1360 cm^{-1}; NMR ($CDCl_3$) δ 5.44 (d, 1H, J = 5 Hz), 5.04 (s, 1H), 4.99 (s, 1H), 3.97 (dd, 1H, J = 4, 12 Hz), 2.62 (m, 1H), 2.34 (m, 1H), 2.04 (s, 3H), 1.78 (s, 3H), 1.30 (s, 3H), 1.18 (s, 3H); mass spectrum m/e (relative intensity) 343,345 (1:1) (1), 316,318 (1), 298,300 (11), 283,285 (5), 265,267 (4), 245,247 (4), 227,229 (4), 219 (18), 201 (21), 177 (38), 159 (40), 147 (65), 135 (100), 114 (70), 107 (70), 95 (30), 93 (30), 81 (27), 72 (65).

Benzoylation of the Diol 13. The diol **13** (17 mg, 0.05 mmol) was dissolved in a mixture of benzoyl chloride (0.5 mL) and pyridine (1 mL) and the resulting solution treated according to the previous procedure (except 20% ether in hexane) to obtain the benzoate (12 mg, 53% theoretical), $[\alpha]^{20}_D$ −17° (c = 1.2, $CHCl_3$).

The Diol 14. A solution of the acetate **16** (20 mg, 0.06 mmol) in dry ether (1 mL) was added to a stirred suspension of lithium aluminium hydride (100 mg, 3 mmol) in dry ether (4 mL) at −78 °C. After 15 min, the reaction mixture was warmed to −5 °C and allowed to stir for an additional 15 min. Ethyl acetate (1 mL) was added cautiously, followed by water (0.3 mL), 3 N potassium hydroxide solution (0.3 mL) and water (1.0 mL). The precipitate was removed by filtration and washed with ether (3 × 10 mL). The combined extracts were dried over magnesium sulfate and the solvent evaporated to yield an oil (13 mg). The crude product was purified by TLC on a silica gel plate (20 × 20 × 0.025 cm) using ether as eluent to obtain the diol **14** (10 mg, 57% theoretical): IR (neat) 3200, 2800, 1640, 1380 cm^{-1}; NMR ($CDCl_3$) δ 5.01 (s, 1H), 4.89 (s, 1H), 4.41 (bs, 1H), 4.06 (dd, 1H, J = 4, 12 Hz), 2.53 (m, 1H), 2.35 (m, 1H), 1.75 (s, 3H), 1.34 (s, 3H), 1.18 (s, 3H); mass spectrum m/e (relative intensity) 298,300 (1:1) (3), 283,285 (2), 255,257 (3), 245,247 (4), 229 (14), 228 (14), 227 (14), 226 (10), 219 (30), 177 (13), 165 (25), 159 (16), 149 (86), 148 (91), 147 (100), 135 (21), 133 (27), 107 (94), 105 (51), 95 (37), 93 (42), 91 (36), 81 (40), 71 (46), 69 (37), 57 (19), 55 (26), 43 (39), 41 (18).

Oxidation of Diols 13 and 14 to the Ketone 17. Jones' reagent (40 μL, 0.04 mmmol of CrO_3) was added dropwise to a stirred solution of either diol **13** or **14** (10 mg, 0.04 mmol) in dry acetone (2 mL) at 0 °C. After 15 min, the reaction mixture was quenched with water (2 mL) and the organic material extracted with diethyl ether (3 × 10 mL). The combined extracts were dried over magnesium sulfate and the solvent evaporated to yield an oil (9 mg) which was purified on a silica gel plate (20 × 20 × 0.025 cm) using diethyl ether as eluent to obtain the ketone **17** (6 mg, 60% theoretical). Both alcohols **13** and **14** gave the same ketone **17**, having identical properties with the exception of the optical rotations, which were: $[\alpha]^{20}_D$ −71° (0.5, $CHCl_3$) from

13, $[\alpha]^{20}_D$ −53° (1.2, $CHCl_3$) from 14: IR ($CHCl_3$) 3650, 2980, 1675, 1635, 1460, 1380, 1330 cm^{-1}; λ_{max} 219 nm; NMR ($CDCl_3$) δ 6.05 (s, 1H), 5.84 (s, 1H), 4.11 (dd, 1H, J = 4, 12 Hz), 3.77 (dt, 1H, J = 4, 11, 11 Hz), 1.91 (s, 3H), 1.24 (s, 3H), 0.91 (s, 3H); mass spectrum *m/e* (relative intensity) 299,301 (1:1) (5), 296,298 (7), 245,247 (17), 227,229 (10), 226,228 (10), 217 (29), 165 (43), 147 (48), 123 (38), 107 (43), 69 (100); high resolution mass measurement, observed 301.0625, $C_{14}H_{20}O_2Br$ requires 301.0621.

Ozonolysis of Ketone 17. A stream of ozone in oxygen was bubbled through a solution of the ketone 17 (3 mg, 0.01 mmol) in methanol (3 mL) at −78 °C for 2 min. The resulting blue solution was warmed to room temperature and the solvent evaporated to yield a crystalline acid (2 mg), mp 152–153 °C. The acid was dissolved in dry ether and treated with an excess of a solution of diazomethane in ether at room temperature for 30 min. The solvent was evaporated to yield the methyl ester 18 (2 mg, 70% theoretical) as an oil: $[\alpha]^{20}_D$ −5° (1.9, $CHCl_3$)]; IR ($CHCl_3$) 3560, 2960, 1730, 1460, 1385 cm^{-1}; NMR ($CDCl_3$) δ 3.94 (dd, 1H, J = 4, 13 Hz), 3.62 (s, 3H), 2.92 (dt, 1H, J = 4, 12, 12 Hz), 1.11 (s, 3H), 1.00 (s, 3H); mass spectrum *m/e* (relative intensity) 289,291 (1:1) (7), 273,275 (2), 257,259 (7), 224 (17), 207 (8), 193 (11), 183 (42), 151 (57), 147 (52), 123 (100), 107, (67), 81 (70), 71 (45), 55 (52).

Ozonolysis of Oppositol (1). A stream of ozone in oxygen was bubbled through a solution of oppositol (1) (70 mg, 0.3 mmol) in methanol (25 mL) at −78 °C for 15 min. The resulting solution was warmed to room temperature under a stream of nitrogen and the solvent was evaporated to yield an oil. The oil was dissolved in chloroform (25 mL) and the acid extracted with 1 N sodium bicarbonate solution (3 × 25 mL). The extracts were acidified to pH 1 with 3 N hydrochloric acid and the acid extracted with chloroform (3 × 25 mL). The combined extracts were dried over sodium sulfate and the solvent evaporated to yield a crystalline acid, mp 152–153 °C. The methyl ester 18, prepared as in the previous procedure, was identical in all respects with the material from ketone 17.

Dehydration of Oplopanone (20). Phosphorus oxychloride (45 μL, 75 mg, 0.5 mmol) was added dropwise to a stirred solution of oplopanone (2.5 mg, 0.01 mmol) in dry pyridine (0.5 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 24 h and quenched with water (1 mL). The organic material was extracted with ether (2 × 10 mL) and the combined extracts were washed with 3 N hydrochloric acid (3 × 10 mL). The extract was dried over magnesium sulfate and the solvent was evaporated to yield 8(15)-dehydrooplopanone (**26**) (2 mg, 87% theoretical) mp 67–68 °C; IR ($CHCl_3$) 2980, 1710, 1660, 1530, 1430, 1360 cm^{-1}; NMR ($CDCl_3$) δ 4.61 (s, 1H), 4.51 (s, 1H), 2.61 (m, 1H), 2.36 (m, 1H), 2.09 (s, 3H), 0.89 (d, 3H, J = 7 Hz), 0.64 (d, 3H, J = 7 Hz); mass spectrum *m/e* (relative intensity) 220 (17), 205 (4), 202 (2), 187 (4), 177 (100), 159 (7), 150 (15), 135 (42), 133 (35), 121 (50), 119 (35), 107 (78), 95 (75), 93 (67), 91 (60), 81 (75), 59 (80); high resolution mass measurement, observed 220.1817, $C_{15}H_{24}O$ requires 220.1821.

Dehydration of the Diol 21. (a) Dimethyl sulfoxide (170 μL), pyridine (3 μL), trifluoroacetic acid (2 μL), and dicyclohexylcarbodiimide (25 mg, 0.12 mmol) were added, in order, to a solution of the diol 21 (10 mg, 0.04 mmol) in dichloromethane (170 μL) and the mixture was allowed to stand at 25 °C for 24 h. The solvent was evaporated and the resulting brown oil chromatographed on a silica gel plate (20 × 20 × 0.025 cm) using 25% ether in hexane as eluent to obtain 8(15)-dehydrooplopanone (**26**) (7 mg, 75% theoretical), mp 67–68 °C. (b) A 12% solution of phosgene in benzene (5 mL) was added dropwise to a solution of the diol (10 mg, 0.004 mmol) in benzene (1 mL) containing pyridine (1.5 mL) and the reaction mixture was stirred for 2 h at 25 °C. The reaction mixture was poured onto ice (10 g) and the organic material extracted with ether (3 × 20 mL). The combined extracts were washed with 3 N nydrochloric acid (2 × 25 mL), dried over magnesium sulfate, and the solvent evaporated to obtain 8(15)-dehydrooplopanone (10 mg), identical in all respects with the authentic sample.

7-Acetoxy-10-hydroxy-3-isopropyl-10-methyl-6-methylene-*trans*-cyclodecene (25). The diol **21** (5 mg, 0.02 mmol) was dissolved in acetic anhydride (0.5 mL) and pyridine)1 mL), and the resulting solution was stirred for 16 h at 25 °C. The solvents were evaporated in vacuo and the resulting oil was purified on a silica gel plate (5 × 20 × 0.025 cm) using diethyl ether as eluent to obtain the monoacetate **25** (3 mg, 51% theoretical as an oil: NMR ($CDCl_3$) δ 5.35 (d, 2H, J = 6 Hz), 5.20 (s, 1H), 5.02 (dd, 1H, J = 8, 3 Hz), 5.00 (s, 1H), 1.98 (s, 3H), 1.28 (s, 3H), 0.88 (d, 3H, J = 7 Hz), 0.83 (d, 3H, J = 7 Hz); mass spectrum *m/e* (relative intensity) 238 (2), 220 (10), 205 (5), 202 (5), 177 (25), 162 (20), 159 (25), 119 (40), 107 (75), 43 (100).

Synthesis of 1-Hydroxyalloaromadendrene (27). Selenium dioxide (55 mg, 0.49 mmol) was added in a single portion to a solution of alloaromadendrene (100 mg, 0.46 mmol) in 95% ethanol (25 mL) at 70 °C. The reaction mixture was stirred for 2 h, then concentrated in vacuo to 10 ml. The product was partitioned between sodium bicarbonate solution (20 mL) and ether (3 × 50 mL). The combined ether extracts were dried over magnesium sulfate and the solvent evaporated to yield an oil (92 mg) which was purified on a silica gel plate (20 × 20 × 0.15 cm) using 35% ether in hexane as eluent to obtain 1-hydroxyalloaromadendrene (25 mg, 23% theoretical), identical in all respects except optical rotation, $[\alpha]^{20}_D$ −105° (1.7, $CHCl_3$), with the natural alcohol.

Acknowledgments. We wish to thank Dr. K. Takeda and Oliver McConnell for authentic samples of oplopanone and alloaromadendrene, respectively. This research was supported by grants from the National Science Foundation (PCM72-02539) and the National Institutes of Health (AI-11969). The UCSD NMR Facility was supported by a grant from the National Institutes of Health (RR-708). S.J.W. wishes to thank the National Science Foundation for a graduate fellowship.

Registry No.—**1**, 50906-52-0; **2**, 63181-28-2; **3**, 62311-74-7-4; **5**, 63181-29-3; **E-7**, 36431-73-9; **Z-7**, 63229-90-3; **E-9**, 63181-30-6; **Z-9**, 63229-91-4; **E-10**, 63181-31-7; **Z-10**, 63229-92-5; **E-11**, 63268-01-9; **Z-11**, 63181-32-8; **E-12**, 63181-33-9; **Z-12**, 63229-93-6; **13**, 63196-03-2; **14**, 63267-66-3; **15**, 63181-34-0; **16**, 63181-35-1; **17**, 63181-36-2; **18**, 63181-37-3; **19**, 63181-38-4; **20**, 1911-78-0; **21**, 63181-39-5; **25**, 63181-40-8; **26**, 28305-60-4; **27**, 63181-41-9; **28**, 25246-27-9; **29**, 63181-42-0.

References and Notes

(1) W. H. Fenical, *J. Phycol.*, **11**, 245 (1975).
(2) S. S. Hall, D. J. Faulkner, J. Fayos, and J. Clardy, *J. Am. Chem. Soc.*, **95**, 7187 (1973).
(3) T. Irie, T. Suzuki, Y. Yasunari, E. Kurosawa, and T. Masamune, *Tetrahedron*, **25**, 459 (1969).
(4) R. Kazlauskas, P. T. Murphy, R. J. Quinn, and R. J. Wells, *Aust. J. Chem.*, **29**, 2533 (1976).
(5) Since the compounds **2** and **3** are bicyclic, they are more accurately described as derivatives of laurene than of laurinterol, which has a different carbon skeleton.
(6) E. Kurosawa, A. Fukuzawa, and T. Irie, *Tetrahedron Lett.*, 4135 (1973).
(7) A. Fukuzawa, E. Kurosawa, and T. Irie, *Tetrahedron Lett.*, 3 (1972); A. Furusaki, E. Kurosawa, A. Fukuzawa, and T. Irie, *ibid.*, 4579 (1973).
(8) K. Nakanishi, "Matural Products Chemistry," Vol. I, K. Nakanishi, T. Goto, S. Ito, S. Natori, and S. Nozoe, Ed., Academic Press, New York, N.Y., 1974, p 33, and references cited therein.
(9) K. Takeda, H. Minato, and M. Ishikawa, *Tetrahedron Suppl.*, **7**, 219 (1966).
(10) J. G. Moffatt, *Org. Syn.*, **47**, 25 (1967).
(11) We isolated traces of a third alcohol, molecular formula $C_{15}H_{24}O$, which appeared to be the epimeric tertiary alcohol [NMR ($CDCl_3$) δ 0.46 (m, 1H), 0.53 (m, 1H), 0.99 (s, 3H), 1.01 (s, 3H), 1.05 (d, 3H, J = 7 Hz), 1.19 (s, 3H), 5.45 (bs, 1H).
(12) F. Cafieri, E. Fattorusso, S. Magno, C. Santacroce, and D. Sica, *Tetrahedron*, **29**, 4259 (1973); E. Fattorusso, S. Magno, L. Mayol, C. Santacroce, and D. Sica, *ibid.*, **30**, 3911 (1974).

Stereochemical Control of Reductions. 6.[1] The Hydroxymethyl Group as a Hinge for Internal Reagent Delivery[2]

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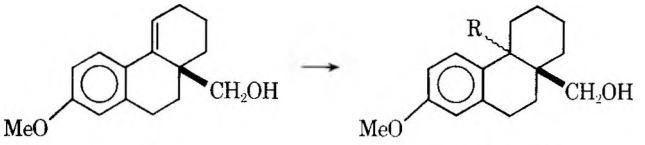
Received January 12, 1977

Esters of 7-methoxy-1,2,3,9,10,10a-hexahydrophenanthrene-10a-carboxylic acid have been synthesized by two routes. Reduction provided 7-methoxy-10a-hydroxymethyl-1,2,3,9,10,10a-hexahydrophenanthrene (**1**), whose cis (**2**) and trans (**3**) reduction products have previously been characterized. Treatment of **1** with $LiAlH_4$ in refluxing dibutyl ether gave 90% of a 95:5 mixture of **2** and **3**, implying internal hydride transfer and a cyclic Al species. The extreme slowness of this reaction compared to the analogous reduction of cinnamyl alcohol is attributed to the *p*-methoxyl group, the trisubstituted styrene, and particularly the requirement of a seven-center hydride transfer. Reduction of **1** and of its salts with insufficiencies of N_2H_2 gave 48–60% conversions to mixtures containing the following ratios of **2** and **3**: 1 (pure **2**), Li (99:1), Na (58:42), K (52:48). These results are discussed in terms of attractive electrostatic vs. repulsive steric interactions.

We have already reported instances of the use of substrate hydroxymethyl groups to control the sterochemistry of olefin reduction in heterogeneous[1,3] and homogeneous[4] catalytic hydrogenation. The availability of compound **1** and its cis and trans reduction products **2** and **3** in connection with some of these studies,[1,4] prompted us to examine several methods of using the hydroxymethyl group in **1** as a reagent



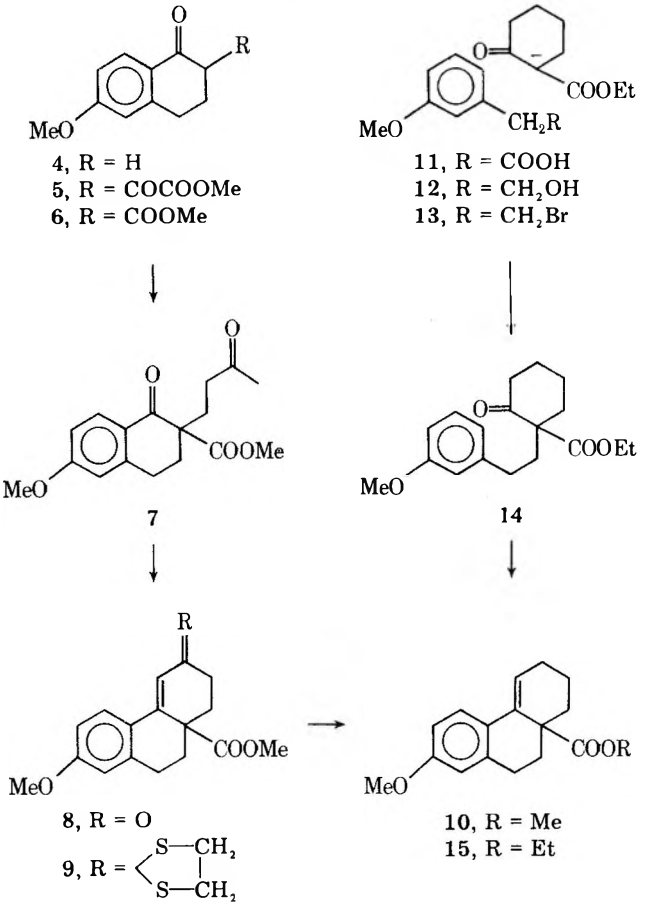
1 **2**, R = —H; **3**, R = ···H

guide or "hinge" in other olefin reduction processes. Compound **1** seemed well suited to this kind of study for reasons similar to those which had made it attractive for hydrogenation studies,[1] viz., planarity (apart from the CH_2OH) so that both sides of the molecule are accessible, stereochemical simplicity, and positional stability of the styrene double bond. In addition, **1** combines a reasonable degree of crystallinity with sufficiently low molecular weight to allow VPC analysis and is readily available by reduction of the corresponding esters **10** and **15**. As indicated in Scheme I, these esters were synthesized by two independent routes, the previously reported[5] Friedel–Crafts cyclization providing **15** in an overall yield of 23% from **11**, and the alternate route through compounds **4–9** giving **10** in 26% yield; the relationship of **10** and **15** was demonstrated by transesterification. We have previously described the sequences used to establish the stereochemistry of the cis and trans reduction products **2** and **3**.[1]

The reactions we wished to examine were ones for which reports exist of successful utilization of a hydroxyl group as an internal proton donor or reagent hinge. However, in both of the instances reported here the use of the hydroxyl group for stereo- or even regioselective control has been successfully demonstrated in only a single case or single series of compounds. We have examined these reactions mechanistically and for wider utility by applying them to system **1**.

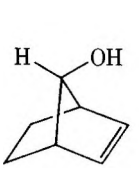
Lithium Aluminum Hydride Reduction of 1. The general rule that alkenes are not reduced by $LiAlH_4$ at ordinary pressures and temperatures[6] has a number of exceptions.[7] Almost all involve conjugated double bonds which are polarizable in such a way as to provide stabilization for the negative charge localized on the carbon where a C–Al bond is formed. Thus in essence these exceptions entail conjugate addition of hydride. Several of the systems involved, such as α,β-unsaturated carbonyl compounds,[8] are ones providing such good

Scheme I

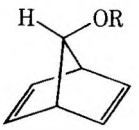


anion stabilization that they normally undergo a wide variety of other conjugate additions. Others, such as diphenylethylenes,[9] do not and require generally higher reaction temperatures, while some compensate for poorer anion stabilization by permitting intramolecular hydride addition and incorporation of the C–Al bond into relatively unstrained rings.[10] The well known cinnamyl case,[7,11] in which carbonyl reduction precedes alkene reduction, falls into the last category.

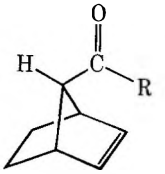
The only examples we are aware of involving reactions at "normal" temperatures which do not involve such conjugate addition also fall into the last category and happen as well to be the sole examples which demonstrate regio- or stereochemical control by the group which confers intramolecularity. These are all reductions on variants of the homallylic systems **16** and **17**.[12] The reactivity of **16** and **17** is evidently the result of a fortuitous arrangement of bonds and angles in a highly



16



17a, R = H
17b, R = COMe



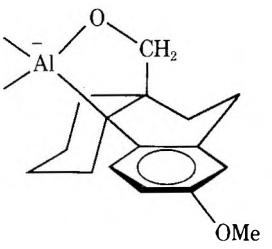
18a, R = H
18b, R = OMe

rigid system, and possibly also a result of the strained character of such alkenes.[6c,12c]

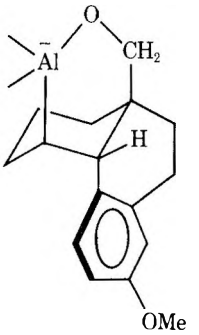
In **1** we were able to examine a case which, like cinnamyl systems, has only modest carbanion stabilization by a single phenyl, combined with the geometry for formation of a 5-membered Al ring. However **1** differs markedly from cinnamyl systems in the requirement of a 7-center hydride-transfer process in place of a 5-center one. Our results indicate that this change is drastically detrimental to olefin reduction. Successive attempts at reduction of **1** with $LiAlH_4$ in Et_2O, THF, DME, and dioxane established that the reaction does not proceed at a synthetically useful rate at the reflux temperatures of these solvents. However, in refluxing dibutyl ether (142 °) the reduction proceeded with a half-life on the order of 4 h, so that after 24–30 h the reaction was essentially complete and 90% yields of a mixture of **2** and **3** were isolable. Although several groups have reported increased rates of alkene reduction in more basic ethereal solvents,[11c,13] we desired a system whose temperature would be self-regulated by reflux and so did not explore the use of diglyme (bp 162 °C). We observed no evidence of the cyclopropane formation encountered in high-temperature $LiAlH_4$ treatment of cinnamyl systems.[14]

There are three obvious sources for this large diminution in the rate of reduction of **1** compared to cinnamyl alcohol: the presence of a deactivating *p*-methoxyl group, an additional alkyl substituent on the double bond, and the requirement of a 7-centered process for hydride transfer. Consistent with the accepted intramolecular mechanism, presence of para electron-donating groups has been found to decrease the rate of such styrene reductions by $LiAlH_4$. Two studies provide direct rate data on ethereal $LiAlH_4$ reduction of cinnamyl vs. *p*-methoxycinnamyl alcohols.[13,15] Both indicate that the decrease in rate when this substituent is introduced can be compensated for by a temperature rise of 30–40 °C, more probably the lower of these two values. Less information appears to exist concerning the effect of adding an alkyl group at the olefin being reduced. The only useful data we are aware of deals with the preparative reduction of 2-methylcinnamic acid with $LiAlH_4$ in ether.[16] This reaction proceeded in high yield with no alkene reduction when carried out at 0 °C for 24 h. Since "at higher temperatures a mixture of the allylic and saturated alcohols was obtained", it appears that the introduction of this methyl group adds an energy barrier which, again, can be overcome by raising the temperature perhaps 30–40 °C. Even taken together, these two factors fail to account adequately for the extremely high temperature required for reduction of **1**. Since stereochemical evidence (*vide infra*) indicates the reaction to be intramolecular, we believe that the third factor mentioned, the apparently unfavorable stereochemistry of the hydride-transfer process, must be invoked to explain this very low reactivity.

At least two examples of alkene reduction are known which involve direct comparison of homologs and which may be pertinent. The previously noted reduction of system **16** and its variants proceeds by way of a 6-center hydride transfer to yield a 5-membered Al species.[12c] When the conditions for these reactions were applied to **18**, in which the cyclic process and species contain one more member, no alkene reduction product was detectable (2 h, 35 °C, Et_2O).[17] It is also reported that alkyne reduction in 4-phenyl-3-butynol was undetectable even after many hours under conditions where reduction of its lower homolog, phenylpropargyl alcohol, was 50% complete in 5 min (20 °C, Et_2O).[15] While both of these cases possess special features which may qualify any generalities drawn, it seems safe to conclude that the rates of these reactions must be very sensitive functions of the stereochemistry of the hydride-transfer process. Consistent with this, the reduction of coumarin is reported to proceed without olefin involvement under conditions which lead to complete double bond saturation when ethyl *o*-coumarate is reduced.[18]



19



20

Our reduction of **1** with $LiAlH_4$ in refluxing Bu_2O produced a mixture of **2** and **3** in the ratio of 95:5, clearly implying internal hydride transfer and the intermediacy of an internally bonded species like **19** or **20**. The mechanism represented by the latter structure, involving a less disadvantageous, 6-center hydride transfer, would also require a less conventional addition to the styrene bond, but one which would be aided instead of hindered by the resonance effects associated with the *p*-methoxy group.

In **20**, where ring-juncture stereochemistry is presumably fixed during hydride transfer, the small amount of trans product observed could only be due to intermolecular reactions. If **19** is the intermediate, trans material could arise either from intermolecular reactions or from incomplete retention in the C–Al bond hydrolysis. Such hydrolyses are almost certainly kinetically controlled, since they are known to be extremely fast and they have been shown to be highly stereoretentive, at least in the case of vinylalanes[6e,19] and of **16** and **17**.[12c]

While present evidence does not allow us to distinguish conclusively between the mechanisms represented by **19** and **20**, we are inclined to favor the former. In either case our conclusion concerning **1** is that, while hydroxy groups can be used as reagent hinges for stereochemical control of olefin reduction by $LiAlH_4$ in carefully selected cases, such reactions are generally limited by extreme stereochemical sensitivity of the hydride-transfer process and by narrow requirements of other aspects of the reaction, such as carbanion stabilization and perhaps Al ring size.

Diimide Reduction of 1 and Its Salts. In 1967 Baird, Franzus, and Surridge[20] demonstrated in the reactions of diimide with the same norbornadienyl system cited above (**17**) a selectivity which ran counter to expectations based on steric grounds and thus appeared to involve an electrostatic complexation of the C-7 oxygen atom with N_2H_2. Since rates of olefin reduction with diimide fall off sharply with increasing substitution,[21] relatively few instances of reduction of tri- or tetra-substituted alkenes have been reported. Consequently, as far as we are aware no use has been made of this principle in regio- or stereoselectively controlling olefin reduction aside from the case of **17**. However, the evident enhancement in rate for N_2H_2 addition where such chelative effects operate, plus the possibility of further rate enhancement based on anion

Table I. Products from Reduction of 1 and Its Salts with HN=NH

Group	% Isolated yield	Composition of product mixture Ratio of 1:2:3[a]	Ratio of 2:3[a]
CH_2OH[b]	91	37:63:0	100:0
CH_2OH	90	37:63:0	100:0
CH_2OLi	90	47:52.5:0.5	99:1
CH_2ONa	90	33:39:28	58:42
CH_2OK	90	34:34:32	52:48

[a] Nonzero values considered accurate to ±2%, e.g., 37 ± 2:63 ± 2:0. [b] First (91%) determination carried out in refluxing diglyme, all others in refluxing 3:1 Bu_2O–diglyme.

formation, prompted us to examine the reaction of diimide with 1 and its salts.

The results, shown in Table I, clearly suggest for compound 1 and its Li salt the sort of chelative effect observed with 17. None of the results with the salts offer evidence that increased electron density on oxygen favors this effect. On the contrary, while the Li salt gives stereochemical results comparable to those from 1 itself, it appears that beyond Li, stereochemistry is increasingly controlled by the demands of cation size. This is consistent with what is already known about the sensitivity of N_2H_2 reductions to steric factors.[21,22]

Our experiments with 1 and its salts were not carried out to complete reduction (3 equiv of N_2H_2) and did not involve any appreciable excesses of base. Since toluenesulfinic acid ($pK_a \sim 1.66$) is a by-product of the thermal elimination of diimide from our precursor (*p*-toluenesulfonyl hydrazide), and since alkoxides are stronger bases than hydrazines, the alkoxy salts of 1 originally present obviously became protonated as these reactions proceeded. This change in the composition of the starting materials with reaction progress would cause the results with the salts to resemble those for neutral 1 more closely than if pure salts persisted throughout. Nevertheless the loss of stereochemical control for the Na and K salts is quite marked and is consistent only with much smaller chelative effects than for 1 or the Li salt.

It should be noted that the stereoselectivity exhibited in reduction of 1 and its Li salt is greater than for any other method of reduction we have attempted except homogeneous catalytic hydrogenation of the alkali metal salts.[1,4] Hence, although enhanced selectivity based on chelation with alkoxide ions did not materialize in our system, control of diimide reductions by internal chelation with hydroxyl groups is confirmed as a powerful stereochemical tool.

Experimental Section[23]

10a-Carbethoxy-7-methoxy-1,2,3,9,10,10a-hexahydrophenanthrene (15).[5] In a modification of a literature procedure,[24] a solution of 5.32 g (47 mmol) of KO-*t*-Bu in 104 mL of dry *t*-BuOH was stirred under N_2 during addition of 7.99 g (47 mmol) of 2-carbethoxycyclohexanone in 150 mL of *t*-BuOH. After 15–20 min, a solution of 10.2 g (47 mmol) of 3-methoxyphenethyl bromide (13)[25] in 100 mL of *t*-BuOH was added with stirring and the mixture was refluxed for 80 h and worked up as described.[24] Fractional distillation gave 7.3 g (53%) of 14 as a liquid, bp 130–155 °C at 0.08 mm (lit.[5] bp 150–160 °C at 0.1 mm); NMR δ 1.25 (3Ht, *J* = 7 Hz), 1.2–3.0 (12H complex), 3.75 (3Hs), 4.1 and 4.15 (2H, 2q, each *J* = 7), 6.5–7.3 (4H complex).

The above product (4.0 g, 13 mmol) was cyclized by refluxing in HOAc–HCl–H_2O according to the described procedure[5] to yield 3.3 g (86%) of solid 15, whose melting point after two recrystallizations from MeOH was 85 °C (lit.[5] mp 87–88 °C); IR 1720 cm^{-1}; UV 220, 261.5, 296 nm; NMR δ 1.05 (3Ht, *J* = 7 Hz), 1.2–2.9 (10H complex), 3.7 (3Hs), 4.0 (2Hq, *J* = 7), 6.1 (1 Ht, *J* = 4), 6.35–6.75 (2H complex), 7.4 (1 Hd, *J* = 9); MS *m/e* 286 (85%, M^+), 213 (100%), 212 (87%).

2-Carbomethoxy-2-(γ-ketobutyl)-6-methoxy-1-tetralone (7). 2-Methoxyoxalyl-6-methoxy-1-tetralone (5)[26] was thermally decarbonylated to provide 2-carbomethoxy-6-methoxy-1-tetralone (6);[26] NMR δ 2.0–3.2 (5H complex). 3.75 (3Hs), 3.8 (3Hs), 6.6–7.0 (2H complex), 8.0 (1 Hd. *J* = 8.5 Hz). A solution of 19.2 g (82 mmol) of 6 in 100 mL of dry benzene was added to a solution prepared by dissolving 1.90 g (82.5 mg-atoms) of Na in 100 mL of dry MeOH. The reaction of 25.0 g (174 mmol) of 1-diethylamino-3-butanone with 25.0 g (176 mmol) of MeI for 30 min at 0 °C gave a precipitate which was washed twice with dry Et_2O to remove excess MeI.[27] A solution of this methiodide in 100 mL of dry MeOH was added to the solution of sodium enolate described above. The resulting mixture was stirred overnight at 25 °C under N_2, refluxed 2 h, and worked up in the usual way to provide 21.6 g (87%) of 7 as the crude solid. Recrystallization from EtOAc–MeOH gave material melting 85 °C; IR 1725, 1680 cm^{-1}; UV 212.5, 230, 280 nm; NMR δ 2.0–3.2 (8H complex), 2.1 (3Hs), 3.65 (3Hs), 3.8 (3Hs), 6.55–7.0 (2H complex,) 8.0 (1 Hd, *J* = 9 Hz); MS *m/e* 304 (19%, M^+), 234 (94%), 202 (58%), 148 (100%), 120 (55%).

Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.12; H, 6.72.

10a-Carbomethoxy-7-methoxy-1,9,10,10a-tetrahydrophenanthren-3(2*H*)-one (8). A solution of 20.0 g (66 mmol) of 7 in 1 L of dry MeOH was added under N_2 to a solution prepared by dissolving 21.23 g (923 mg-atoms) of Na in 1 L of dry MeOH. The solution was stirred overnight at 25 °C and then refluxed 2 h under N_2, becoming dark and cloudy. The benzene extracts from the cooled mixture, when neutralized, dried, and concentrated, provided 14.2 g (75%) of 8 as the crude solid, mp 153 °C after recrystallization from EtOAc; IR 1730, 1663 cm^{-1}; UV 243.5, 330 nm; NMR δ 1.65–3.1 (8H complex), 3.65 (3Hs), 3.8 (3Hs), 6.6 (1 Hs), 6.6–6.95 (2H complex), 7.75 (1 Hd, *J* = 9 Hz); MS *m/e* 286 (97%), M^+), 230 (79%), 227 (100%), 226 (77%), 215 (60%), 171 (73%).

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.33; H, 6.41.

7-Methoxy-1,9,10,10a-tetrahydrophenanthren-3(2*H*)-one. A 100-mg sample of 8 (0.35 mmol) in 10 mL of 50% aqueous MeOH was refluxed 30 min with 10 mg (0.15 mmol) of 85% KOH. The usual workup provided 68 mg (85%) of the decarbomethoxylated material, mp 115–116 °C after recrystallization from EtOH (lit.[28] mp 114–115.5 °C); IR 1670 cm^{-1}; NMR δ 1.2–3.1 (9H complex), 3.8 (3Hs), 6.5 (1 Hd, *J* = ca. 1 Hz), 6.55–6.95 (2H complex), 7.7 (1 Hd, *J* = 9). This NMR spectrum is identical with that of another sample of this material, mp 110–112 °C, obtained in this laboratory[29] as a by-product in the synthesis of 7-methoxy-3,4,9,10-tetrahydrophenanthren-1(2*H*)-one.[30]

10a-Carbomethoxy-3,3-ethylenedithio-7-methoxy-1,2,3,9,-10,10a-hexahydrophenanthrene (9). A mixture of 286 mg (1.0 mmol) of 8, 0.20 mL (2.40 mmol) of ethanedithiol, 5.0 mL of HOAc, and 0.10 mL of freshly distilled BF_3OEt_2 was prepared at 0 °C and allowed to stand overnight at 25 °C. The yellowish needles formed were recrystallized in the mixture by adding hot MeOH and cooling. The collected solid was washed twice with cold MeOH to give 300 mg (85%) of 9 as white needles, which melted at 167–167.5 °C after recrystallization from MeOH; IR 1730 cm^{-1}; UV 217, 277 nm; NMR δ 1.3–3.1 (8H complex), 3.4 (4Hm), 3.6 (3Hs), 3.8 (3Hs), 6.3 (1 Hs), 6.5–6.9 (2H complex), 7.6 (1 Hd, *J* = 9 Hz); MS *m/e* 362 (2%, M^+), 167 (37%), 149 (100%).

Anal. Calcd for $C_{19}H_{22}O_3S_2$: C, 62.95; H, 6.12. Found: C, 63.24; H, 6.16.

10a-Carbomethoxy-7-methoxy-1,2,3,9,10,10a-hexahydrophenanthrene (10) by Desulfurization of 9. A mixture of 100 mg (0.276 mmol) of 9, 1.00 g of W-4 Raney Ni which had been deactivated by refluxing 2.5 h in acetone, and 10 mL of absolute EtOH was refluxed 24 h. Filtration, concentration, and sublimation gave 37 mg (49%) of 10, mp 111.5–112 °C, identical with the subsequently described 10, prepared from 15, by comparison of spectra.

Preparation of 10 by Transesterification of 15. A solution of 429 mg (1.50 mmol) of 15 in 5.0 mL of dry MeOH was added to a solution prepared by dissolving 505 mg (22.0 mg-atoms) of Na in 25 mL of dry MeOH. After 24 h of refluxing under N_2, the mixture was neutralized, extracted, and concentrated to give 368 mg of crude solid. Recrystallization from MeOH provided 350 mg (85%) of 10 as short needles, mp 113–113.5 °C; IR 1725 cm^{-1}; UV 218, 264, 297.5 nm; NMR δ 1.1–2.85 (10H complex), 3.5 (3Hs), 3.7 (3Hs), 6.1 (1 Ht, *J* = 4 Hz), 6.3–6.7 (2H complex), 7.35 (1 Hd, *J* = 9); MS *m/e* 272 (95%, M^+), 214 (51%), 213 (96%), 212 (100%), 171 (61%).

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.74; H, 7.37.

Reduction Procedures. Lithium Aluminum Hydride. A solution of 24.4 mg (0.10 mmol) of 1 in 3.0 mL of dry Bu_2O was added with stirring under N_2 to a suspension of 5.0 mg (0.125 mmol) of 95% $LiAlH_4$ in 1.0 mL of dry Bu_2O. After this mixture had been refluxed 30 h under N_2 it was worked up by anaerobic addition of saturated

aqueous Na_2SO_4. Separation and concentration of the organic portion gave an oil distilled at ca. 0.1 mm in a sublimation apparatus, whose cold finger was weighed immediately before and after removal of the distillate for subsequent VPC analysis. The product consisted of 22.2 mg (90%) of a liquid mixture of **2** and **3** in the ratio of 95:5.

Diimide. For reduction of the alcohol 18.6 mg (0.10 mmol) of *p*-toluenesulfonyl hydrazide was combined with 24.4 mg (0.10 mmol) of **1** in 4.0 mL of dry solvent (see Table I) and refluxed under N_2. For the salts 24.4 mg (0.10 mmol) of **1**, dissolved in a variable amount of dry solvent, was combined with 1.1 equiv of base under N_2; the mixture was stirred 2 min at 35 °C for formation of the Li salt (ethereal MeLi, no other solvent), refluxed for 24 h to produce the Na salt (NaH, 1 mL of diglyme), and refluxed 2 h in the case of the K salt (KH, 3 mL of Bu_2O). These procedures had previously been shown to give complete conversion to alkoxides.[1] For each salt the solvent was then adjusted to give a total of 4 mL of 3:1 Bu_2O–diglyme, 18.6 mg (0.10 mmol) of *p*-toluenesulfonyl hydrazide was added, and refluxing under N_2 was begun. For all reactions another 0.10-mmol portion of reagent was added after 3 h and again after 6 h of reflux. When each mixture had been refluxed 12 h under N_2, it was worked up by addition of water, aqueous HCl, and pentane. Separation and concentration of the organic portions gave an oil which was chromatographed on Al_2O_3 and then distilled and collected for VPC analysis as described above.

Analysis of Product Mixtures. The entire distillate was washed from the sublimator cold finger with solvent and this solution was used directly for VPC analysis. NMR did not provide adequate resolution of the appropriate peaks at 60 MHz to be useful for mixture analysis. Typical VPC retention times for **1**, **2**, and **3**, respectively, were 6, 10, and 13 min with the Apiezon column at 270 °C and 6, 13, and 16 min for the SE-30 column at 235 °C. Traces were integrated by planimeter and calibrated with traces from prepared mixtures of **2** and **3**.

Control Reductions. Except in one instance, control reactions to establish absence of equilibration were run on the trans product (**3**) since evidence indicates it is the less stable epimer.[1,30,31] These reactions employed $LiAlH_4$ with **2** and with **3**, and *p*-toluenesulfonyl hydrazide with **3** and with the K salt of **3**, utilizing 0.05-mmol quantities and the reduction procedures indicated above. Material recoveries were 96–100% and in no instance was evidence detected for epimerization.

Acknowledgments. Financial support from the Rutgers Research Council is gratefully acknowledged. In addition, thanks are due to Lever Brothers Research Center, Givaudan Corp., and Hoffmann-La Roche Inc. for making facilities available to E. M. Gratitude is expressed to Gree Loober Spoog for helpful consultations.

Registry No.—**1**, 53547-99-2; **1** (Li salt), 63215-76-9; **1** (Na salt), 63215-77-0; **1** (K salt), 63215-781; **5**, 6935-48-4; **6**, 40153-87-5; **7**, 63215-79-2; **8**, 63215-80-5; **9**, 63215-81-6; **10**, 63215-82-7; **13**, 2146-61-4; **14**, 63215-83-8; **15**, 59434-75-2; 2-carbethoxycyclohexanone, 1655-07-8; 1-diethylamino-3-butanone, 3299-38-5; 1-diethylamino-3-butanone methiodide, 43025-83-8; 7-methoxy-1,9,10,10a-tetrahydrophenanthren-3(2*H*)-one, 5869-03-4; ethanedithiol, 540-63-6.

References and Notes

(1) Part 5: H. W. Thompson, E. McPherson, and B. L. Lences, *J. Org. Chem.*, **41**, 2903 (1976).
(2) Taken in part from the Ph.D. Thesis of E. M., Rutgers University, 1975.
(3) (a) H. W. Thompson, *J. Org. Chem.*, **36**, 2577 (1971); (b) H. W. Thompson and R. E. Naipawer, *ibid.*, **37**, 1307 (1972); (c) H. W. Thompson and R. E. Naipawer, *J. Am. Chem. Soc.*, **95**, 6379 (1973).
(4) H. W. Thompson and E. McPherson, *J. Am. Chem. Soc.*, **96**, 6232 (1974).
(5) R. A. Barnes, H. P. Hirschler, and E. R. Bluestein, *J. Am. Chem. Soc.*, **74**, 32 (1952).
(6) (a) J. R. Sampey and J. M. Cox, *J. Am. Chem. Soc.*, **71**, 1507 (1949); (b) I. Goodman, *J. Chem. Soc.*, 846 (1951); (c) K. Ziegler, *Angew. Chem.*, **64**, 323 (1952); (d) K. Ziegler, H. G. Gellert, H. Martin, K. Nagel, and J. Schneider, *Ann.*, **589**, 91 (1954); (e) E. F. Magoon and L. H. Slaugh, *Tetrahedron*, **23**, 4509 (1967); (f) R. Laiande and Y. Ducasse, *C. R. Acad. Sci.*, **252**, 2114 (1961).
(7) (a) W. G. Brown, *Org. React.*, **6**, 481 (1951); (b) N. G. Gaylord, "Reduction with Complex Metal Hydrides", Wiley-Interscience, New York, N.Y., 1956, p 925 ff; (c) H. O. House, "Modern Synthetic Reactions" 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 89 ff.
(8) R. E. Lutz and D. F. Hinkley, *J. Am. Chem. Soc.*, **42**, 7091 (1950); W. J. Bailey and M. E. Hermes, *J. Org. Chem.*, **29**, 1254 (1964); H. C. Brown and H. M. Hess, *ibid.*, **34**, 2206 (1969).
(9) I. Granoth, Y. Segall, H. Leader, and R. Alkabets, *J. Org. Chem.*, **41**, 3682 (1976); *cf.* D. Lavie and E. D. Bergmann, *Bull. Soc. Chim. Fr.*, 250 (1951).
(10) E. B. Bates, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 1854 (1954); M. Santelli and M. Bertrand, *Tetrahedron Lett.*, 3905 (1970); W. T. Borden, *J. Am. Chem. Soc.*, **92**, 4898 (1970). *Cf.* S. Wolfe, M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **24**, 1034 (1959); J. Klein and E. Dunkelblum, *Tetrahedron Lett.*, 6047 (1966).
(11) (a) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **69**, 2548 (1947); (b) F. A. Hochstein and W. G. Brown, *ibid.*, **70**, 3484 (1948); (c) E. I. Snyder, *J. Org. Chem.*, **32**, 3531 (1967).
(12) (a) P. D. Bartlett and W. P. Giddings, *J. Am. Chem. Soc.*, **82**, 1240 (1960); (b) P. R. Story, *J. Org. Chem.*, **26**, 287 (1961); (c) B. Franzus and E. I. Snyder, *J. Am. Chem. Soc.*, **87**, 3423 (1965).
(13) M. J. Jorgenson and A. F. Thacher, *Chem. Commun.*, 973 (1968).
(14) (a) M. J. Jorgenson and A. W. Friend, *J. Am. Chem. Soc.*, **87**, 1815 (1965); (b) R. T. Uyeda and D. J. Cram, *J. Org. Chem.*, **30**, 2083 (1965); (c) M. J. Jorgenson and A. F. Thacher, *J. Chem. Soc., Chem. Commun.*, 1290 (1969).
(15) F. Bohlmann, R. Enkelmann, and W. Plettner, *Ber.*, **97**, 2718 (1964).
(16) L. Li and W. H. Elliott, *J. Am. Chem. Soc.*, **74**, 4089 (1952); *cf.* ref 14b.
(17) R. K. Bly and R. S. Bly, *J. Org. Chem.*, **28**, 3165 (1963).
(18) P. Karrer and P. Banerjea, *Helv. Chim. Acta*, **32**, 1692 (1949); *cf.* F. A. Hochstein, *J. Am. Chem. Soc.*, **71**, 305 (1949).
(19) J. J. Eisch and W. C. Kaska, *J. Am. Chem. Soc.*, **88**, 2213 (1966); K. H. Henold and J. P. Oliver in "Organometallic Reactions", Vol. 5, E. I. Becker and M. Tsutsui, Ed., Wiley-Interscience, New York, N.Y., 1975, p 387.
(20) W. C. Baird, Jr., B. Franzus, and J. H. Surridge, *J. Am. Chem. Soc.*, **89**, 410 (1967).
(21) S. Hünig, H. R. Müller, and W. Thier, *Angew. Chem., Int. Ed. Engl.*, **4**, 271 (1965); E. W. Garbisch, Jr., S. M. Schildcrout, D. B. Patterson and C. M. Sprecher, *J. Am. Chem. Soc.*, **87**, 2932 (1965).
(22) E. E. van Tamelen and R. J. Timmons, *J. Am. Chem. Soc.*, **84**, 1067 (1962).
(23) Melting points were determined with a Mel-Temp apparatus and are uncorrected, as are boiling points. Infrared spectra were taken using a Beckman IR-10 spectrometer and, unless otherwise specified, CCl_4 solutions. Ultraviolet spectra were taken with a Beckman DB-5 grating spectrometer, with 95% EtOH as the solvent. NMR spectra were taken on a Varian A-60 instrument, using CCl_4 or $CDCl_3$ solutions with Me_4Si and/or CH_2Cl_2 internal standards. Mass spectra were determined with an Atlas CH-5 magnetic sector instrument at 70 eV ionization potential. VPC analyses were carried out using 4 ft × 0.25 in. columns packed with 10% Apiezon L on 80–100 mesh firebrick (Hewlett-Packard 5750) and with SE-30 on 80–100 mesh firebrick (Varian Aerograph 1520). The Bu_2O and diglyme used in reductions were distilled from $LiAlH_4$ and stored over 4A molecular sieves. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.
(24) S. J. Daum, P. E. Shaw, and R. L. Clarke, *J. Org. Chem.*, **32** 1427 (1967).
(25) (a) J. H. Hunter and J. A. Hogg, *J. Am. Chem. Soc.*, **71**, 1922 (1949); (b) C. L. Hewett, *J. Chem. Soc.*, 50 (1936).
(26) W. E. Bachmann and D. G. Thomas, *J. Am. Chem. Soc.*, **64**, 94 (1942).
(27) A. L. Wilds and C. H. Shunk, *J. Am. Chem. Soc.*, **65**, 469 (1943); S. Swaminathan and M. S. Newman, *Tetrahedron*, **2**, 88 (1958).
(28) G. N. Walker, *J. Am. Chem. Soc.*, **80**, 645 (1958).
(29) H. W. Thompson and J. M. Gottlieb, unpublished results.
(30) A. J. Birch, H. Smith, and R. E. Thornton, *J. Chem. Soc.*, 1339 (1957).
(31) (a) F. Sondheimer and D. Rosenthal, *J. Am. Chem. Soc.*, **80**, 3995 (1958); R. J. Ball, B. Rao, and L. Weiler, *Can. J. Chem.*, **49**, 3135 (1971); (b) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Am. Chem. Soc.*, **89**, 1483 (1967); W. S. Johnson, *Acc. Chem. Res.*, **1**, 1 (1968); (c) H. W. Thompson, G. E. Linkowski, and J. M. Gottlieb, unpublished results. (d) F. E. Ziegler and J. A. Kloek, *Tetrahedron Lett.*, 315 (1974); J. W. Huffman and P. G. Harris., *J. Org. Chem.*, **42**, 2357 (1977).

Concerning the Nature of Dimethylvinylidenecarbene

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Received February 23, 1977

Dimethylvinylidenecarbene has been generated as the free species by use of the crown ether, 18-crown-6, and its relative olefin selectivity has been studied. These studies give evidence which indicates that the reactive species is the potassium ion associated carbenoid when the usual *t*-BuOK-induced reaction is used in the absence of 18-crown-6. Relative olefin selectivities of the species when generated from either phase-transfer catalysis or *t*-BuOH-complexed *t*-BuOK are also discussed.

Dimethylvinylidenecarbene (A) exhibits singlet and electrophilic characteristics in its reactions with olefins. This species is considered as a free carbene rather than a carbenoid because of its nearly identical olefin selectivity when generated from different precursors.[2] However, a carbene–anion pair has been suggested as the possible reactive species.[3]

Phase-transfer catalysts[4] and crown ethers[5] have proven advantageous for generating A in high yields as discerned from the yields of adducts with olefins. Since olefin selectivity studies have proven invaluable for describing the nature of carbenic species,[6] we have expanded our earlier studies on phase-transfer catalyzed and potassium *tert*-butoxide induced generation of A,[4a] and have included an investigation on the olefin selectivity of A generated in the presence of the crown ether, 18-crown-6.[5] The results of these studies are reported for the purpose of providing a better understanding of the nature of the dimethylvinylidenecarbene species.

Results and Discussion

Dimethylvinylidenecarbene (A) was generated from 1-bromo-3-methyl-1,2-butadiene (1)[7] under basic conditions

$$\underset{1}{(CH_3)_2C{=}C{=}CHBr} \longrightarrow \underset{A}{(CH_3)_2C{=}C{=}C:} \longrightarrow (CH_3)_2C{=}C{=}C\!\!\triangleleft\!\!\triangleright$$

in the presence of a large excess of cyclohexene and a second olefin. Analysis of the reaction mixtures by use of GLC and authentic samples for product identification furnished the product ratios from which relative reactivities were calculated. Identical runs were performed until at least three results within ±1% were obtained. Cross-checks were performed to ensure internal consistency; these results were within ±5% of the cyclohexene standard results. The results are reported in Table I.

Potassium ion is particularly well complexed by 18-crown-6 ether, thereby effecting ready solubility of *t*-BuOK in nonpolar solvents.[9,10,11] Moss and Pilkiewicz[12] elegantly showed that this extreme complexing ability allows the generation of free phenylhalocarbenes from benzal halides and *t*-BuOK in the presence of 1 equiv of 18-crown-6 ether; the carbenoid was formed in the absence of 18-crown-6 ether. Stang and Mangum[13] used this approach to show that isopropylidenecarbene ($(CH_3)_2C{=}C:$) generated from *t*-BuOK and 2-methylpropenyl triflate in the presence and absence of 18-crown-6 was the free carbene. The data in Table I show that large differences are observed in the *t*-BuOK-induced formation of A in the presence and absence of 18-crown-6 ether. Since previous studies have revealed independence of A from the leaving group,[2] we conclude that a potassium ion associated vinylidene carbene complex is the reactive species when elimination is effected from free *t*-BuOK alone.

The results obtained for both the phase-transfer catalyzed and *t*-BuOH/*t*-BuOK induced reactions seem surprisingly close to the results obtained for the 18-crown-6 ether data and suggest unexpected freeness for A in these systems. Phase-transfer catalytic generation of carbenes may involve complexed species;[14] alcohol mediated carbene reactions may involve carbene–ylide intermediates.[15] However, since these are comparisons between reactions conducted in protic media and reactions conducted under aprotic conditions, an accurate description of A for the protic systems may not obtain.

The yields of dimethylvinylidene adducts are reported in Table II. Previous reports from these laboratories and others[4] have shown that phase-transfer-catalyzed reactions generally give better product yields than does the use of *t*-BuOK. Recently, crown-ether-catalyzed reactions have been reported to give even better results than phase-transfer-catalyzed methods, and sensitive olefinic substrates could be used.[5] Our results show that 18-crown-6, when used in stoichiometric amounts, is not as effective as either the phase-transfer method or the catalytic crown ether method. Furthermore, this stoichiometric crown ether method is not economical and the reaction workup is difficult.

Experimental Section

General. Temperature readings are uncorrected. IR spectra were determined as neat samples on a Perkin-Elmer Model 337 spectrometer. NMR spectra were determined in deuteriochloroform solution with tetramethylsilane internal standard (δ 0.0) on a Varian T-60 spectrophotometer. Analytical GLC was performed on a Varian 1440 flame ionization gas chromatograph equipped with a 5 ft × 1/8 in. stainless steel column of 3% SE-30 on Chrom W (80/100 mesh).

Materials. Aldrich potassium *tert*-butoxide was sublimed immediately before use. Potassium *tert*-butoxide/*tert*-butyl alcohol complex was prepared according to Johnson[16] and the complex stoichiometry was determined by titration. Aliquat-336 (tricaprylylmethylammonium chloride) was obtained from General Mills, Kankakee, Ill.

1-Bromo-3-methyl-1,2-butadiene[7] and 18-crown-6[17] were prepared according to published procedures. All olefins were obtained from commercial sources and purified by distillation before use.

Relative Reactivity Procedures. Stock solutions containing cyclohexene (30 mmol), competing olefin (30 mmol), and 1-bromo-3-methyl-1,2-butadiene (3.0 mmol) were mixed and allowed to react under the following conditions: (a) 0–5 °C, 1 h, 18-crown-6 (3.0 mmol), sublimed *t*-BuOK (3.0 mmol); (b) same as (a) but without 18-crown-6; (c) same as (a) except *t*-BuOK/*t*-BuOH (3.0 mmol) was used; and (d) room temperature, 1 h, 1.5 mL of 50% NaOH (or KOH) solution, and 0.1 g of aliquat-336. The magnetically stirred solutions were analyzed directly by GLC. Peak areas were standardizd with authentic samples and relative olefin reactivities were determined by the Doering–Skell equation.[6]

Preparation of Authentic Adducts. (a) Sublimed *t*-BuOK. A 125-mL Erlenmeyer flask was charged with 20–30 mL of pure olefin and sublimed *t*-BuOK (3.3 g, 0.03 mol). The stirred mixture was cooled to 0–5 °, and 1-bromo-3-methyl-1,2-butadiene (1) (3.0 g, 0.02 mol) was added. After 1 h, water was added and the mixture was thoroughly extracted with ether. The residue from the dried and concentrated ether extract furnished the pure adduct on short-path distillation.

(b) *t*-BuOK/*t*-BuOH. The procedure used was the same as in (a) except that *t*-BuOK containing 1 equiv of *t*-BuOH (0.03 mol) was

Table I. Relative Reactivity of Dimethylvinylidenecarbene with Olefins under Various Conditions of Generation

Substrate	Registry no.	Relative reactivity[a]				
		t-BuOK/ 18-crown-6	NaOH(KOH)[b] Aliquat-336	*t*-BuOK/ *t*-BuOH	*t*-BuOK	*t*-BuOK[c]
2,3-Dimethyl-2-butene	563-79-1	16.9	19.3	14.7	7.4	15.8
2-Methyl-2-butene	513-35-9	7.6	6.6	5.5	4.3	4.9
Dihydropyran	110-87-2	1.1	2.1	1.5	2.7	
2-Methyl-1-buten-3-yne	78-80-8	3.1	1.9		2.0	
Cyclohexene	110-83-8	1.0	1.0	1.0	1.0	1.0
1-Hexene	592-41-6	0.1	0.2	0.2	0.3	0.2

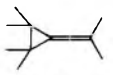
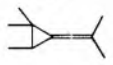
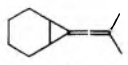
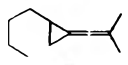
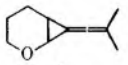
[a] Cyclohexene internal standard, 0–5 °C. [b] Room temperature. [c] A was generated at −10 °C from 1-chloro-3-methyl-1-butyne and *t*-BuOK, ref 8a.

Table II. Yields of Dimethylvinylidenecarbene–Olefin Adducts

Substrate	% yield[a]				
	t-BuOK/ 18-crown-6	NaOH/ Aliquat-336	*t*-BuOH/ *t*-BuOK	*t*-BuOK	*t*-BuOK[d]
2,3-Dimethyl-2-butene	47	68 (16)[c]	22	48	47
2-Methyl-2-butene	12 (37)[b]	82 (25)	15	46	36
Dihydropyran	29 (38)[b]	51 (5)	19	37	
2-Methyl-1-buten-3-yne	35	48 (24)	0	31	
Cyclohexene	25	60 (48)	14	18	26
1-Hexene	3.4	26 (25)	2	4	12

[a] Isolated yields. [b] Crown-ether-catalyzed method with KOH, ref 5. [c] Time (h) required for maximum yield. [d] Reference 8b.

Table III. Properties of Dimethylvinylidenecarbene–Olefin Adducts

Registry no.	Product	Bp, °C (torr)	IR, cm^{-1} (neat)	NMR, δ (CCl_3D)	Rel retention GLC
13303-30-5	 2	35–45 (0.30) mp 42	2965, 2880, 2000 (allene), 2700, 1040 (cyclopropyl), 820 (cyclopropyl)	1.75 (s, 6 H, CH_3) 1.20 (s, 12 H, CH_3)	0.43
14803-30-6	 3	35–45 (0.40)	2965, 2880, 2700, 2010 (allene), 1015 (cyclopropyl, 840 (cyclopropyl)	1.75 (m, 6 H, CH_3) 1.20 (m, 10 H, CH_3, CH)	0.35
4544-26-7	 6	55–60 (0.20)	2965, 2920, 2850, 2700, 2020 (allene), 1020 (cyclopropyl), 860 (cyclopropyl)	1.80 (d, 8 H, CH_3, CH) 1.30 (m, 8 H, CH_2)	1.0
53376-36-6	 7	45–55 (0.5)	2965, 2920, 2850, 2030 (allene), 1050 (cyclopropyl)	1.80 (d, 7 H, CH_3, CH) 1.45 (m, 8 H, CH_2) 1.00 (m, 3 H, CH_3)	0.94
59055-17-3	 4	55–65 (0.15)	2965, 2920, 2850, 2700, 2000 (allene), 1050 (cyclopropyl), 860 (cyclopropyl), 830, 810	4.10 (m, 1 H, CH) 3.60 (m, 2 H, CH_2) 2.00 (m, 3 H, CH_2, CH) 1.80 (d, 6 H, CH_3) 1.50 (m, 2 H, CH_2)	1.11
58668-76-1	 5	25–27 (0.15)	3280 (acetylene), 2965, 2920, 2850, 2700, 2100 (acetylene), 2010 (allene), 1060 (cyclopropyl), 880 (cyclopropyl)	2.00 (s, 1 H, CH) 1.80 (s, 6 H, CH_3) 1.40 (d, 2 H, CH_2) 1.30 (s, 3 H, CH_3)	0.40

used. This procedure was unsuccessful with the enyne, 2-methyl-1-buten-3-yne.

(c) 18-Crown-6, *t*-BuOK. The same procedure as that described in (a) was used except that 18-crown-6 (8.0 g, 0.03 mol) was mixed with the sublimed *t*-BuOK before 1 was added.

(d) Aliquat-336. A 125-mL Erlenmeyer flask was charged with olefin (20–30 mL), aliquat-336 (1 g), and 50% sodium hydroxide solution (7 mL). The reaction mixture was stirred (23–27 °C) and analyzed periodically by GLC (tetralin internal standard) for maximum yield. The reaction was worked up according to (a).

All reactions except (d) were performed under a dry nitrogen atmosphere. Adduct yields are reported in Table II. Physical and spectral data are reported in Table III. The adducts 1,1,2,2-tetramethylisobutylidenecyclopropane (2),[8] 1,1,2-trimethylisobutylidenecyclopropane (3),[8] 2-oxa-7-isobutylidenebicyclo[4.1.0]heptane (4),[5] 2-ethynyl-2-methylisobutylidenecyclopropane (5),[18] 7-isobutylidenebicyclo[4.1.0]heptane (6),[8] and 2-*n*-butylisobutylidenecyclopropane (7)[8] are all known.

Acknowledgments. We thank the Office of Research and Projects, Southern Illinois University, for supporting this work. We are grateful to Drs. R. A. Moss and P. J. Stang for their valuable comments and suggestions.

Registry No.—A, 4209-13-6; **1**, 6214-32-0.

References and Notes

(1) Taken in part from the M.S. thesis of D.J.S., Southern Illinois University, 1976.
(2) For a complete review see: H. D. Hartzler, "Carbene Chemistry", Vol. II, R. Moss and M. Jones, Jr., Eds., Wiley, New York, N.Y., 1975, pp 43–100.
(3) W. J. le Noble, Y. Tatsukami, and H. F. Morris, *J. Am. Chem. Soc.*, **92**, 5681 (1970).
(4) (a) T. B. Patrick, *Tetrahedron Lett.* 1407 (1974); (b) S. Julia, D. Michelot, and G. Linstrumelle, *C. R. Acad. Sci., Ser. C.*, **278**, 1523 (1974); (c) T. Sasaki, S. Eguchi, and T. Ogawa, *J. Org. Chem.*, **39**, 1927 (1974).
(5) T. Saski, S. Eguchi, M. Ohno, and F. Nakata, *J. Org. Chem.*, **41**, 2408 (1976).
(6) Reviewed by R. A. Moss, "Carbene Chemistry", Vol. I, R. Moss and M. Jones, Jr., Ed., Wiley, New York, N.Y., 1973, pp 153–304.
(7) S. R. Landor, A. N. Patel, P. F. Whiter, and P. M. Gravis, *J. Chem. Soc. C*, 1223 (1966).
(8) (a) H. D. Hartzler, *J. Org. Chem.*, **29**, 1311 (1964); (b) *J. Am. Chem. Soc.*, **83**, 4997 (1961).
(9) C. J. Pedersen, *J. Am. Chem. Soc.*, **89**, 7017 (1967); **92**, 386, 391 (1970).
(10) R. N. Greene, *Tetrahedron Lett.*, 1793 (1972); M. Shporer and A. Lutz, *J. Am. Chem. Soc.*, **97**, 665 (1975).
(11) R. A. Bartsch and K. E. Wiegers, *Tetrahedron Lett.*, 3891 (1972); M. J. Maskornick, *ibid.*, 1797 (1972); R. A. Bartsch, G. M. Pruss, R. L. Buswell, and R. A. Bushaw, *ibid.*, 2621 (1972); J. N. Roitman and D. J. Cram, *J. Am. Chem. Soc.*, **93**, 2231 (1971).
(12) R. A. Moss and F. G. Pilkiewicz, *J. Am. Chem. Soc.*, **96**, 5632 (1974).
(13) P. J. Stang and M. G. Mangum, *J. Am. Chem. Soc.*, **97**, 6478 (1975).
(14) V. Gani, C. Lapinte, and P. Viout, *Tetrahedron Lett.*, 4435 (1973); K. Martinek, A. V. Levashov, and I. V. Berezin, *ibid.*, 1275 (1975).
(15) W. Kirmse, "Carbene Chemistry", 2nd ed, Academic Press, New York, N.Y., 1971, p 423.
(16) W. S. Johnson and G. H. Daub, *Org. React.*, **6**, 1 (1951).
(17) G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, and F. D. Cook, *J. Org. Chem.*, **39**, 2445 (1974).
(18) D. J. Pasto, J. K. Borchardt, T. P. Fehlner, H. F. Baney, and M. E. Schwartz, *J. Am. Chem. Soc.*, **98**, 526 (1976).

Hydrogen Migration in 2-Carbena-6,6-dimethylnorbornane[1]

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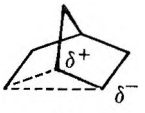
Received March 15, 1977

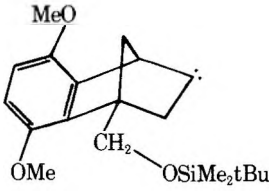
A study of the dry salt pyrolysis and the photolysis of the lithium salts of the tosylhydrazone of 6,6-dimethylnorbornan-2-one, *exo*-3-deuterio-6,6-dimethylnorbornan-2-one, and *endo*-3-deuterio-6,6-dimethylnorbornan-2-one revealed a preference for exo-C-3 → exo-C-2 over endo-C-3 → endo-C-2 hydride migration of approximately 20:1. This stereoselectivity is interpreted in terms of torsional interactions in the hydride migration transition state of a classical singlet carbene.

Although studies of the chemistry of the 2-norbornyl carbonium ion have absorbed the attention of many chemists over the past 25-year period,[3] and substantial effort has been expended in investigations of the nature of the related radical intermediate,[4] much less is known concerning the analogous carbanion[5] and carbene intermediates.[6] A consideration of this history suggests that characterization of 2-carbenanorbornane might be of considerable interest, since, in the singlet state, delocalization involving the empty p orbital at C-2 and the C-1–C-6 σ bond is possible (**1**).



1

Since most alicyclic carbene intermediates react by way of intramolecular rather than intermolecular pathways,[7] characterization of a 2-carbenanorbornane intermediate would appear to require the analysis of an insertion or hydrogen migration reaction. The nature of the 2-norbornyl carbonium ion has been revealed to some degree through studies of the stereospecificity of 3,2-hydride shifts. Investigations by Collins[8] and Berson[9] have shown that exo-C-3 to exo-C-2 hydride migration is preferred over endo-C-3 to endo-C-2 migration ($k_{\text{exo-exo}}:k_{\text{endo-endo}} > 100$). Since 1,2 hydrogen shifts are common intramolecular reaction pathways for bivalent carbon intermediates,[7] it appeared to us that a study of the stereochemistry of the C-3–C-2 hydride shift in 2-carbenanorbornane would be an excellent approach to an understanding of the chemistry of this intermediate. Unfortunately, 2-carbenanorbornane reacts predominantly via C-6 insertion with C-3–C-2 hydrogen migration as a barely detectable component of the reaction (nortricyclene–norbornene = 99.5:0.5).[6a] This difficulty was circumvented in a recent study by Kyba and Hudson,[10] who studied the benzo-2-carbenanorborene intermediate **2**, whereas Nickon and co-workers[11] have investigated 2-carbenanorbornane species **3**, which possesses a built-in bias favoring exo-C-3 hydrogen migration, since the additional bridge twists the exo-C-3 hydrogen into coplanarity with the empty p orbital of the adjacent singlet carbene center. Our approach is to consider 2-carbena-6,6-dimethylnorbornane (**12**), since much of the simplicity and symmetry of the parent system is preserved and γ C–H insertion is blocked, C–C insertion being a rarely observed process.[12]



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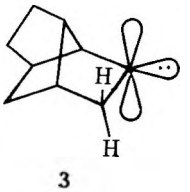

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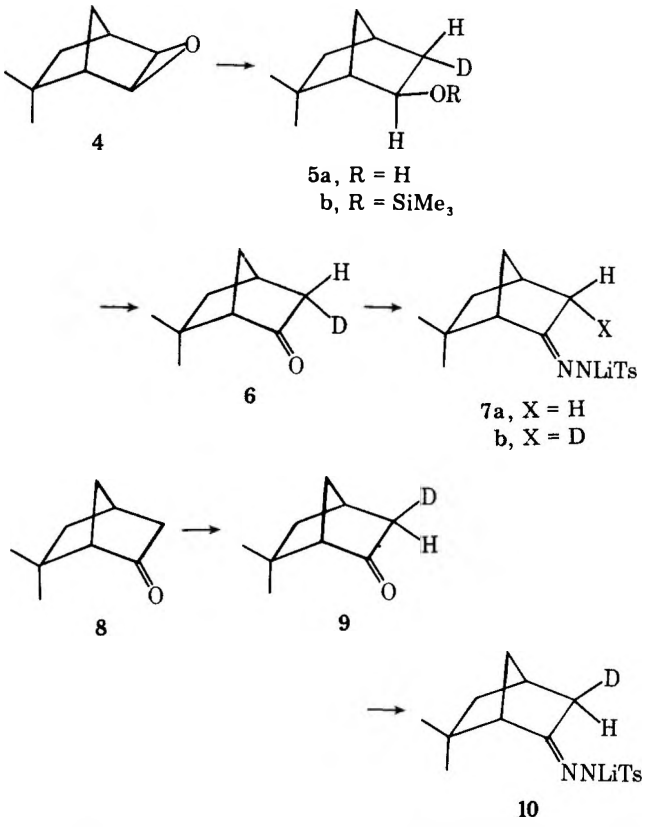
The required *endo*- and *exo*-deuterated tosylhydrazone lithium salts (**7b** and **10**) were prepared starting with 5,5-dimethylnorbornene epoxide (**4**)[13] and 6,6-dimethylnorcamphor (**8**).[13] Epoxide **4** with lithium aluminum deuteride treatment followed by chromic acid oxidation produces *endo*-3-deuterio-**6**. Treatment of **6** with $TsNHNH_2/H^+$ yields tosylhydrazone, which is converted to lithium salt with an equivalent of methyllithium. Ketone **8** was converted to *exo*-deuteriotosylhydrazone salt by treatment with CH_3ONa/CH_3OD, conversion to tosylhydrazone and subsequently to lithium salt **10** as in the endo case.

Table I. Results of Decompositions of Tosylhydrazone Salts 10 and 7b

Run	Salt	Type	Mass spectra of 11			NMR integration of 4	
			d_0	d_1	d_2	C-2	C-3
1	10	Pyr.[a]	17.9 ± 0.9[c]	78.3 ± 2.1	3.8 ± 1.5	0.938 ± 0.097	0.222 ± 0.090
2	10	Pyr.	9.4 ± 0.3	82.2 ± 1.1	8.4 ± 0.7	0.844 ± 0.028	0.149 ± 0.060
3	7b	Pyr.	3.4 ± 0.4	96.6 ± 0.4	0.0	0.097 ± 0.011	0.937 ± 0.077
4	10	Phot.[b]	43.4 ± 0.5	56.6 ± 0.5	<0.5	0.979 ± 0.071	0.456 ± 0.046
5	7b	Phot.	5.2 ± 0.2	94.8 ± 0.2	0.0	0.104 ± 0.030	0.947 ± 0.039

[a] Dry salt pyrolysis. [b] Photolysis in THF. [c] One standard deviation.



Analysis of the stereochemistry of hydride migration in the labeled 2-carbena-6,6-dimethylnorbornane species generated from tosylhydrazones 7b and 10 will not be hindered by the presence of undeuterated tosylhydrazone (corrected for in the NMR analysis) nor by dideuterated tosylhydrazone (undetected in the NMR analysis). Only epimerization in the preparation of 7b and 10 would present an analytical problem. A complication of this nature was tested for by conversion of 5a to the trimethylsilyl derivative 5b (97.8 ± 0.1% d_1) and then transforming 5a → 6 → 7b. Lithium salt 7b was reconverted to tosylhydrazone (HOAc) and then to 6 (97.8 ± 0.1% d_1), using the NBS treatment[14] previously determined not to affect C_α.[15] Since epimerization would presumably occur through enolate formation and since deuterated enolate would re-form 6 much more rapidly than epimer 9, the rate of enolate formation would be considerably greater than the rate of epimerization. Allowing for an isotope effect of perhaps 4–7 for exo hydrogen abstraction, epimerization that occurs should be accompanied by deuterium loss.[51] Since no deuterium loss occurs, there is no epimerization. In the case of *exo*-3-deuterio-9, *exo*-3-deuterium loss should predominate over *endo*-3-hydrogen abstraction[51,m,n] and, as a consequence, any epimerization which might occur should be accompanied by a large amount of deuterium loss. Ketone 9 was analyzed by NMR, with the aid of an Eu(fod)$_3$ chemical shift study, before conversion to tosylhydrazone (7.0% d_0) and after reconversion to ketone (NBS) from tosylhydrazone (6.0% d_0). A similar experiment which included lithium salt 10 in the cycle revealed no deuterium loss (less than 2%). Even though the preparation of the desired carbene precursors 7 and 10 appears to be free of complications, we took the additional precaution of preparing the tosylhydrazone of ketone 9 using deuterated tosylhydrazine and solvent.

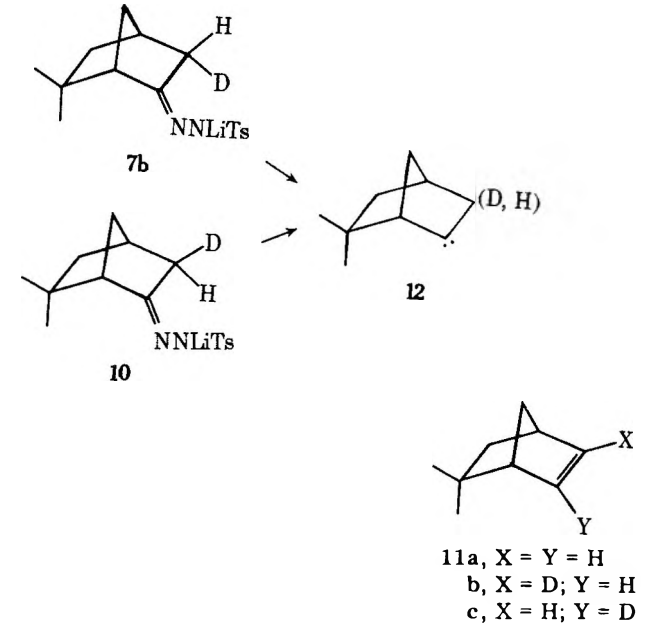


Table II. Product Composition in the Decomposition of Tosylhydrazone Salts 7b and 10

Tosylhydrazone	Type	11b	11c
10	Dry salt	4.6 ± 1.2%[a]	95.4 ± 2.0%
10	Dry salt	5.8 ± 1.2	94.2 ± 2.0
7b	Dry salt	93.5 ± 1.6	6.5 ± 1.2
10	Photolysis	3.9 ± 1.4	96.1 ± 2.7
7b	Photolysis	94.5 ± 1.3	5.5 ± 0.4

[a] Standard deviation.

Carbene formation was effected by either thermal (dry salt, 160–180 °C at 0.1 Torr) or photochemical (450-W high-pressure lamp, THF, 25 °C) decomposition of tosylhydrazone 7a. The 3,2-hydride shift product, 5,5-dimethylnorbornene (11a) was formed as the sole volatile product in 75% (thermal) and 50% (photochemical) yields. When the deuterated tosylhydrazones were decomposed, all the deuterium was found to reside in the olefinic positions in the product alkene. Since the olefinic protons are not differentiated by NMR at 100 Hz, 5,5-dimethylnorbornene was converted to the exo epoxide by treatment with peracetic acid. The deuterium distribution in 11 was then easily determined, since the corresponding epoxide protons have different chemical shifts (C-2, τ 7.04; C-3, 6.90). The NMR data along with low voltage mass spectral analyses of product 5,5-dimethylnorbornene are given in Table I. These data were then used to calculate product composition in terms of monodeuterated alkenes 11b and 11c (Table II).

The results of Table II show that the stereoselectivity of hydride migration in both the thermal and photolytic decompositions is about 95:5 exo/endo. Thus, instead of the greater than 100:1 exo/endo selectivity found in the norbornyl cation, the carbene selectivity is approximately 20:1, which is in rather close agreement with the ratio (13) observed with **2**[10] and contrasts with the exo/endo migration ratio of 138 observed for **3**.[11]

The product formation observed in this analysis is assumed to be that due to a singlet state carbene intermediate, since evidence has been presented which suggests that triplet carbenes do not undergo hydrogen migration.[16] Some experimental support for this view was obtained by irradiating tosylhydrazone **7a** in the presence of benzophenone sensitizer (Pyrex filter); nitrogen was evolved (ca. 1 equiv), but the yield of 5,5-dimethylnorbornene dropped dramatically to less than 5%. If one assumes a single product determining intermediate, the observation of significant endo hydride migration argues against delocalization of the C-1–C-6 σ bond, for this would require a front side displacement of C-2 in the hydride migration transition state. A significant advantage of an analysis of hydrogen migration in 2-carbena-6,6-dimethylnorbornane (**12**) relative to carbene **3** is the local symmetry of the exo and endo C-3–H bonds with respect to the empty p orbital at C-2. As a consequence, there should be no preference for either exo or endo hydrogen migration based upon orbital overlap considerations.[17] The intramolecular relationships should, in fact, be closely similar to a classical 2-norbornyl cation, where torsional effects have been estimated to favor exo over endo C-3–C-2 hydride migration by a maximum of 6 kcal/mol.[18] One would expect considerably less difference than this maximum for the transition states for the 2-carbenanorbornane intermediate under consideration, however, since the isotope effects, $k_H/k_D = 0.90 \pm 0.18$ for thermolysis and $k_H/k_D = 0.84 \pm 0.18$ for photolysis,[19] found in the present instance and the small values previously observed for β C–H migration (k_H/k_D = 1.1–1.4) in diazoalkane decompositions[11,20,21] suggest that hydrogen bridging is not well developed in the migration step. Therefore, on the basis of the present evidence, we conclude that small differences in torsional interactions in the transition states for exo and endo hydride migration, rather than σ-bond delocalization, are responsible for the stereoselectivity observed for 2-carbene-6,6-dimethylnorbornane.

Experimental Section

Melting points were determined using a Büchi melting point apparatus and are uncorrected. All boiling points are also uncorrected. Infrared spectra were recorded on either a Beckman IR-9 infrared spectrophotometer or a Perkin-Elmer 621 infrared spectrophotometer. Proton NMR spectra were recorded on a Varian Associates A-60 or HA-100 NMR spectrometer. Mass spectra were run on an Atlas CH-7 or Finnigan 1015 S/L mass spectrometer. Elemental analyses were performed by Alfred Bernhardt, Microanalytisches Laboratorium, 5251 Elback Uber Engelskirchen, Fritz-pregl-strasse 14-26, West Germany. VPC analyses were carried out with an F and M Model 700 Chromatograph equipped with dual columns and thermal conductivity detectors. The following columns were used: (1) 10 ft × 0.25 in. aluminum containing 10% Carbowax 20M on Anakrom 70–80 ABS; (2) 8 ft × 0.25 in. aluminum containing 8% Carbowax 20M on Anakrom 70–80 ABS; (3) 8 ft × 0.25 in. aluminum 5% OV-17 on 60–80 Chromosorb G; (4) 9 ft × 0.25 in. aluminum containing 10% Carbowax 20M and 1% XF-1150 on Anakrom 70–80 ABS; (5) 18 ft × 0.125 in. stainless steel containing 10% UCW-98 on 80–100 Diatoport S. Products ratios and percentage yields calculated from chromatographic data are based on relative peak areas as measured by a Hewlett-Packard 3373B Integrator.

Preparation of 5,5-Dimethyl-2,3-*exo*-epoxynorbornene (4). The procedure of Donaldson[13] was used with only minor modifications. Sublimation of the resulting product (20 Torr, pot temperature 70 °C) yielded the title compound in 75% yield; NMR (CCl_4, 100 MHz) δ 3.10 (doublet of doublets, J = 3.5, 0.7 Hz, 1 H, C-3 proton), 2.96 (doublet of doublets, J = 3.5, 0.7 Hz, 1 H, C-2 proton), 2.34 (unresolved, 1 H, bridgehead C-1 proton), 1.90 (broadened singlet, 1 H, bridgehead C-4 proton), 1.34 (broadened doublet, J = 4 Hz, 1 H, exo-C-6 proton), 1.22 (broadened doublet, J = 4 Hz, 1 H, endo-C-6 proton), 1.15 to 0.80 (complex signals including two singlets for the two methyl groups on C-5 at δ 1.05 and 1.02, 8 H).

Preparation of 6,6-Dimethylnorbornan-2-ol. The procedure of Donaldson[13] was used. Purification by preparative VPC yielded NMR (CCl_4, 100 MHz): δ 4.07 (doublet, J = 6 Hz, 1 H, proton α to hydroxyl), 2.20 (multiplet, 1 H, proton on C-4), 1.68 (singlet, 1 H, C-1 bridgehead proton), 1.63 to 0.73 (complex series of absorptions including methyl singlets at δ 1.00 and 0.97, 12 H).

Preparation of *endo*-3-Deuterio-6,6-dimethylnorbornan-2-ol (5a). The reaction was run as described[13] except that 3 equivalents of lithium aluminum deuteride (99.5% *d*) was heated at reflux with **4** for 3 days. After workup, VPC analysis on column 1 showed the product to consist of a mixture of alcohol and epoxide in a ratio of 70:30.

Analysis of the extent of deuteration was carried out by treating alcohol **5a** (0.23 g, 0.0016 mol) with 1 mL of Me_2SO and 0.4 mL of Trisil (Pierce Chemical Co.). The mixture was shaken for 5–10 min and left undisturbed overnight. The organic layer was separated, and the Me_2SO layer was extracted once with hexane. The organics were combined and washed once with H_2O, then dried over $CaCl_2$. The trimethylsiloxynorbornane derivative was purified by preparative VPC (column 2). Low voltage mass spectrum showed $\%D_1$ as 97.8 ± 0.1%. There was no D_2.

Preparation of 6,6-Dimethylnorbornan-2-one (6). 6,6-Dimethylnorbornan-2-ol was oxidized by the procedure of Donaldson.[13] Distillation of the title ketone (bp 80–83 °C, 18 Torr; lit. bp 74–75 °C, 12 Torr) yielded 51.5% (calculated from epoxide **4**); NMR (CCl_4, 100 MHz): δ 2.75 (unresolved, 1 H, bridgehead proton at C-4), 2.02 (slightly, broadened singlet, C-1 bridgehead), 1.97–0.80 (complex absorptions including methyl singlets at δ 1.07 and 0.96, 12 H).

Oxidation of *endo*-3-Deuterio-*exo*-6,6-Dimethylnorbornan-2-ol. The crude mixture of **5a** and **4** was treated with chromic acid in acetone as described.[13] Distillation yielded **6**.

Deuteration of 6,6-Dimethylnorbornan-2-one. The title ketone (1.0 g) was dissolved in 25 mL of methanol-O-*d* (99% d_1) with a catalytic amount of sodium methoxide and stirred for 2 h at room temperature. After quenching with D_2O and dilution with water, the solution was extracted with pentane. The pentane was washed with water and brine and dried over sodium sulfate. After removal of most of the pentane by distillation, the ketone was used without further purification for the preparation of tosylhydrazone. Samples for spectral analysis were separated using VPC column 3. The extent of deuteration at the exo and endo C-3 position was determined by NMR aided by a lanthanide induced shift. Eu(fod)$_3$ was added until the difference between the exo, endo, and bridgehead positions became large enough to permit accurate determination of the relative areas. The bridgehead hydrogen (C-1) was used as the standard. When the bridgehead hydrogen was at δ 10.34, the exo-3 and endo-3 protons absorbed at δ 10.77 and 10.03, respectively.

Preparation of 6,6-Dimethyl-2-norbornanone *p*-Toluenesulfonylhydrazone. A mixture of 4.5 g (0.033 mol) of 6,6-dimethylnorbornan-2-one and 6.2 g (0.033 mol) of tosylhydrazine in 35 mL of 95% ethanol with 2 drops of concentrated hydrochloric acid was heated at reflux for 3 h. Several milliliters of water was added, and the solution was cooled to room temperature, then placed in a refrigerator, yielding 5.1 g (0.017 mol), 51%, mp 150–154 °C. Recrystallization from ethanol yielded mp 157.5–159 °C; IR (0.1 mm, $CHCl_3$): 3200 cm^{-1} (m, N–H stretching), 1662 (m, C=N stretching), 1598 (m, aromatic C=C stretching) and 1170 (s, SO_2–N stretching); NMR (100 MHz, $CDCl_3$): δ 7.89 (singlet, 1 H, N–H), δ 7.84 and 7.26 (each a doublet, 2 H each, aromatic protons), δ 2.38 (singlet, 3 H, aromatic methyl), δ 2.34 (multiplet, 2 H, C-1 and C-4 bridgehead protons), δ 2.2 to 1.2 (complex signals, 5 H), δ 0.96 (1 H, buried under methyl) δ 0.96 and 0.56 (singlets, 3 H each, methyls on C-6).

Anal. Calcd for $C_{16}H_{22}N_2O_2S$: C, 62.71; H, 7.24. Found: C, 62.70; H, 7.21.

Preparation of *endo*-3-Deuterio-6,6-dimethylnorbornan-2-one Tosylhydrazone. This preparation was carried out in a manner identical with that described above for the undeuterated tosylhydrazone. Recrystallization from methanol gave mp 156.5–158 °C.

Preparation of *exo*-3-Deuterio-6,6-dimethylnorbornan-2-one Tosylhydrazone. The exo-deuterated ketone (about 1 g, 0.08 mol) was placed in 10 mL of methanol-*O*-*d* (99% d_1) with 1.5 g (0.08 mol) of tosylhydrazine (previously recrystallized from methanol-*O*-*d*) and a drop of DCl in D_2O. The solution was heated at reflux for 3 h; D_2O was added, and the solution was allowed to cool to room temperature, then placed in a refrigerator. The crystalline product was recrystal-

lized from methanol-*O*-*d*-D_2O yielding purified tosylhydrazone with mp 156–158°.

Dry Salt Pyrolysis of the Lithium Salt of 6,6-Dimethylnorbornan-2-one Tosylhydrazone. A 25-mL flask was charged with 306 mg (1.00 mmol) of tosylhydrazone. To this was added 10 mL of anhydrous ether, and then 450 μL of 2.2 M methyllithium in ether (1.0 mmol) was added to the solution with swirling. When gas evolution ceased, the ether was evaporated by blowing dry nitrogen over the solution while swirling. When most of the ether had evaporated, the white lithium salt covered the inside of the flask. The salt was then warmed to 40 °C and any remaining volatile material was pumped off at 0.1 Torr. The dry salt was then placed in an oil bath maintained at 180 °C, pressure 0.1 Torr, and the volatile products were collected in a trap maintained at −78 °C. After 1 h the volatile material in the trap was washed out with pentane, and the resulting pentane solution was analyzed by VPC on columns 1, 4, and 5. Only one product was detectable by VPC, and it had IR, NMR, and VPC retention time identical with 5,5-dimethylnorbornene. The yield (internal VPC standard) was 75%.

Irradiation of the Lithium Salt of 6,6-Dimethylnorbornan-2-one Tosylhydrazone. In a 50-mL flask, 306 mg (1.00 mmol) of tosylhydrazone was dissolved in 25 mL of tetrahydrofuran (which had been freshly distilled from lithium aluminum hydride) and 95 mg of decane (for VPC internal standard). Methyllithium (460 μL of 2.2 M, 1.0 mmol) in ether was added with stirring at 0 °C. A small aliquot was withdrawn and set aside, and the rest was irradiated with a 450-W Hanovia high-pressure mercury lamp until the theoretical amount of nitrogen was evolved and evolution stopped. The solution was then diluted with 200 mL of water and extracted with 5 × 15 mL of pentane. The pentane extracts were combined, washed with 5 × 250 mL of water and 1 × 100 mL of brine and dried over anhydrous sodium sulfate. The solution was concentrated by distilling off most of the solvent through a Vigreux column. VPC analysis on column 5 showed there were two peaks other than the decane internal standard. The peak with the shorter retention time, formed in variable yield, had VPC retention time and infrared identical with that of toluene. The other peak had VPC retention time, IR, and NMR identical with 5,5-dimethylnorbornene. Internal VPC standard indicated the yield to be 50%. The aliquot set aside was worked up in an identical manner as the irradiated mixture, and VPC analysis indicated there was no (<0.1%) alkene formed by methyllithium elimination.[22]

Irradiation of the Lithium Salt of 6,6-Dimethylnorbornan-2-one Tosylhydrazone in the Presence of Benzophenone. To a solution of the lithium salt in tetrahydrofuran as described above was added 1.0 equivalent of reagent grade benzophenone. The solution was irradiated through a Pyrex filter until nitrogen evolution ceased (approximately 1 equiv). After workup similar to that described above, VPC analysis on column 5 gave a low yield (<5%) of 5,5-dimethylnorbornene as the only volatile product.

Decomposition of Deuteriated Tosylhydrazones. Deuterated tosylhydrazones were decomposed in exactly the same manner as described above for undeuterated tosylhydrazones.

Preparation of Deuterated 4 for NMR Analysis. Deuterated 5,5-dimethylnorbornene, formed from tosylhydrazone decompositions in runs 1–5, was collected by preparative VPC (usually ca. 20 mg), and placed in a small vial with 50 μL of chloroform, 250 μL of 40% peracetic acid, and 5 mg of anhydrous sodium acetate. After warming to 40 °C for 5 min, the solution was diluted with 2 mL of water, and 250 μL of 40% sodium hydroxide was added with cooling. The solution was then extracted 3 times with 200 μL of pentane. The pentane extracts were washed with 500 μL of water and 200 μL of brine and dried over anhydrous sodium sulfate. Epoxide 4 was then collected by preparative VPC and subjected to NMR analysis.

NMR Analysis of Deuterated 4. Epoxide **4**, generated as described above from the deuterated alkene **11a** produced in runs 1–5, was subjected to NMR analysis in CCl_4 at 100 MHz. Integration of the absorptions at δ 3.10 and 2.96 due to the protons at C-3 and C-2 was compared with the integration of the signals at δ 2.34 and 1.90 due to the C-1 and C-4 bridgehead protons. In all cases, the deuterium content was found to be, within experimental error, the same as the deuterium content determined by mass spectral analysis. The ratio of the areas under the peaks at δ 3.10 and 2.96 yielded, after correcting for the amount of undeuterated alkene (available from mass spectral analysis), the ratio of products **11b** and **11c**. The integrals are given in Table I and the calculated ratios of products are given in Table II.

Mass Spectral Analysis of Deuterated 11a. Deuterated 5,5-dimethylnorbornene from runs 1–5 was collected by preparative VPC and subjected to mass spectral analysis at low ionizing potentials. At 14 eV the parent − 1 ion had been reduced to <0.5%. The peak heights, after correcting for the natural abundance of C-13, yielded the amounts of d_0, d_1, and d_2. These values are presented in Table I.

Registry No.—**4**, 63089-27-0; **5a**, 63089-28-1; **6**, 63089-29-2; **7a**, 63089-30-5; **7b**, 63089-31-6; **9**, 63089-32-7; **10**, 63089-33-8; **11b**, 63089-34-9; **11c**, 63089-35-0; 6,6-dimethylnorbornan-2-ol, 63122-47-4; 6,6-dimethyl-2-norbornone tosylhydrazone, 58728-89-5; *endo*-3-deuterio-6,6-dimethylnorbornan-2-one tosylhydrazone, 63089-36-1; *exo*-3-deuterio-6,6-dimethylnorbornan-2-one tosylhydrazone, 63089-37-2; 5,5-dimethylnorbornene, 497-28-9.

References and Notes

(1) (a) We express our appreciation for partial support of this work by a grant from the National Science Foundation. (b) Presented in part at the 27th Annual Northwest Regional Meeting of the American Chemical Society, Corvallis, Oregon, Paper No. 152, June 16, 1972.

(2) Postdoctoral research participant in the RPCT program supported by the National Science Foundation, Summer 1971.

(3) J. A. Berson, "Molecular Rearrangements", P. de Mayo, Ed., Interscience, New York, N.Y., 1963, Part I, Chapter 2; G. D. Sargent, *Q. Rev., Chem. Soc.*, **20**, 301 (1966); G. E. Gream, *Rev. Pure Appl. Chem.*, **16**, 25 (1966); H. C. Brown, *Chem. Brit.*, **2**, 199 (1966); H. C. Brown, *Chem. Eng. News*, **45**, (7), 87 (1967); T. W. Bentley, *Annu. Rep. Prog. Chem.*, **71**, 119 (1974), and earlier reviews: G. D. Sargent, "Carbonium Ions", G. Olah and P. V. R. Schleyer, Ed., Vol. III, Chapter 24, Wiley, New York, N.Y., 1972; H. C. Brown, *Acc. Chem. Res.*, **6**, 377 (1973); H. C. Brown, *Tetrahedron*, **32**, 179 (1976); G. A. Olah, *Acc. Chem. Res.*, **9**, 41 (1976).

(4) D. I. Davies and S. J. Cristol, *Adv. Free-Radical Chem.*, **1**, 155 (1965); P. D. Bartlett, G. N. Fickes, F. C. Haupt, and R. Helgeson, *Acc. Chem. Res.*, **3**, 177 (1970).

(5) (a) A. Nickon and J. L. Lambert, *J. Am. Chem. Soc.*, **88**, 1905 (1966); (b) A. Nickon, J. L. Lambert, and J. E. Oliver, *ibid.*, **88**, 2787 (1966); (c) A. Nickon, J. L. Lambert, R. O. Williams, and N. H. Werstiuk, *ibid.*, **88**, 3354 (1966); (d) A. F. Thomas and B. Willhalm, *Tetrahedron Lett.*, 1309 (1965); (e) J. M. Jerkunica, S. Borčić, and D. E. Sunko, *ibid.*, 4465 (1965); (f) K. Humski, S. Borčić, and D. E. Sunko, *Croat. Chem. Acta*, **38**, 55 (1966); (g) A. F. Thomas, R. A. Schneider, and J. Meinwald, *J. Am. Chem. Soc.*, **89**, 68 (1967); (h) P. Barraclough and D. W. Young, *Tetrahedron Lett.*, 2293 (1970); (i) T. T. Tidwell, *J. Am. Chem. Soc.*, **92**, 1448 (1970); (j) S. P. Jindal, S. S. Sohoni, T. T. Tidwell, *Tetrahedron Lett.*, 779 (1971); (k) S. P. Jindal and T. T. Tidwell, *ibid.*, 783 (1971); (l) G. A. Abad, S. P. Jindal, and T. T. Tidwell, *J. Am. Chem. Soc.*, **95**, 6326 (1973); (m) S. Banerjee and N. H. Werstiuk, *Can. J. Chem.*, **53**, 1099 (1975); (n) S. Banerjee and N. H. Werstiuk, *ibid.*, **54**, 678 (1976).

(6) (a) P. K. Freeman, D. E. George, and V. N. M. Rao, *J. Org. Chem.*, **29**, 1682 (1964); (b) L. Friedman and H. Schechter, *J. Am. Chem. Soc.*, **83**, 3159 (1961); (c) H. Krieger, S. E. Masar, and H. Rnotsalainen, *Suom. Kemistil. B*, **39**, 237 (1966); (d) J. H. Hammons, E. K. Probasco, L. A. Sanders, and E. J. Whalen, *J. Org. Chem.*, **33**, 4493 (1968); (e) J. A. Berson and R. G. Bergman, *J. Am. Chem. Soc.*, **89**, 2569 (1967); (f) R. H. Shapiro, J. H. Duncan, and J. C. Clopton, *ibid.*, **89**, 1442 (1967); (g) J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959); (h) R. R. Sauers and R. J. Kiesel, *J. Am. Chem. Soc.*, **89**, 4695 (1967); (i) J. K. Crandall, *J. Org. Chem.*, **29**, 2830 (1964); (j) W. Reusch, M. W. DiCarlo, and L. Traynor, *ibid.*, **26**, 1171 (1961).

(7) W. Kirmse, "Carbene Chemistry", Academic Press, New York, N.Y., 1971, pp 236–250.

(8) C. J. Collins, Z. K. Cheema, R. G. Werth, and F. M. Benjamin, *J. Am. Chem. Soc.*, **86** 4913 (1964); B. M. Benjamin and C. J. Collins, *ibid.*, **88**, 1556 (1966).

(9) J. A. Berson, J. H. Hammonds, A. W. McRowe, R. G. Bergman, A. Remanick, and D. Huston, *J. Am. Chem. Soc.*, **89**, 2590 (1967).

(10) E. P. Kyba and C. W. Hudson, *J. Am. Chem. Soc.*, **98**, 5696 (1976).

(11) A. Nickon, F. Huang, R. Weglein, K. Matsuo, and H. Yogi, *J. Am. Chem. Soc.*, **96**, 5264 (1974).

(12) K. B. Wiberg, G. M. Lampman, R. P. Ciula, D. S. Connor, P. Schertler, and J. Lavanish, *Tetrahedron*, **21**, 2749 (1965).

(13) P. v. R. Schleyer, M. M. Donaldson, and W. E. Watts, *J. Am. Chem. Soc.*, **87**, 375 (1965); M. M. Donaldson, Ph.D. Thesis, Princeton University, 1960.

(14) G. Rosini, *J. Org. Chem.*, **39**, 3504 (1974).

(15) P. K. Freeman and J. R. Balyeat, *J. Org. Chem.*, **42**, 3205 (1977).

(16) M. B. Sohn and M. Jones, Jr., *J. Am. Chem. Soc.*, **94**, 8280 (1972); I. Moritani, Y. Yamanoto, and S-I. Murahashi, *Tetrahedron Lett.*, 5697 (1968); for closely related work on alkyl migration see M. Jones, Jr., and W. Ando, *J. Am. Chem. Soc.*, 2200 (1968).

(17) Differences in facility for intramolecular C–H insertion have been explained in terms of differences in distance between the carbene carbon and the center of the C–H bond on a pathway perpendicular to the C–H bond; C. D. Gutsche, G. L. Bachman, W. Udell, and S. Bäuerlein, *J. Am. Chem. Soc.*, **93**, 5172 (1971).

(18) P. v. R. Schleyer, *J. Am. Chem. Soc.*, **89**, 699 (1967).

(19) The k_H/k_D values were calculated making the assumption that the isotope effect is the same for exo and endo hydride migration.

(20) W. Kirmse, H. D. von Scholz, and H. Arold, *Justus Liebigs Ann. Chem.*, **711**, 22 (1968).

(21) The assumption[19] made in calculating k_H/k_D values makes it somewhat difficult to assess why our k_H/k_D values differ from that for carbene **2**. Apparently both hydrogen migration ratios and k_H/k_D values are sensitive to subtle steric changes. In fact the difference may lie in only one migratory pathway (exo or endo), the endo environment differing for species **2** and **12**.

(22) J. Meinwald and F. Uno, *J. Am. Chem. Soc.*, **90**, 800 (1968); R. H. Shapiro and M. J. Heath, *ibid.*, **89**, 5734 (1967).

Ruthenium(II) Catalyzed Rearrangement of Diallyl Ethers. A Synthesis of γ,δ-Unsaturated Aldehydes and Ketones

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Received April 4, 1977

Synthesis and selective tris(triphenylphosphine)ruthenium(II) dichloride catalyzed rearrangement of unsymmetrical diallyl ethers to γ,δ-unsaturated aldehydes and ketones are reported. Presumably ruthenium regiospecifically promotes olefin isomerization to allyl vinyl ethers which undergo Claisen rearrangement. Isomerization of monosubstituted olefins occurs more rapidly than isomerization of vicinally disubstituted olefins. Geminally disubstituted or trisubstituted olefins do not isomerize readily. Remarkably, an allyl ether rearranges six times more readily than an α-methylallyl ether.

The aliphatic Claisen rearrangement, first observed in enol allyl ethers in 1912,[1] was not recognized[2] as a generally useful and important reaction until recently.[3] The rearrangement was extended to simple allyl vinyl ethers 26-years later.[4] It has been studied mechanistically by a number of investigators.[5] The high stereoselectivity for the formation of (*E*)-di- and trisubstituted olefins upon Claisen rearrangement of vinyl ethers of secondary allylic alcohols has recently found many applications in organic synthesis.[6] This stereoselectivity extends to the creation of asymmetric centers in high optical yield.[7,8] The Claisen rearrangement is now recognized as an important general, stereoselective method for olefin synthesis. The above types of Claisen rearrangements as well as some more recent variants have found extensive application in the synthesis of natural products.[9]

The allyl vinyl ether substrates for Claisen synthesis of γ,δ-unsaturated aldehydes or ketones are generally prepared by acid-catalyzed decomposition of diallyl acetals[4,10] or transvinylation.[11,12] Schemes involving allyl ethers of halohydrins,[4,13] vinylation[14] of α-halo ethers, or Wittig olefination[15] have also been employed. Allyl enol ethers of acetoacetic esters[1] and zinc enolates of allyl or propargyl esters[16] are also useful. We now report that selective rearrangement of diallyl ethers catalyzed by tris(triphenylphosphine)ruthenium(II) dichloride is a valuable new route for the synthesis of γ,δ-unsaturated aldehydes and ketones. Preliminary rearrangement to allyl vinyl ethers followed by Claisen rearrangement presumably is involved.

Results

Preparation of Diallyl Ethers. Unsymmetrical diallyl ethers **2** are readily available in high yields by *O*-alkylation of allyl alcohols **1** with allyl halides (Table I).

Ruthenium Catalyzed Rearrangement of Diallyl Ethers. The diallyl ethers were heated at 200 °C in the presence of 0.1 mol % tris(triphenylphosphine)ruthenium dichloride in sealed Pyrex tubes for 1–4 h. Simple short-path distillation of the reaction product mixture gave good to excellent yields of γ,δ-unsaturated carbonyl compounds **3** which were often better than 90% pure according to GLC and ^{1}H NMR analysis. In principle, two different isomeric γ,δ-unsaturated carbonyl compounds could be produced from each unsymmetrical diallyl ether. Generally, however, the isomer shown in Table II was the only carbonyl product obtained.

2d → **3d**

2d'

The structures assigned to the products **3a–i** are supported by their ^{1}H NMR spectra (see below and Experimental Section). The rearrangement of **2d** to **3d** was accompanied by the formation of the ether **2d'** (13%) and methylallyl alcohol (10%). The ether **2d'** was identified by ^{1}H NMR and GLC comparison with an authentic sample prepared by *O*-alkylation of Δ^3-cyclopentenol with methallyl chloride.

3c **3e** **3f**

The ^{1}H NMR spectra of the product aldehydes **3c, 3e,** and **3f** suggested the presence of two diastereomers. Two doublets with equal coupling constants were observed in each case for the methyl group α to the carbonyl. The diastereomers of **3e** were separable by GLC.

2i → **3i** **3i'** (6:1)

Rearrangement of **2i** gave predominantly **3i.** The *E* configuration of the C–C π bond in **3i** is assumed due to the known stereoselectivity of such Claisen rearrangements.[6] The aldehyde was readily separated quantitatively from the reaction product mixture as the water-soluble sodium bisulfite addition product. The water insoluble product mixture yielded the ketone **3i'** (9%) and starting material **2i** (30%). The ketone **3i'** was identified by ^{1}H NMR and GLC comparison with an authentic sample.[20] The aldehyde **3i** was recovered from the aqueous phase after treatment with saturated sodium bicarbonate. Ozonolysis of the major product **3i** followed by oxidation gave methylsuccinic acid (**4i**) exclusively.

3i → (1. O_3; 2. HCOOH, H_2O_2) → **4i**

Table I. Synthesis of Unsymmetrical Diallyl Ethers

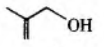
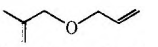
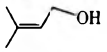
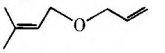
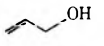
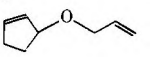
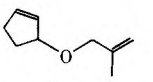
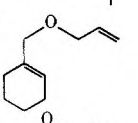
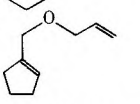
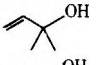
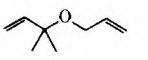
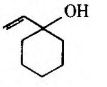
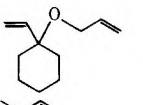
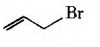
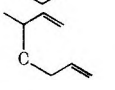
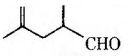
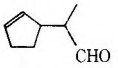
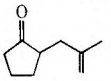
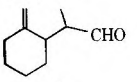
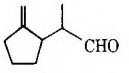
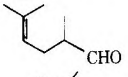
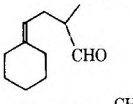
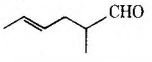
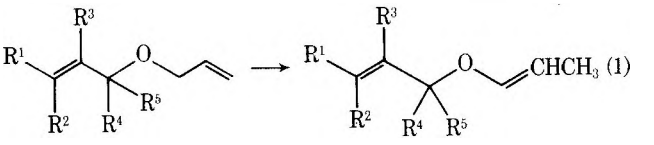
Alcohol	Registry no.	Halide	Registry no.	Ether	Yield, %	Registry no.
1a 	513-42-8		106-95-6	2a 	88	14289-96-4
1b 	556-82-1			2b 	91	63163-49-5
1c 	107-18-6		96-40-2	2c 	80	63163-50-8
1d 	3212-60-0		563-47-3	2d 	89	63163-51-9
1e 	4845-04-9			2e 	79	63163-52-0
1f 	1120-80-5			2f 	81	63163-53-1
1g 	115-18-4			2g 	92	63163-54-2
1h 	1940-19-8			2h 	86	63163-55-3
1i 	598-32-3			2i 	85	37027-64-8

Table II. Ruthenium Catalyzed Rearrangement of Unsymmetrical Diallyl Ethers

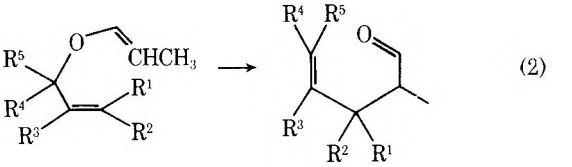
Diallyl ether	Product	Reaction time, h	Isolated yield, %	GC purity, %
2a	3a 	1	92	89[a]
2b	3b 	1	90	99
2c	3c 	1.5	71	100
2d	3d 	3	56	70[b]
2e	3e 	1.5		95[c]
2f	3f 	1.5	84	93
2g	3g 	4	80	92
2h	3h 	2	78	83[d]
2i	3i 	4	55[e]	100

[a] Distilled reaction product mixture contained 8% starting ether 2a. [b] Also isolated: Δ^3-cyclopentenyl methylallyl ether and methylallyl alcohol, see below. [c] Diastereomers separable on 10 ft × ¼ in. 10% Carbowax 20M on 60/80 Chromosorb W. [d] Distilled reaction product mixture contained 7% starting ether 2h. [e] Isolation of 3i was affected by sodium bisulfite extraction—see Experimental Section.

Transition metal catalyzed conversion of monoallyl ethers into vinyl ethers is known.[17] Platinum hydrides promote *cleavage* of diallyl ethers to give aldehydes and π-allylplatinum(II) complexes rather than rearrangement.[18] We now find that tris(triphenylphosphine)ruthenium(II) dichloride catalyzes *rearrangement* of diallyl ethers to give γ,δ-unsaturated carbonyl compounds. These ruthenium catalyzed rearrangements of diallyl ethers almost certainly involve generation (eq 1) and subsequent Claisen rearrangement (eq 2) of allyl vinyl ethers.

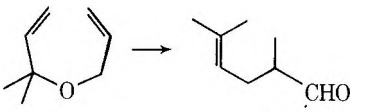


(1)

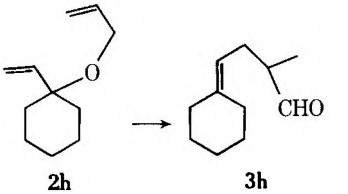


(2)

The rearrangements listed in Table II exhibit two noteworthy features. Allylic rearrangement is *highly regiospecific*. Secondly, the products 3 of the Claisen rearrangement do not undergo further ruthenium catalyzed allylic rearrangement. These features are readily understandable if it is recognized that ruthenium catalysis of allylic hydrogen migration occurs less readily for substituted olefins. The ease of olefin isomerization shows a strong sensitivity to structural factors and rates of rearrangement vary greatly with olefin structure.[19]



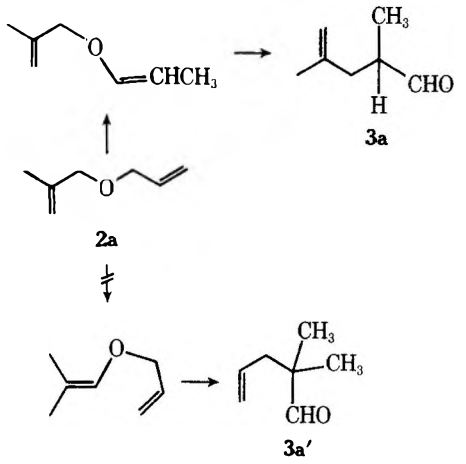
2g 3g



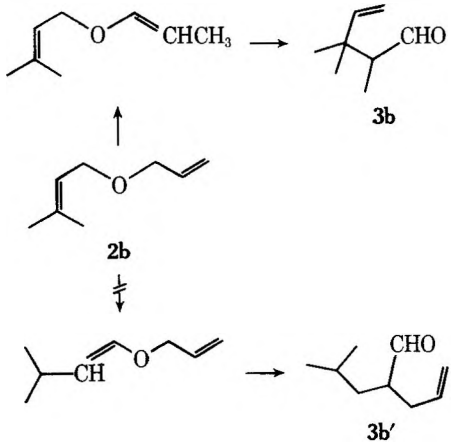
2h 3h

Of course, for the ethers **2g** and **2h,** migration of an allylic hydrogen can occur from only one position. Thus, Claisen rearrangement of the intermediate allyl vinyl ether results in a single product **3g** or **3h.**

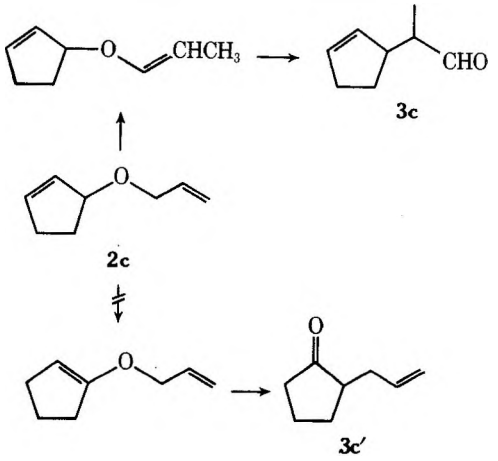
The influence of olefin substitution on the relative ease of allylic hydrogen migration may be deduced from a consider-



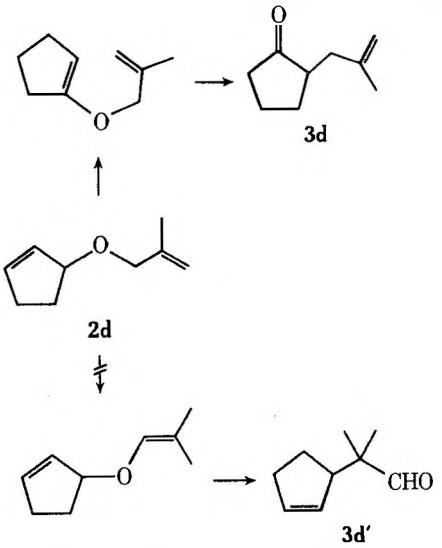
ation of the rearrangements observed for **2a–f** and **2i.** The ether **2a** contains a geminally disubstituted olefin and a monosubstituted olefin. Only a single Claisen product is observed. Only the monosubstituted π bond undergoes ruthenium catalyzed allylic rearrangement. An ^1H NMR spectrum of the crude reaction product mixture shows the complete disappearance of the CH vinylic methine proton of **2a** and the absence of a six-hydrogen singlet which is expected for the *gem*-dimethyl substituents α to the carbonyl in **3a'.**



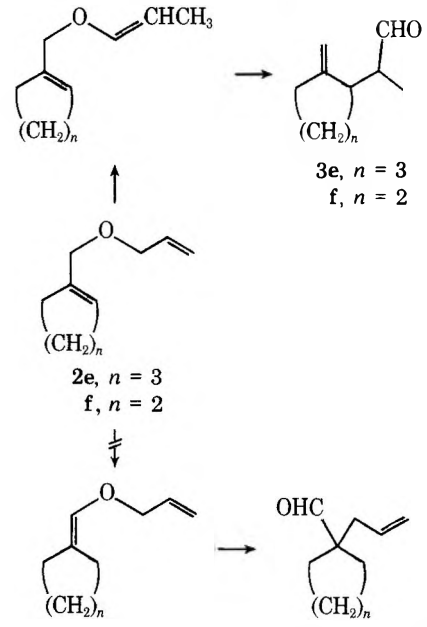
Ether **2b** contains a trisubstituted olefin and a monosubstituted olefin. Again, only the monosubstituted π bond undergoes ruthenium catalyzed allylic rearrangement, and only a single Claisen product is observed. Inspection of the ^1H NMR spectrum of the crude reaction mixture shows a six-proton singlet which is accounted for by quaternary *gem*-dimethyl substituents in **3b.** The alternative product **3b'** would show a six-hydrogen doublet due to its *gem*-dimethyl substituents. Such a doublet is not observed.



In the case of **2c** the monosubstituted olefin isomerizes in preference to the vicinally disubstituted olefin. An ^1H NMR spectrum shows a one-proton doublet assignable to the aldehydic hydrogen corresponding to the structure **3c.** Also, a single downfield tertiary ring proton is observed, which is due to the allylic methine in **3c,** and two diastereomeric methyl doublets appear at δ 1.04 and 1.07 (J = 7 Hz). Interestingly in **2d,** in contrast with **2c,** only the vicinally disubstituted π bond migrates and therefore no aldehyde **3d'** is produced.

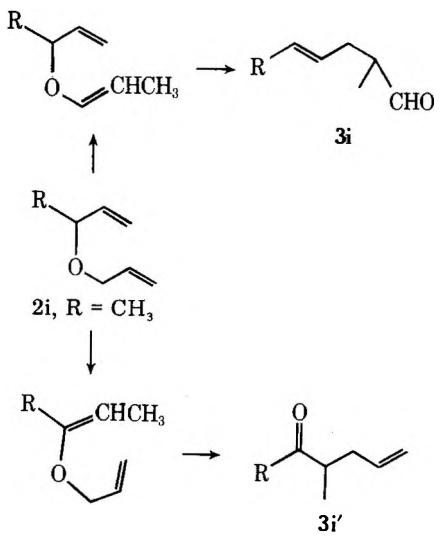


Not surprisingly, olefin isomerization followed by Claisen rearrangement in **2e** and **2f** results in a single rearrangement product. A ^1H NMR spectrum shows two diastereomeric al-



dehydic proton doublets for both the crude and GC isolated products from **2e.** Also, as for **3c,** both **3e** and **3f** show diastereomeric methyl groups.

The most remarkable example of selectivity in ruthenium catalyzed rearrangement of diallyl ethers occurs in **2i.** The products **3i** and **3i'** are formed in the ratio of 6:1 where R = CH_3. This unexpected result suggests that even *allylically substituted monoolefins direct the specificity of ruthenium catalyzed allylic hydrogen isomerization.* This extraordinary



reaction should be general and highly regiospecific for any derivative of **2i** in which R has steric requirements equal to or greater than a methyl group.

Conclusion

Unsymmetrical diallyl ethers give γ,δ-unsaturated ketones or aldehydes upon heating in the presence of tris(triphenylphosphine)ruthenium dichloride. Presumed intermediate allyl vinyl ethers produced by an initial ruthenium catalyzed 1,3-hydrogen shift give the observed products by Claisen rearrangement. Rearrangement of unsymmetrical diallyl ethers is predictably regiospecific, since 1,3-hydrogen migration occurs readily only with mono and vicinally disubstituted olefins. Furthermore, the rates of rearrangement vary considerably with olefin substitution. Isomerization of monosubstituted olefins occurs more rapidly than isomerization of vicinally disubstituted olefins. Even a mere allylic methyl substituent markedly retards 1,3-hydrogen migration.

Experimental Section

General. All vessels were flame dried and reactions, whenever possible, were carried out under an atmosphere of nitrogen. Solvents were freshly distilled. All GC work was performed with a Varian Model 90-P using a 6 ft SE 30 15% on Chromosorb W 60/80; NMR spectra recorded with a Varian A60A or HA-100 with Fourier transform using CCl_4 and 1% Me_4Si as solvent. All sealed tube reactions were done behind a safety shield.

Ether Synthesis A. Allyl Methylcyclopentenyl Ether (2f). NaH (2.0 g, 46 mmol, 57% oil dispersion) in a 100-mL three-necked flask equipped with reflux condenser, mechanical stirrer, and addition funnel was washed with pentane (two 10-mL portions). THF (75 mL) was then added followed by the portionwise addition of cyclopentene-1-carbinol (3.0 g, 30 mmol), and the resulting mixture was stirred under reflux for 2 h. Then while the mixture was still warm, HMPA (15 mL) was added followed by allyl bromide (5.5 g, 45 mmol) at such a rate as to maintain a gentle reflux. Upon addition, the mixture was again boiled under reflux for 2 h. The reaction mixture was allowed to cool to room temperature, quenched with 10% aqueous HCl (25 mL), and extracted with pentane (two 50-mL portions). The combined organic fractions were washed with 10% aqueous HCl, saturated $NaHCO_3$, H_2O, and saturated NaCl, and dried ($MgSO_4$). Solvent removal with rotary evaporation and distillation of the crude product yielded the title ether, 3.4 g (81%), bp 62 °C (10 mm).

Method B. Allyl Δ²-Cyclopentenyl Ether (2c). Δ²-Cyclopentenyl chloride (102 g, 1 mol) was added dropwise with vigorous mechanical stirring to a suspension of $NaHCO_3$ (170 g, 2 mol) in allyl alcohol (464 g, 8 mol) at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 15 h. Inorganic salts were removed by suction filtration and the organic solution was distilled. Excess allyl alcohol was recovered and then the product was obtained, 98 g (80%), bp 131–132 °C.

Yield Optimization for Claisen Rearrangement. Maximum yields for the ruthenium catalyzed Claisen rearrangements were determined as follows: six to ten half-filled sealed Pyrex tubes were prepared, each containing 150 μL of a solution obtained from 1.0–1.5 g of the starting ether and 0.1 mol % tris(triphenylphosphine)ruthenium dichloride. The catalyst was first dissolved in the neat ether by gentle heating and shaking. The sealed tubes were placed in a 200 °C oil bath. One tube was removed every 0.5 h and the contents were analyzed by ^1H NMR.

Preparative Claisen Rearrangements. In general the starting ether (5 g) and tris(triphenylphosphine)ruthenium dichloride (0.1 mol %) were vacuum sealed in a Pyrex tube (i.d. 1.3 cm, o.d. 1.6 × 25 cm). The tubes, when sealed, were never more than half filled. The mixtures were then heated in an oil bath at 200 °C for a predetermined time, cooled to room temperature, and carefully opened. The product mixtures were vacuum transferred to remove all traces of catalyst and carefully distilled.

Separation of 2-Methylhex-4-enal (3i). The crude reaction mixture (3.4 g) was vacuum transferred to remove catalyst and shaken with sodium bisulfite (6.4 g, 0.062 mol) in water (10 mL). After several minutes of agitation the aqueous layer was extracted with ether (two 2-mL portions). The combined organic fractions were dried ($MgSO_4$) and the solvent was removed by distillation, yielding a mixture of starting material (1.0 g) and 4-methylhex-1-en-5-one (0.3 g). To the aqueous layer was cautiously added saturated $NaHCO_3$ (vigorous) until CO_2 evolution ceased. The aldehydic product was then obtained (1.9 g, 55%) by continuous ether extraction (12 h) of the aqueous mixture and removal of the solvent by careful distillation.

2-Methylsuccinic Acid.[21] 2-Methylhex-4-enal (500 mg, 4.45 mmol) in methanol (15 mL) was ozonized at −70 °C until the solution appeared slightly blue. The methanol was then removed and 98% formic acid (6 mL) and 30% hydrogen peroxide (3 mL) were added and heat was cautiously applied until a vigorous reaction began. After the reaction subsided, the mixture was boiled under reflux for 30 min. After cooling, the volatile by-products were removed with rotary evaporation and then under high vacuum to yield the title compound (510 mg, 87%, mp 115 °C). Its NMR spectrum was compared with that of an authentic sample.[22]

Allyl 2-Methylallyl Ether (2a): bp 109 °C; NMR (CCl_4) δ 1.72 (3 H, s, CH_3), 3.75–4.00 (4 H, m, CH_2OCH_2), 4.7–6.2 (5 H, m, vinyl).[23]

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 74.86; H, 10.40.

Allyl 3,3-Dimethylallyl Ether (2b): bp 145 °C; NMR (CCl_4) δ 1.65 (3 H, s, CH_3), 1.75 (3 H, s, CH_3), 3.87 (4 H, m, CH_2OCH_2), 4.9–6.18 (4 H, m, vinyl).[24]

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.41; H, 11.30.

Allyl Δ²-Cyclopentyl Ether (2c): bp 131–132 °C; NMR (CCl_4) δ 1.48–2.73 (4 H, m, ring CH_2's), 3.91 (2 H, d, J = 5 Hz, CH_2), 4.53 (1 H, br d, J = 5 Hz, CH), 4.90–5.36 (2 H, m, vinyl CH_2), 5.63–6.25 (3 H, m, vinyl CH, ring CH=CH).[25]

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 76.93; H, 9.60.

Δ²-Cyclopentenyl 2-Methylallyl Ether (2d): bp 165–167 °C; NMR (CCl_4) δ 1.71 (3 H, s, CH_3), 1.50–2.58 (4 H, m, ring CH_2's), 3.81 (2 H, s, CH_2), 4.48 (1 H, br d, J = 5 Hz, CH), 4.84 (2 H, br d, J = 6 Hz, vinyl CH_2), 5.88 (2 H, m, ring CH=CH).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.96; H, 10.54.

Allyl 1-Cyclohexenylmethyl Ether (2e): bp 54 °C (8.9 mm); NMR (CCl_4) δ 1.40–2.16 (8 H, m, ring CH_2's), 3.68–3.92 (4 H, m, CH_2OCH_2), 4.94–6.18 (4 H, m, vinyl).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.91; H, 10.82.

Allyl 1-Cyclopentenylmethyl Ether (2f): bp 62 °C (10.0 mm); NMR (CCl_4) δ 1.41–2.50 (6 H, m, ring CH_2's), 3.8–4.0 (4 H, m, CH_2OCH_2), 4.9–6.2 (4 H, m, vinyl).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.83; H, 10.24.

Allyl 1,1-Dimethylallyl Ether (2g): bp 120 °C; NMR (CCl_4) δ 1.24 (6 H, s, $2CH_3$'s). 3.78 (2 H, dt, J = 5 and 1 Hz, CH_2), 4.87–5.33 (4 H, m, 2 vinyl CH_2's), 5.50–6.18 (2 H, m, 2 vinyl CH's).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.03; H, 11.14.

Allyl 1-Vinylcyclohexyl Ether (2h): bp 47 °C (1.8 mm); NMR (CCl_4) δ 1.0–2.0 (10 H, m, ring CH_2's), 3.72 (2 H, dt, J = 5 and 1.2 Hz, CH_2), 4.84–5.39 (4 H, m, 2 vinyl CH_2's), 5.46–6.11 (2 H, m, 2 vinyl CH's).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.77; H, 10.82.

Allyl 1-Methylallyl Ether (2i): bp 96 °C; NMR (CCl_4) δ 1.23 (3 H, d, J = 6.5 Hz, CH_3), 3.62–4.12 (3 H, m, CH_2CH), 4.94–5.43 (4 H, m, vinyl CH_2's), 5.47–6.27 (2 H, m, vinyl CH's).

Anal. Calcd for $C_7H_{12}O$: C, 74.98; H, 10.78. Found: C, 74.81; H, 10.30.

2,4-Dimethylpent-4-enal (3a): bp 128 °C; NMR (CCl_4) δ 1.07 (3 H, d, J = 6 Hz, CH_3), 1.73 (3 H, br s, CH_3), 1.76–2.60 (3 H, m, CH_2CH), 4.75 (2 H, m, vinyl CH_2), 9.56 (1 H, d, J = 1.8 Hz, CHO).

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 75.05; H, 11.05.

2,3,3-Trimethylpent-4-enal (3b): bp 140 °C; NMR (CCl_4) δ 0.99 (3 H, d, J = 7 Hz, CH_3), 1.09 (6 H, s, $2CH_3$), 2.17 (1 H, qd, J = 7 and 2 Hz, CH), 4.78–5.20 (2 H, m, vinyl CH_2), 5.59–6.14 (1 H, m, vinyl CH), 9.64 (1 H, d, J = 2.5 Hz, CHO).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C,76.09; H, 11.23.

2-(Δ^2-Cyclopentenyl)propanal (3c): bp 150–155 °C; NMR (CCl_4) δ 1.04 (1 H, d, J = 7 Hz, CH_3), 1.07 (2 H, d, J = 7 Hz, CH_3), 1.50–2.54 (5 H, m, ring CH_2's), 2.98 (1 H, br s, CH), 5.5–5.9 (2 H, m, CH=CH), 9.71 (1 H, d, J = 2 Hz, CHO).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.43; H, 9.81.

2-(2-Methylallyl)cyclopentanone (3d): bp 82–84 °C (10.0 mm); NMR (CCl_4) δ 1.26–2.68 (9 H, m, ring CH_2's, ring CH, CH_2), 1.73 (3 H, s, CH_3), 4.68 (2 H, s, vinyl CH_2).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.52; H, 10.25.

2-(2-Methylenecyclohexyl)propanal (3e): NMR (CCl_4) δ, two GLC separable diasteriomers. Isomer 1: 1.00 (3 H, d, J = 7 Hz, CH_3), 1.60 (8 H, br s, ring CH_2's), 2.15–2.69 (2 H, m, CH), 4.69 (2 H, d, J = 9 Hz, vinyl CH_2), 9.52 (1 H, d, J = 4 Hz, CHO). Isomer 2: 1.07 (3 H, d, J = 7 Hz, CH_3), 1.57 (8 H, br s, ring CH_2's), 1.71–2.77 (2 H, m, CH), 4.64 (2 H, d, J = 15 Hz, vinyl CH_2), 9.58 (1 H, d, J = 2 Hz, CHO).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.15; H, 10.59.

2-(2-Methylenecyclopentyl)propanal (3f): bp 65 °C (9.0 mm); NMR (CCl_4) δ 1.06 (1.5 H, d, J = 7 Hz, CH_3), 1.02 (1.5 H, d, J = 7 Hz, CH_3), 1.34–2.97 (8 H, m), 4.68–5.07 (2 H, m, vinyl CH_2), 9.65 (1 H, m, CHO).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.21; H, 10.44.

2,5-Dimethylhex-4-enal (3g): bp 148 °C; NMR (CCl_4) δ 1.07 (3 H, d, J = 6 Hz, CH_3), 1.68 (6 H, d, J = 4.5 Hz, $2CH_3$'s), 1.96–2.44 (3 H, m, CH_2, CH), 4.91–5.25 (1 H, m, vinyl CH), 9.56 (1 H, d, J = 1.5 Hz, CHO).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.30; H, 11.27.

4-Cyclohexylidene-2-methylbutanal (3h): bp 85–90 °C (5.3 mm); NMR (CCl_4) δ 1.06 (3 H, d, J = 6 Hz, CH_3), 1.56 (6 H, m, ring CH_2's), 2.83–2.54 (7 H, m), 5.02 (1 H, br t, J = 7 Hz, vinyl CH), 9.58 (1 H, d, J = 1.2, CHO).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.19; H, 10.66.

2-Methylhex-4-enal (3i): bp 101 °C; NMR (CCl_4) δ 1.08 (3 H, d, J = 6 Hz, CH_3), 1.67 (3 H, d, J = 4 Hz, CH_3), 1.92–2.56 (3 H, m, CH, CH_2), 5.29–5.76 (2 H, m, CH=CH), 9.55 (1 H, d, J = 1 Hz, CHO).

Anal. Calcd for $C_7H_{12}O$: C, 74.98; H, 10.78. Found: C, 74.75; H, 10.56.

Δ^3-Cyclopentenyl 2-Methylallyl Ether (2d'): NMR (CCl_4) δ 1.70 (3 H, s, CH_3), 2.2–2.6 (4 H, m, ring CH_2's), 3.76 (2 H, s, CH_2), 4.09–4.21 (1 H, m, ring CH), 4.81 (2 H, d, J = 9 Hz, vinyl CH_2), 5.61 (2 H, s, CH=CH).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.12; H, 10.25.

4-Methylhex-1-en-5-one (3i'): NMR (CCl_4) δ 1.04 (3 H, d, J = 6 Hz, CH_3), 1.98 (3 H, s, CH_3), 1.88–2.65 (3 H, m, CH, CH_2), 4.63–5.05 (2 H, m, vinyl CH_2), 5.19–5.92 (1 H, m, vinyl CH).

2-Methylsuccinic Acid (4i): mp 111 °C (reported[22] mp 115°C); NMR ($CDCl_3$) δ 1.45 (3 H, d, J = 6 Hz, CH_3), 2.50–3.29 (3 H), 9.42 (2 H, s, COOH).

Acknowledgment. We thank the National Science Foundation for generous support of our investigations on homogeneous catalysis in organic synthesis.

Registry No.—**2d'**, 63163-56-4; **3a**, 5187-72-4; **3b**, 61740-76-9; **3c** isomer I, 63163-57-5; **3c** isomer II, 63163-60-0; **3d**, 57133-53-6; **3e** isomer I, 63163-58-6; **3e** isomer II, 63163-61-1; **3f** isomer I, 63163-59-7; **3f** isomer II, 63163-62-2; **3g**, 870-17-1; **3h**, 32803-38-6; **3i**, 16134-69-3; **3i'**, 2550-22-3; **4i**, 498-21-5; ruthenium, 7440-18-8.

References and Notes

(1) L. Claisen, *Ber.*, **35**, 3157 (1912).
(2) Review: D. S. Tarbell, *Org. React.*, **2**, 1 (1944).
(3) Reviews: (a) A. Jefferson and F. Scheinmann, *Q. Rev., Chem Soc.*, **22**, 391 (1968); (b) S. J. Rhoads and N. R. Raulins, *Org. React.*, **22**, 1 (1975).
(4) C. Hurd and M. Pollack, *J. Am. Chem. Soc.*, **60**, 1905 (1938).
(5) (a) R. Hoffmann and R. B. Woodward, *J. Am. Chem. Soc.*, **87**, 4388 (1965); (b) K. Fukui and H. Fujimoto, *Tetrahedron Lett.*, 251 (1966); (c) A. Brown, M. J. S. Dewar, and W. Schoeller, *J. Am. Chem. Soc.*, **92**, 5516 (1970).
(6) Review: D. J. Faulkner, *Synthesis*, 175 (1971).
(7) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice Hall, Englewood Cliffs, N.J., 1971, p 375, and references cited therein.
(8) (a) R. K. Hill and N. W. Gilman, *Chem. Commun.*, 619 (1967); (b) R. K. Hill, R. Soman, and S. Sawada, *J. Org. Chem.*, **37**, 3737 (1972), and references cited therein.
(9) (a) A. W. Burgstahler and I. C. Nordin, *J. Am. Chem. Soc.*, **83**, 198 (1961); (b) W. S. Johnson, T. J. Brocksom, P. Loew, D. H. Rich, L. Werthemann, R. A. Arnold, T.-T. Li, and D. J. Faulkner, *ibid.*, **92**, 4463 (1970); (c) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-T. Li, D. J. Faulkner, and M. R. Petersen, *ibid.*, **92**, 741 (1970).
(10) (a) N. B. Lorette and W. L. Howard, *J. Org. Chem.*, **26**, 3112 (1961); (b) K. C. Brannock, *J. Am. Chem. Soc.*, **81**, 3379 (1959); (c) P. Cresson, *Bull. Soc. Chim. Fr.*, 2618 (1964); (d) D. S. Sethi, P. Yates, *J. Am. Chem. Soc.*, **95**, 3820 (1973).
(11) W. Watanabe and L. Conlon, *J. Am. Chem. Soc.*, **79**, 2828 (1957).
(12) A. F. Thomas, *J. Am. Chem. Soc.*, 91, 3281 (1969).
(13) R. Paul, G. Roy, M. Fluchaire, and G. Collardeau, *Bull. Soc. Chim. Fr.*, 121 (1950).
(14) P. Cresson, *Bull. Soc. Chim. Fr.*, 2629 (1964).
(15) E. J. Corey and J. I. Shulman, *J. Am. Chem. Soc.* **92**, 5522 (1970).
(16) J. E. Bladwin and J. A. Walker, *J. Chem. Soc., Chem. Commun.*, 117 (1973).
(17) (a) P. Golborn and F. Scheinmann, *J. Chem. Soc., Perkin Trans. 1*, **2870** (1973); (b) H. C. Clark and H. Kurosawa, *Inorg. Chem.*, **12**, 1566 (1973); (c) E. J. Corey and J. W. Suggs, *J. Org. Chem.*, **38**, 3224 (1973).
(18) H. C. Clark and H. Kurosawa, *Inorg. Chem.*, **12**, 2497 (1971).
(19) For example, see J. E. Lyons, *J. Org. Chem.*, **36**, 2497 (1971).
(20) J. Colonge and G. Clerc, *Bull. Soc. Chim. Fr.*, 836 (1955).
(21) For example see: P. S. Bailey, *Ind. Eng. Chem.*, **50**, 993 (1958).
(22) F. A. L. Anet, *Can. J. Chem.*, **39**, 2262 (1961).
(23) M. Tamele, C. J. Ott, K. E. Marple, and G. Hearne, *Ind. Eng. Chem.*, **33**, 115 (1941).
(24) B. A. Arbusov and O. N. Nuretdinova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2137 (1963); *Chem. Abstr.*, **60**, 10576e (1964).
(25) F. C. Frostick, Jr., B. Phillips, and P. S. Starcher, *J. Am. Chem. Soc.*, **81**, 3350 (1959).

Reactions of Unsaturated Sulfides with Carbenes. 22. Reactivities of Sulfur and Double Bond, and Formation of Unsaturated Sulfonium Ylides[1,2]

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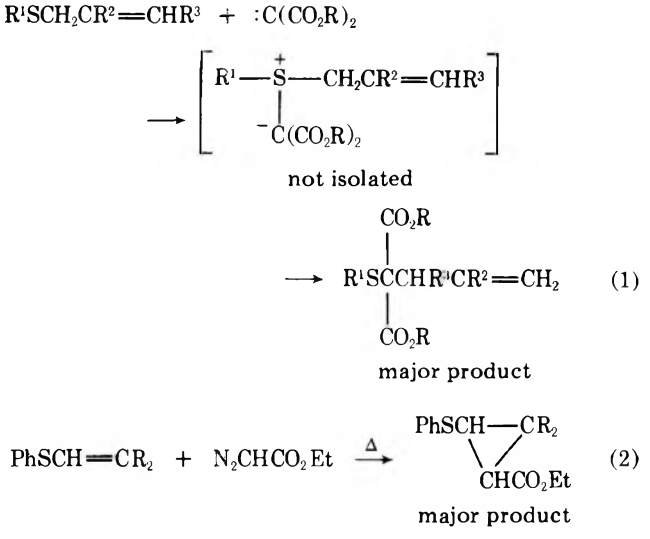
Received March 15, 1977

The reaction of vinyl sulfides with carbomethoxycarbene leads to the formation of methyl vinylthioacetate as major product and some cyclopropane adduct as minor product. The reaction of vinyl sulfides with biscarbomethoxycarbene leads to the corresponding stable sulfonium ylide which decomposed thermally to vinylthiomalonate. The NMR spectra of vinyl sulfides and vinyl sulfonium biscarbomethoxymethylide are discussed. Although the reactions of vinyl sulfide with dichlorocarbene lead to the formation of cyclopropane derivatives, the reaction of allyl vinyl sulfide inhibits the formation of cyclopropane adduct from the double bond of the vinyl sulfide part. The course of these reactions is also discussed.

In previous studies, we observed that the reaction of allylic sulfides with carboalkoxycarbenes under thermal and photolytic conditions produced the C–S insertion products and some addition products to the olefin as a minor process[3,4] (eq 1 and 2). It was suggested that the reaction with allyl sulfide may involve a sulfur ylide intermediate followed by a 2,3-sigmatropic rearrangement, since the carbene attacks a sulfur atom more rapidly than a carbon–carbon double bond. On the other hand, in the thermolysis of ethyl diazoacetate in phenyl vinyl sulfide, Kaiser[5] reported only the formation of cyclopropane. In more recent studies, Parham[6,7] observed also the formation of cyclopropane as a major reaction product in the reaction of dichlorocarbene with several vinyl sulfides. The remarkable differences in behavior of these two olefins were attributed to the difference in nucleophilicity of the two double bonds relative to sulfur, since vinyl sulfides are known to be electron-rich olefins due to the M effect of the sulfur atom (eq 3 and 4). However, a contribution of the structure of Ib is also possible owing to the capability of a sulfur atom to expand its valence shell. This contribution may enhance the reactivity of the sulfur atom toward electrophilic carbenes.



(1)

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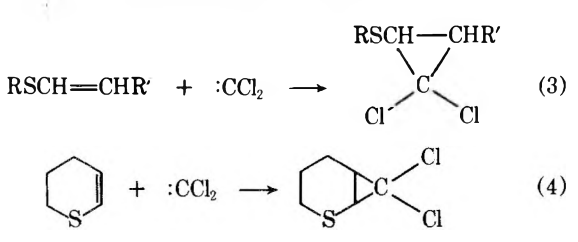


(3)

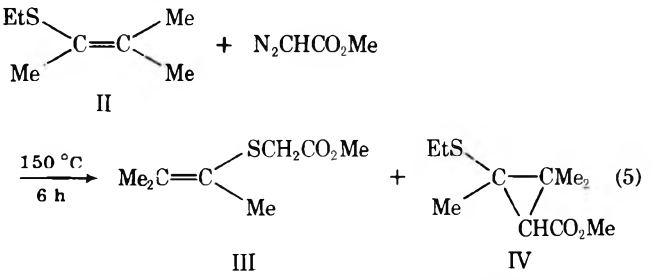
(4)

$$\text{RSCH}{=}\text{CH}_2 \leftrightarrow \text{RS}^+{=}\text{CHCH}_2^- \leftrightarrow \text{RS}^-{=}\text{CHCH}_2^+$$
I Ia Ib

In order to learn more about the generality and mechanism of these interesting transformations, an investigation of the reaction of vinyl sulfides and the reaction of unsaturated cyclic sulfides with various carbenes was carried out under the thermal and photochemical conditions. This paper presents the data concerning the isolation of intermediate sulfur ylides and the reactivities of unsaturated sulfides for the carbenes.

Results and Discussion

Thermolysis of Methyl Diazoacetate in Vinyl Sulfides.[8] Methyl diazoacetate (6.7 mmol) was dissolved in 30 mmol of trimethyl(ethylthio)ethylene (II) and heated at 150 °C for 6 h. Vapor-phase chromatographic analysis using several stationary phases detected two products III and IV formed in ca. 39 and 5% yields, respectively (eq 5). The product III proved to be methyl 1,2-dimethyl-1-propenylthioacetate, and the product IV was found to be the expected carbene addition product to the double bond. The structures of these products were determined by NMR and IR spectra and elemental analyses.



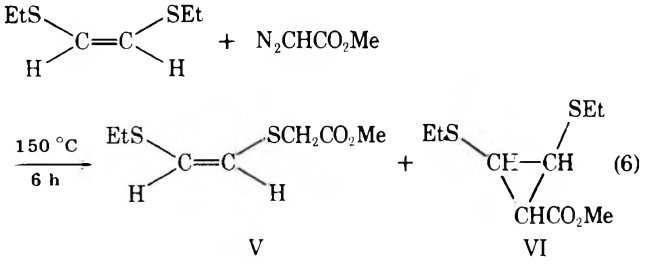
(5)

A study of methyl diazoacetate with *cis*-diethylthioethylene affords a 38% yield of the thioacetate V and 6% of the addition product of carbomethoxycarbene to the olefin (eq 6). The corresponding cyclopropane from the addition of carbene to the olefin is expected to form syn and anti forms, but this detail of structure could not be deduced from the spectral data.

A number of substituted vinyl sulfides gave rise to the

Table I. Yields of the Products from Vinyl Sulfides and Methyl Diazoacetate at 150 °C

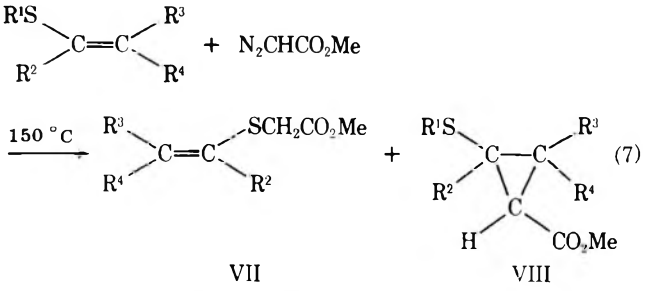
Product	R^1	R^2	R^3	R^4	VII, %	VIII, %
a	Me	H	Me	Me		12
b	Et	H	Me	Me	21	3
c	Et	Me	H	Me	29	5
d	Et	H	H	Me	25	18
e	*i*-Pr	H	Me	Me	32	15
f	*i*-Pr	Me	Me	H	36	Tr
g	*t*-Bu	H	Me	Me	37	10
h	Ph	H	H	H		58
i	Ph	H	Me	Me		15



(6)

V VI

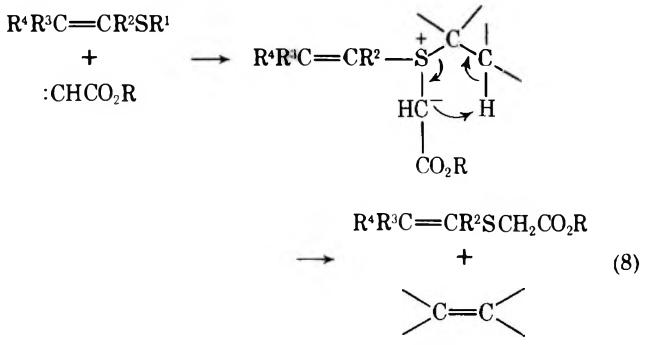
thioacetate as major product when treated with methyl diazoacetate as shown in eq 7 (see also Table I).



(7)

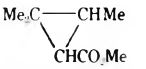
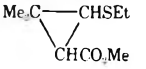
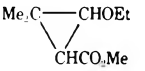
VII VIII

While we have not confirmed the existence of a sulfur ylide intermediate, we have been able to show that the formation of these thioacetates may be formulated as involving an attack of carbomethoxycarbene on the sulfur atom to form the vinylsulfonium ylide followed by a cyclic elimination of olefin, and that the sulfide sulfur inhibits the formation of carbene addition products[9] (eq 8). Data reveal that an attack of carbomethoxycarbene on sulfur appears to be four to five times faster than addition on the double bond. 1-Phenyl-2-methyl-1-propene, which can form a sulfonium ylide that cannot undergo elimination of an olefin, apparently polymerizes to unknown compounds. On the other hand, the inhibiting effect of the sulfide sulfur on cyclopropane formation was not observed in the reaction of carbomethoxycarbene with phenyl vinyl sulfide. This may suggest that the intermediate sulfur ylide may react with either an intramolecular or intermolecular olefin to give the cyclopropane adduct (eq 9). An alternative explanation is that ylide formation is reversible, and when an intramolecular rearrangement is not possible,

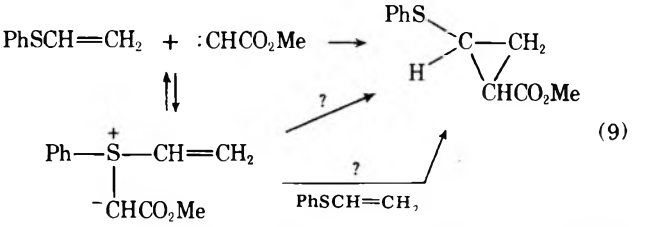


(8)

Table II. Competitive Reaction for Cyclopropane Formation in the Reaction with Carbomethoxycarbene at 160 °C

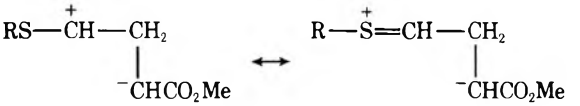
Olefin	Product	Rate
$Me_2C{=}CHMe$		1.0
$Me_2C{=}CHSEt$		1.9
$Me_2C{=}CHOEt$		4.3

as it is not with phenyl or methyl, then the cyclopropane is ultimately formed by the addition of carbene on the double bond.



(9)

There are some electronic effects visible in the cyclopropane formation reactions. These can be evaluated from data on the competing reactivity of different olefins for the carbene formed on thermolysis of methyl diazoacetate at 160 °C (Table II). Data in Table II indicate the high reactivity of vinyl sulfide toward carbomethoxycarbene assuming the ylide is not sources of the cyclopropane. The double bond of vinyl sulfide is 1.9 times as reactive as that of trimethylethylene, but less reactive than of vinyl ether. A possible transition state for the carbene addition to vinyl sulfide may be IX, in which

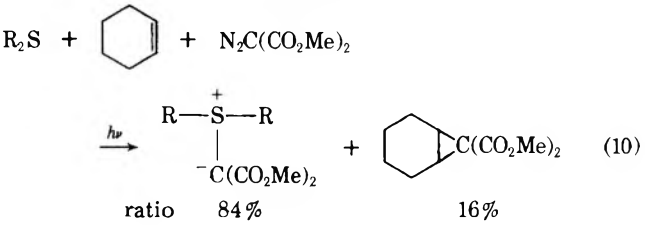


IX

the contribution of sulfur 2p–3pπ is not as large as that of oxygen electrons (2p–2pπ).

The photolysis of methyl diazoacetate in 1-*tert*-butylthio-2-methyl-1-propene was also investigated. The vinyl thioacetate and cyclopropane were formed in only 1 and 9% yield, respectively; the major products of the reaction were observed, but not identified. In view of the low yield, the formation of the sulfur ylide in this case is uncertain. The reaction at low temperature has not provided much useful data to date.

Reaction of Dimethyl Diazomalonate in Vinyl Sulfides. Biscarbomethoxycarbene generated from direct photolysis of dimethyl diazomalonate reacts with alkyl and aryl sulfides to give stable sulfonium biscarbomethoxymethylides[10,11] (eq 10). The formation of sulfonium ylides was proposed to be the result of attack of the singlet carbene on a lone pair of the sulfur atom, which was found to proceed six times as fast as with double bond of cyclohexene.



(10)

From this, we can expect that biscarbomethoxycarbene

might form stable sulfonium ylides in the reaction with vinyl sulfides. Irradiation of dimethyl diazomalonate in 1-methylthio-2-methyl-1-propene was carried out in a Pyrex tube with a high-pressure mercury lamp for 6 h until the evolution of N_2 gas ceased. The reaction products were analyzed by TLC and gas chromatography, and showed the formation of the principal product Xa in 47% yield and the minor product XIa in 9% yield, respectively (eq 11). The principal product Xa was

$$RSCH{=}CMe_2 + N_2C(CO_2Me)_2 \xrightarrow{h\nu} R{-}\overset{+}{S}{-}CH{=}CMe_2 \;\; {}^{-}C(CO_2Me)_2 \;\; (X) \;+\; RSCH(CMe_2)C(CO_2Me)_2 \;\; (XI) \qquad (11)$$

	X	XI
a, R = Me	47%	9%
b, R = Et	43%	9%
c, R = *t*-Bu	Tr	9%
d, R = Ph	44%	7%

found to be 2-methyl-1-propenylmethylsulfonium biscarbomethoxymethylide: ν (C=O) 1665 and 1635 cm^{-1}; NMR δ ($CDCl_3$) 1.91 (s, 3 H), 2.07 (s, 3 H), 2.90 (s, 3 H), 3.58 (s, 6 H), and 6.55 (s, 1 H). The proton shift of the $>S^+$–Me and the carbonyl shift in product Xa are analogous to those observed in dimethylsulfonium biscarbomethoxymethylide [ν (C=O) 1675 and 1625 cm^{-1}; NMR δ ($CDCl_3$) 2.89 for $>S^+$–Me and 3.71 for $-CO_2Me$). The product XIa was found to be a cyclopropane adduct.

Similar type of reactions in a variety of vinyl sulfides showed the formation of the corresponding alkyl vinylsulfonium biscarbomethoxymethylides as the major product. Reaction of *tert*-butylthio-2-methyl-1-propene with dimethyl diazomalonate did afford the corresponding sulfonium ylide, but in very low yield because of the steric effect of the *tert*-butyl group on the sulfur atom.

The most marked change in going from direct photolysis to sensitized photolysis is in the ratio of yield of the sulfonium ylide to cyclopropane derivatives. Benzophenone photosensitized decomposition of dimethyl diazomalonate in 1-methylthio-2-methyl-1-propene gave 24% of the corresponding sulfonium ylide and 18% of the cyclopropane derivative (eq 12). An appropriate control experiment showed that under

$$RSCH{=}CMe_2 + N_2C(CO_2Me)_2 \xrightarrow{Ph_2C=O,\ h\nu} X + XI \qquad (12)$$

	X	XI
a, R = Me	24%	18%
b, R = Et	25%	21%

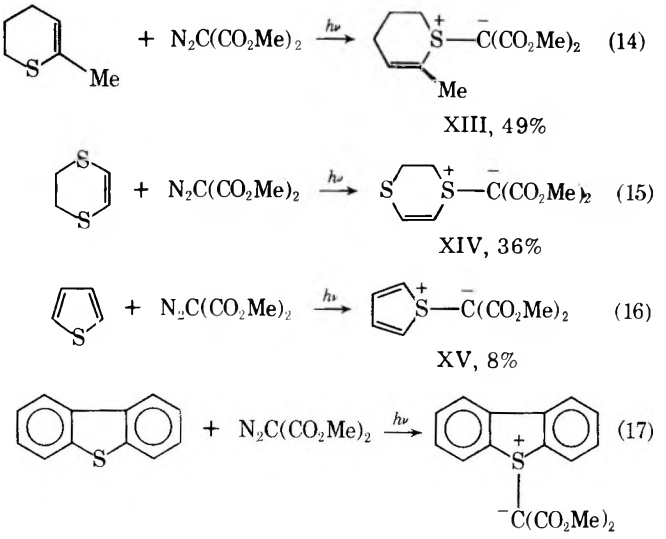
the reaction conditions the product neither isomerized nor was destroyed. One explanation is that the photosensitized reaction of dimethyl diazomalonate will give a triplet species which reacts selectively with a carbon–carbon double bond, but also that triplet species will equilibrate with the singlet species, which might react preferentially with the vinyl sulfide sulfur to give the sulfonium ylide.[12] However, there may be other plausible explanations for the formation of some sulfonium ylide in the photosensitized reaction. For instance, the charge-transfer complex which results from triplet benzophenone and sulfide may decrease the formation of the triplet carbene species.

Thermal reaction of dimethyl diazomalonate in vinyl sulfides in the presence of copper sulfate at 120 °C gave the corresponding sulfonium ylide in 45–50% yields, and did not afford any cyclopropane derivatives by the addition of carbene to the double bond.

We have also examined the thermal behavior of the sulfonium biscarbomethoxymethylide. When ethyl 2-methyl-1-propenyl(ethyl)sulfonium biscarbomethoxymethylide was heated in sealed tube at a temperature above 200 °C for 1 h, 2-methyl-1-propenyl thiomalonate was obtained in 61% yield together with the formation of ethylene (eq 13). The elimi-

$$EtSCH{=}CMe_2 + N_2C(CO_2Me)_2 \xrightarrow[CuSO_4]{120\ ^\circ C} Et{-}\overset{+}{S}{-}CH{=}CMe_2 \;\; {}^{-}C(CO_2Me)_2 \;\; (45\%\ \text{yield}) \xrightarrow{200\ ^\circ C} Me_2C{=}CHSCH(CO_2Me)_2 \;\; (XII,\ 61\%\ \text{yield}) + CH_2{=}CH_2 \qquad (13)$$

native decomposition of the sulfonium ylide is probably a cis elimination through a five-membered cyclic transition state.[9] Those observations give support to the proposed ylide mechanism in the reaction of carbomethoxycarbene with vinyl sulfide, which gave a vinylthioacetate together with the formation of olefin. In the reaction of dimethyl diazomalonate with unsaturated cyclic sulfides, the corresponding sulfonium ylides were also obtained as stable compounds (eq 14–17).



(14) (15) (16) (17)

Irradiation of dimethyl diazomalonate in 2,3-dihydro-6-methyl-4*H*-thiapyran gave the corresponding sulfonium ylide in 49% yield. The study of the reaction of carbene with conjugated vinyl sulfides is particularly interesting. Thiophene and dibenzothiophene,[12] in which the lone pair of sulfur is highly delocalized, are efficient traps for the carbene, and gave the corresponding sulfonium ylides in the reaction with dimethyl diazomalonate under either thermal or photochemical conditions. The stabilized thiophenium ylide showed: ν (C=O) at 1645 cm^{-1}; NMR δ ($CDCl_3$) at 3.67 (s, 6 H), 7.07 (br s, 2 H), and 7.27 (br s, 2 H); *m/e* 214.

Reaction of Acetylenic Sulfides with Diazoacetate and Diazomalonate.[2] Carbenes and carbenoids add to an acetylene less readily than to an olefin, while only a few cases are known of such carbene reactions with hetero-substituted acetylenes. Reactions are conveniently carried out in the absence of solvent at elevated temperature. Heating an equimolar mixture of methyl diazoacetate and phenylethylthioacetylene in the presence of a catalytic amount of anhydrous copper sulfate at 60 °C for 10 min gave a 35% yield (GLC) of compound XVIa (eq 18), in accord with the observed spectral data: ν (C=O) at 1745 cm^{-1}, and ν (C≡C) at 2180 cm^{-1}; NMR δ (CCl_4) 3.51 (s, 2 H), 3.77 (s, 3 H), and 7.2–7.5 (m, 5 H); *m/e* 206. Similar reactions of methyl diazoacetate with the acetylenic sulfides in the presence of copper sulfate lead to the formation of alkynylthioacetates. No cyclopropene derivative or rearranged products were obtained. By analogy with the reaction with alkyl sulfides and vinyl sulfides, the

Table III. Competitive Reaction for Sulfur Atoms in the Reaction with Methyl Diazoacetate in Presence of $CuSO_4$ at 60 °C

Sulfide	Product	Rate
Et_2S	$EtSCH_2CO_2Me$	7.1
$Me_2C{=}CHSEt$	$Me_2C{=}CHSCH_2CO_2Me$	4.6
$MeC{\equiv}CSEt$	$MeC{\equiv}CSCH_2CO_2Me$	9.2
$Me_2C{=}CHMe$	$Me_2C(CHMe)CH(CO_2Me)$	1.0 (standard)

Table IV. Relative Ratio of Sulfur and Double Bond Attack in the Reaction of Arylcarbenes

Sulfide	:CPh_2	:CHPh
t-$BuSCH{=}CMe_2$	3.1	1.4
t-$BuSCH_2CH{=}CH_2$	7.3	4.7

formation of compound XVI may involve an attack of carbomethoxycarbene on the sulfur atom to form the acetylenic sulfonium ylide followed by cyclic elimination of olefin, although trapping of the acetylenic sulfonium ylide was not successful under the reaction conditions.

$$RC{\equiv}CSEt + N_2CHCO_2Me \xrightarrow[CuSO_4]{60^\circ} RC{\equiv}C(CHCO_2Me)S^+(Et)\ {}^-CHCO_2Me \longrightarrow RC{\equiv}CSCH_2CO_2Me \quad (18)$$

XVI

a, R = Ph	35%
b, R = Me	34%
c, R = SEt	15%

We have also examined the reactivity of the sulfur atoms of different unsaturated sulfides in the thermal reaction of methyl diazoacetate in the presence of copper sulfate. Table III shows the relative rates of carbenoid attack on divalent sulfur in the competing reaction with addition to trimethylethylene. The data indicate that the carbenoid attacks divalent sulfur more effectively than it attacks the double bond of trimethylethylene. On the other hand, the electrophilic carbenoid attacks the vinyl sulfide sulfur less efficiently in comparison with the attack on alkyl and acetylenic sulfide sulfurs. It could be argued that the electron density on the vinyl sulfide sulfur is decreased somewhat because the lone-pair electrons of the vinyl sulfide sulfur are delocalized to some extent through the overlap of 3p orbitals of sulfur with the carbon 2p orbitals.[13]

$$R_2C{=}CHSR \leftrightarrow R_2C^-CH{=}S^+R$$

However, in the case of acetylenic sulfide, the electron density of the sulfur atom may be influenced by the inductive effect of the acetylene group, but not by its resonance effect.

The reactivity of acetylenic sulfide sulfur toward carbenes suggested the possibility of isolation of sulfonium ylides. Irradiating a mixture of methyl diazomalonate and the acetylenic sulfide (3 equiv) in a Pyrex tube for 21 h results in an isolated 23% yield of a pure acetylenic sulfonium ylide after preparative thin-layer chromatography (eq 19). The assigned

$$RC{\equiv}CSEt + N_2C(CO_2Me)_2 \xrightarrow{h\nu} RC{\equiv}C(C(CO_2Me)_2)S^+(Et) \quad (19)$$

XVII, R = Ph, 23%
XVIII, R = SEt, 14%

structure of sulfur ylide XVIII is in accord with the observed spectral data: ν (C=O) 1685 and 1650 cm^{-1}; NMR δ ($CDCl_3$) 1.40 (t, 3 H), 3.77 (s, 6 H), 3.80 (q, 2 H), and 7.48 (m, 5 H); *m/e* 292.

Photolysis of Phenyl- and Diphenyldiazomethanes in Vinyl Sulfides. The photolysis of phenyl- and diphenyldiazomethanes in vinyl sulfides was carried out in a Pyrex tube without degassing. The crude reaction mixture in the reaction of phenyldiazomethane and 1-*tert*-butylthio-2-methyl-1-propene did not show the formation of any sulfonium ylide as judged by the examination of either NMR or IR spectra. GLC analyses showed the formation of benzylthio-2-methyl-1-propene and the corresponding cyclopropane derivative together with some stilbene and benzalazine (eq 20).

$$t\text{-}BuSCH{=}CMe_2 + N_2CRPh \longrightarrow PhRCHSCH{=}CMe_2 + t\text{-}BuSCH(CMe_2)C(R)(Ph) \quad (20)$$

XIX XX

	XIX a	XIX b	XX a	XX b
reaction mode	R = H	R = Ph	R = H	R = Ph
$h\nu$	13%	22%	9%	7%
$CuSO_4$ at 40 °C	22	37		
thermal at 120 °C	15	20	4	2

The structure of these products was determined by spectral and elemental analyses. The reactions were also carried out under various other conditions. The results indicate that arylcarbenes prefer to attack the sulfur atom over the double bond; the copper carbenoid exclusively attacks the sulfur atom. Under the photolytic conditions, the relative rate of XIX and XX was about 3.1 in the reaction of diphenylcarbene and 1.4 in the reaction of phenylcarbene. Since the reactivity of the *tert*-butyl allylic sulfide sulfur to the double bond in the allylic sulfide is 7.3 in the diphenylcarbene reaction and 4.7 in the phenylcarbene reaction (Table IV),[14] the change in the ratio may be due to the difference in nucleophilicity between vinyl sulfide sulfur and allylic sulfide sulfur, owing to donation of the 3pπ electron of sulfur to the double bond in vinyl sulfide.

We have also examined the reaction of diphenylcarbene with vinyl sulfide, in which the sulfur bears an alkyl group not containing a β hydrogen. The photolysis of 2.34 mmol of diphenyl diazomethane in 22.7 mmol of 1-methylthio-2-methyl-1-propene was carried out in a Pyrex tube with a high-pressure mercury lamp for 2 h. The reaction products were anlayzed by column chromatography with silica gel and chloroform, ether, and methanol as solvents. Two main products, XXI and XXII, were found in 5 and 13% yield, respectively, together with some diphenylazine and benzophenone (eq 21). Product XXI showed NMR spectra δ ($CDCl_3$)

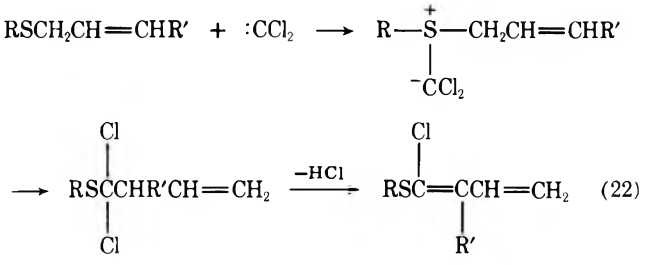
$$MeSCH{=}CMe_2 + N_2CPh_2 \xrightarrow{h\nu} MeS^+(CPh_2)CH{=}CMe_2 + MeSCH(CMe_2)C(Ph)(Ph) \quad (21)$$

XXI XXII

1.93 (s, 3 H), 2.03 (s, 3 H), 2.63 (s, 3 H), 6.12 (s, 1 H), and 7.28 (m, 10 H); *m/e* 268. The signal at δ 2.63 is especially interesting; it is tentatively assigned to the methyl protons of the corresponding sulfonium ylide. The IR spectra would not be expected to have any special band characteristic of sulfonium ylide. The product XXII was found to be the addition product of the carbene on the double bond from the NMR and IR spectral analyses.

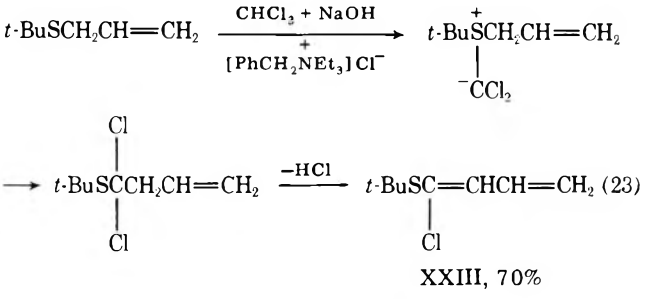
Reactions of Vinyl Sulfides with Dichlorocarbene. The

reaction of dichlorocarbene with noncyclic allyl sulfides leads to the formation of 1-chloro-1-substituted mercaptobutadienes in high yields, together with some olefins derived by addition of hydrogen chloride to the butadienes. An attractive mechanism for the formation of mercaptobutadienes involves sulfonium ylide formation followed by intramolecular allylic rearrangement[15] (eq 22). It was also shown that the sulfide



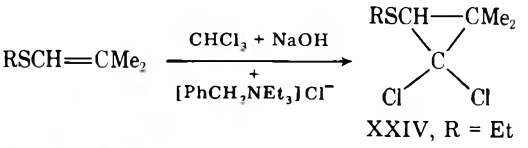
(22)

sulfur inhibits the formation of dichlorocyclopropyl adducts from the double bond. On the other hand, it was reported that the reaction of vinyl sulfide with dichlorocarbene gave the corresponding cyclopropane adducts in high yields. The remarkable difference in behavior of these olefins was explained by the difference in nucleophilicity of two double bonds relative to sulfur.[6,7] In order to learn more about the generality and mechanism of these interesting transformations, an investigation of the reaction of vinyl sulfides and allyl vinyl sulfides was undertaken using chloroform and sodium hydroxide mixtures in the presence of an ammonium salt. The reaction of *tert*-butyl allyl sulfide with chloroform was carried out in benzene–water solvent using conditions described by Makosza[16] (eq 23). A high yield of 1-chloro-1-*tert*-butyl-

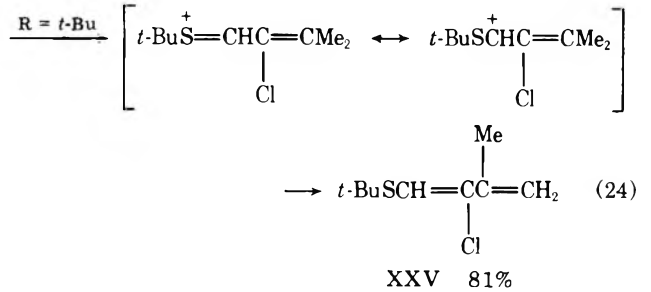


(23)

XXIII, 70%



XXIV, R = Et

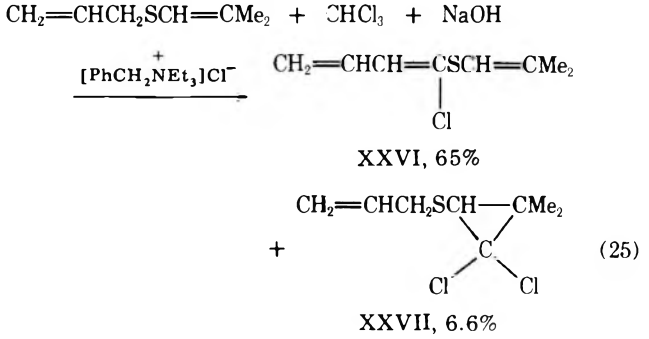


(24)

XXV 81%

mercaptobutadiene (XXIII) was obtained as the product from the transformation of intermediate sulfur ylide. The addition product of dichlorocarbene to the double bond was not observed under the reaction conditions. On the other hand, the reactions of 1-ethyl- or 1-*tert*-butylthio-2-methyl-1-propenes with $CHCl_3$ and NaOH were carried out in benzene–water using conditions previously described for allyl sulfide (eq 24). In each case high yields of either the corresponding cyclopropane or butadiene derivatives were obtained (81–92%). The dichlorocyclopropane and butadiene derivatives were characterized by their composition and spectra.

A study of the reaction of allyl vinyl sulfide with dichlorocarbene was of particular interest in view of the reactivity relationship of these olefins and the sulfur atom with allyl sulfide and vinyl sulfide. Allyl vinyl sulfide reacted readily with dichlorocarbene to give chlorobutadienylthio-1-methyl-1-propene (XXVI) in 65% and the addition product to the vinyl group XXVII in 6.6% yield (eq 25). The formation



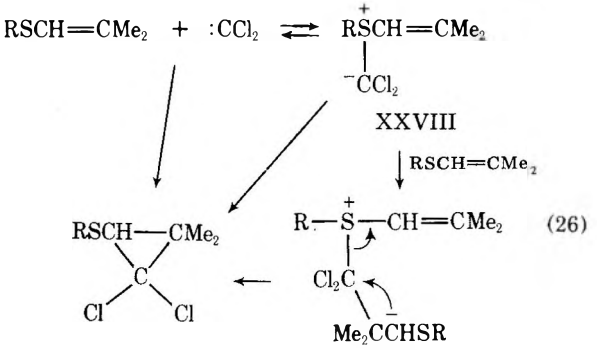
XXVI, 65%

(25)

XXVII, 6.6%

of XXVI is consistent with the expected course of intermediate sulfur ylide rearrangement. The formation of an intermediate sulfur ylide is reasonable in view of the nucleophilic character of sulfide sulfur. Also it can be readily seen that the dichlorocarbene reacts with the vinyl double bond, because of the difference in nucleophilicity. However, one should emphasize that *vinylic sulfide sulfur is more sensitive to electrophilic species than the vinylic double bond.*

An attractive mechanism for the formation of cyclopropane from vinyl sulfide may involve direct carbene attack on the sulfur to form sulfonium ylide XXVIII followed by either intramolecular cyclization or intermolecular reaction with the double bond of another vinyl sulfide molecule (eq 26). How-



(26)

ever, one can not rule out the direct carbene addition on the double bond via reversible carbene formation from intermediate sulfur ylide XXVIII.

Experimental Section

Materials. Methyl diazoacetate,[17] dimethyl diazomalonate,[11] phenyldiazomethane,[18] and diphenyldiazomethane[19] were prepared by known procedures as referenced. The vinyl sulfides, 1-ethylthio-1,2-dimethyl-1-propene (bp 154–156 °C), 1-ethylthio-1-methyl-1-propene (bp 136–138 °C), 1-ethylthio-1-propene (bp 121–123 °C), 1-ethylthio-2-methyl-1-propene (bp 132–133 °C), 1-isopropylthio-2-methyl-1-propene (bp 147 °C), 1-*tert*-butylthio-2-methyl-1-propene [bp 98 °C (118 mmHg)], 1-phenylthio-2-methyl-1-propene [bp 122 °C (48 mmHg)], and 1-*sec*-butylthio-2-methyl-1-propene [bp 103–104 °C (99 mmHg)] were prepared in 30–80% yield by the method of Boostra et al.[20] Phenyl vinyl sulfide[21] was prepared as described by Ford-Moore et al.,[21] giving the product in 64% yield, bp 87–91 °C (25 mmHg). 1-Methylthio-2-methyl-1-propene was prepared as described for the mixture of isobutylaldehyde and methyl mercaptan using zinc chloride. Distillation of the crude product gave 28% yield of the product, bp 120–125 °C.[21,22] 2,3-Dihydro-6-methyl-4*H*-thiapyran was prepared as described by Cohen and Steele.[23] 1,4-Dithiene[24] was prepared by the Parham method. 1-Allylthio-2-

Table V. Analytical Data of the Products Obtained from Vinyl Sulfides and Diazoacetate

Product	Registry no.	IR, cm^{-1} (main peaks)	NMR, ppm downfield from Me_4Si	Calcd, % C	Calcd, % H	Found, % C	Found, % H
III	42954-21-2	2980, 2950, 1740, 1438, 1278, 1130	1.79 (s, 3 H), 1.96 (s, 6 H), 3.21 (s, 2 H), 3.63 (s, 3 H)	55.14	8.10	54.99	8.11
IV	42954-25-6	2930, 1730, 1432, 1376, 1185, 1165, 1140, 1108	1.23 (t, 3 H), 1.28 (s, 3 H), 1.42 (s, 3 H), 1.56 (s, 3 H), 1.94 (s, 1 H), 2.60 (q, 2 H), 3.60 (s, 3 H)	59.32	8.97	59.55	8.90
V	63196-70-3	2930, 1740, 1275, 1150	1.31 (t, 3 H), 2.70 (q, 2 H), 3.22 (s, 2 H), 3.70 (s, 3 H), 5.99 (2, 1 H), 6.30 (s, 1 H)	43.72	6.29	43.86	6.20
VIIb	42954-22-3	2950, 1740, 1435, 1280, 1133	1.75, (s, 3 H), 1.78 (s, 3 H), 3.18 (s, 2 H), 3.68 (s, 3 H), 5.69 (s, 1 H)	52.47	7.55	52.42	7.61
VIIc	42954-23-4	2950, 1740, 1433, 1275, 1130	1.70 (d, 3 H), 1.90 (s, 3 H), 3.27 (s, 2 H), 3.67 (s, 3 H), 5.60 (q, 1 H)	52.42	7.55	52.38	7.49
VIId	63196-71-4	2980, 1740, 1277, 1130	1.72 (d, 3 H), 3.21 (s, 2 H), 3.70 (s, 3 H), 5.50–5.98 (m, 2 H)	49.29	6.89	49.08	7.01
VIIIa	63196-72-5	2930, 1740, 1440, 1210, 1160	1.23 (s, 3 H), 1.33 (s, 3 H), 1.63 (d, 1 H), 2.05 (s, 3 H), 2.18 (d, 1 H), 3.63 (s, 3 H)	55.14	8.10	55.02	8.16
VIIIb	42954-26-7	2930, 1732, 1440, 1220, 1170	1.26 (t, 3 H), 1.30 (s, 6 H), 1.77 (d, 1 H), 2.40 (d, 1 H), 2.53 (d, 2 H), 3.63 (s, 3 H)	57.41	8.57	57.92	8.72
VIIIc	42954-27-8	2930, 1735, 1430, 1265, 1155	1.22 (t, 3 H), 1.47 (s, 6 H), 1.6–1.9 (m 2 H), 2.53 (q, 2 H), 3.63 (s, 3 H)	57.41	8.57	57.56	8.39
VIIId	63196-73-6	2950, 1735, 1430, 1155	1.23 (t, 3 H), 1.28 (d, 3 H), 1.3–2.0 (m, 3 H), 2.47 (q, 2 H), 3.65 (s, 3 H)	51.58	7.58	52.01	7.51
VIIIe	63196-74-7	2960, 1735, 1440, 1220, 1170	1.26 (d, 6 H), 1.27 (s, 6 H), 1.42 (d, 1 H), 2.36 (d, 1 H), 2.92 (m, 1 H), 3.65 (s, 3 H)	59.32	8.97	58.86	8.70
VIIIg	63196-75-8	2960, 1733, 1440, 1280, 1215, 1165	1.23 (s, 6 H), 1.28 (s, 9 H), 1.65 (d, 1 H), 2.05 (d, 1 H), 3.58 (s, 3 H)	61.07	9.32	61.18	9.29
VIIIh	63196-76-9	3050, 2950, 1730, 1485, 1435, 1260, 1200, 1170	1.21 (m, 1 H), 1.77 (m, 2 H), 2.71 (m, 1 H), 3.70 (s, 3 H), 7.23 (m, 5 H)	63.43	5.81	63.59	5.75

Table VI. Reaction Products from Vinyl Sulfides and Dimethyl Diazomalonate

Product	Registry no.	IR, cm^{-1} (main peaks)	NMR, ppm downfield from Me_4Si	Calcd, % C	Calcd, % H	Found, % C	Found, % H
Xa	63196-77-0	1665, 1630, 1320, 1070	1.91 (s, 3 H), 2.07 (s, 3 H), 2.90 (s, 3 H), 3.58 (s, 6 H), 6.55 (s, 1 H)	51.70	6.94	51.92	6.79
Xb	63196-78-1	1690, 1630, 1440, 1320, 1080	1.25 (t, 3 H), 1.96 (t, 3 H), 2.08 (s, 3 H), 3.53 (m, 2 H), 3.65 (s, 6 H), 6.48 (s, 1 H)	53.63	7.37	53.69	7.30
Xc	63196-79-2	2950, 1650, 1440, 1330, 1240, 1080	1.27 (s, 9 H), 1.95 (s, 3 H), 2.07 (s, 3 H), 3.72 (s, 6 H), 6.45 (s, 1 H)	56.91	8.08	57.04	7.98
Xd	63196-80-5	1680, 1640, 1430, 1325, 1080	2.03 (s, 3 H), 2.15 (s, 3 H), 3.65 (s, 6 H), 6.35 (s, 1 H), 7.48 (m, 5 H)	61.20	6.16	61.23	6.19
XII	63196-81-6	1760, 1740, 1430, 1300, 1265, 1145	1.82 (s, 6 H), 3.75 (s, 6 H), 4.07 (s, 1 H), 5.80 (s, 1 H)	49.52	6.48	49.80	6.62
XIII	63196-82-7	1680, 1640, 1430, 1330, 1080, 915	1.90 (s, 3 H), 2.1–2.4 (m, 4 H), 3.0–3.3 (m, 2 H), 3.67 (s, 6 H), 6.20 (s, 1 H)	54.08	6.60	54.57	6.38
XIV	63196-83-8	3000, 1680, 1645, 1435, 1330, 1080	3.5–4.2 (m, 4 H), 3.68 (s, 6 H), 5.95, (d, 1 H), 6.93 (d, 1 H)	43.53	4.87	43.98	4.86
XV	63196-84-9	3090, 1645, 1440, 1245, 1080	3.67 (s, 6 H), 7.07 (s, 2 H), 7.27 (s, 2 H)	50.45	4.71	50.38	4.91
XVIa	36814-62-7	3075, 1745, 1490, 1445, 1440, 1300, 1280, 1170, 1135	3.51 (s, 2 H), 3.77 (s, 3 H), 7.2–7.5 (m, 5 H)	64.06	4.89	63.75	5.13
XVIb	54045-22-6	1745, 1440, 1280, 1160, 1135	1.97 (s, 3 H), 3.37 (s, 2 H), 3.75 (s, 3 H)	49.98	5.59	50.23	5.72
XVIc	54045-23-7	2950, 1745, 1440, 1300, 1265, 1145	1.46 (t, 3 H), 2.70 (q, 2 H), 3.42 (s, 2 H), 3.75 (s, 3 H)	44.18	5.30	44.21	5.29
XVII	63196-85-0	1685, 1650, 1440, 1335, 1245, 1085, 910	1.40 (t, 3 H), 3.77 (s, 6 H), 3.80 (q, 2 H), 7.48 (m, 5 H)	61.62	5.52	61.73	5.59
XVIII	63196-86-1	1675, 1640, 1435, 1330, 1240, 1085	1.35 (t, 3 H), 1.45 (t, 3 H), 2.87 (q, 2 H), 3.68 (q, 2 H), 3.73 (s, 6 H)	47.08	5.84	47.11	5.83

methyl-1-propene was prepared by the addition of allyl mercaptan to isobutylaldehyde in a manner described for 1-ethylthio-1,2-dimethyl-1-propene in 50% yield, bp 80–82 °C (90 mmHg). Phenylethylthioacetylene was prepared as described by Brandsma[25] in 36% yield, bp 108–113 °C (11 mmHg). Methylethylthioacetylene and 1,2-bis(ethylthio)acetylene were prepared in the method described for phenylethylthioacetylene.

General Procedure of Thermal and Photochemical Reactions of Methyl Diazoacetate in Vinyl Sulfides. Thermal or photochemical reactions of 5 mmol of methyl diazoacetate in 30–50 mmol of vinyl sulfides were carried out in Pyrex sealed tube without degassing at >160 °C or with a high-pressure mercury lamp. After the diazo band disappeared from the IR spectrum of the reaction mixture, a known amount of an internal standard was added to the reaction mixture, which was then analyzed by gas chromatography. The structure of the isolated products was determined on the basis of NMR and IR spectra and elemental analysis. The cyclopropane derivatives obtained from the reaction consist of two geometrical isomers. Their configurations were not assigned. The analytical data are reported in Table V.

Reactions of Dimethyl Diazomalonate in Vinyl Sulfides. Most of the vinylsulfonium biscarbomethoxymethylides were prepared by the photolysis of dimethyl diazomalonate in vinyl sulfides. For example, the sulfur ylide, 2-methyl-1-propenylethylsulfonium biscarbomethoxymethylide (Xb) was prepared in 43% yield by photolysis of 0.52 g (3.3 mmol) of dimethyl diazomalonate in 3 mL of 1-ethylthio-2-methyl-1-propene. In 80% decomposition of the diazomalonate, the excess vinyl sulfide was distilled off under reduced pressure. The residue was analyzed by a silica gel column with chloroform, acetone, or methanol. The sulfur ylide Xb was isolated as an oily product,

Table VII. Reaction Products from Vinyl Sulfides and Phenyl- and Diphenyldiazomethanes

Product	Registry no.	IR, cm^{-1} (main peaks)	NMR, ppm downfield from Me_4Si	Calcd, % C	Calcd, % H	Found, % C	Found, % H
XIXa	63196-87-2	3050, 2950, 2900, 1500, 1455, 1375, 790, 770	1.70 (s, 6 H), 3.72 (s, 2 H), 5.54 (s, 1 H), 7.22 (m, 5 H)	74.10	7.91	74.21	7.95
XIXb	63196-88-3	3040, 2950, 1660, 1600, 1490, 1450, 1370, 1320	1.70 (s, 3 H), 1.77 (s, 3 H), 5.15 (s, 1 H), 5.47 (s, 1 H), 7.1–7.4 (m, 10 H)	80.27	7.13	80.34	7.06
XXa	63196-89-4	3000, 2940, 1450, 1360, 1160	0.9–2.2 (m, 17 H), 7.17 (m, 5 H)	76.86	9.46	76.45	9.40
XXb	63196-90-7	3030, 2920, 1480, 1440	1.27 (s, 9 H), 1.30 (s, 6 H), 1.70 (s, 1 H), 7.0–7.4 (m, 10 H)	81.21	8.44	81.39	8.38

Table VIII. Reaction Products from Dichlorocarbene with Vinyl and Allylic Sulfides

Product	Registry no.	IR, cm^{-1} (main peaks)	NMR, ppm downfield from Me_4Si	Calcd, % C	Calcd, % H	Found, % C	Found, % H
XXIII	63196-91-8	2970, 1365, 1165, 990	1.42 (s, 9 H), 5.0–5.6 (m, 2 H), 6.4–7.2 (m, 2 H)	54.38	7.41	54.59	7.58
XXV	63196-92-9	2950, 2905, 1445, 1365, 1160	1.42 (s, 9 H), 2.00 (s, 3 H), 4.95 (s, 1 H), 5.37 (s, 1 H), 6.50 (s, 1 H)	56.68	7.94	56.25	7.48
XXVI	63196-93-0	2900, 1615, 1170, 900, 785	1.83 (s, 6 H), 5.1–5.4 (m, 2 H), 5.84 (s, 1 H), 6.4–7.0 (m, 2 H)	55.01	6.35	55.23	6.31
XXVII	63196-94-1	3100, 3000, 2950, 1620, 1465, 1380, 1235, 1120, 1010, 920, 850, 740	1.30 (s, 3 H), 1.43 (s, 3 H), 2.18 (s, 1 H), 3.25 (d, 2 H), 5.0–6.5 (m, 3 H)	45.72	5.75	45.46	5.94

which was easily dissolved in water and chloroform, but not in carbon tetrachloride. The vinylsulfonium biscarbomethoxymethylides were often prepared with copper or cupric sulfate catalyzed thermal decomposition of dimethyl diazomalonate in the corresponding vinyl sulfides. For example, the stable sulfonium ylide Xb was obtained when a solution of 1.0 g (6.6 mmol) of dimethyl diazomalonate in 5 mL of ethylthio-2-methyl-1-propene was heated at 120 °C for 2 h in the presence of anhydrous cupric sulfate (20 mg). Chloroform was added and the undissolved materials were separated from the reaction mixture. After the chloroform and excess vinyl sulfide were distilled off, the residue was chromatographed on a silica gel column with chloroform or acetone solvents to give Xb in 45% yield. The NMR and IR spectra and other physical properties are recorded in Table VI.

Photochemical Reactions of Phenyl- and Diphenyldiazomethanes. The photolysis of 0.4–2 mmol of phenyl- or diphenyldiazomethanes in 5–20 mmol of a substrate was carried out with a high-pressure mercury lamp in Pyrex tubes without degassing. After the diazo band disappeared from the IR spectrum of the reaction mixture, the reaction mixture was directly analyzed by gas chromatography. In the reaction of diphenyldiazomethane (0.445 g) in 1-methylthio-2-methyl-1-propene (2.31 g), the reaction mixture was analyzed by column chromatography on silica gel. The one of isolated fraction showed NMR spectrum at δ 2.63 which corresponds to $>S^+-Me$ protons.

General Procedure of Cupric Sulfate Catalyzed Thermal Reactions. Thermal reactions were carried out for 0.4–2 mmol of phenyl- and diphenyldiazomethanes in 5–15 mmol of a substrate in the presence of 20 mg of cupric sulfate. Samples were kept at room temperature or at 70 °C for 30 min. The results obtained are independent of the reaction conditions and shown in Table VII.

General Procedure of Thermal Reactions of Aryldiazomethanes. A similar reaction on the same scale was carried out without cupric sulfate. More violent conditions are required to complete the reactions. Samples of phenyldiazomethane were heated at 100 °C and of diphenyldiazomethane at 160 °C for 1 h. The products were examined by GLC.

Catalytic Decomposition of Methyl Diazoacetate in Acetylene Sulfides. A solution of 1 mmol of methyl diazoacetate in 5 mmol of acetylene sulfides with 20 mg of anhydrous cupric sulfate was sealed in Pyrex tubes and heated at 60 °C for 10 min. The reaction mixture was directly analyzed by gas chromatography.

Photolysis of Dimethyl Diazomalonate in Acetylene Sulfides. A solution of 1.2 mmol of dimethyl diazomalonate in 4 mmol of acetylene sulfide was irradiated. The reaction was 60% complete after 21 h. After the excess sulfide and diazomalonate were distilled off under the reduced pressure, the residue was analyzed by thin-layer chromatography. The major fraction was isolated and characterized by NMR and IR spectra and mass spectrum. The results were shown in Table VI.

Reaction of Dichlorocarbene with Vinyl Sulfides and Allylic Sulfides. A solution of 5 mL of 50% sodium hydroxide, 5 mL of benzene, 7 mL of chloroform, and 10 mmol of the corresponding sulfides was stirred rapidly in the presence of 0.2 g of benzyltriethylammonium chloride for 6 h. The reaction was completed when the solution became a strong brown color. The solution was diluted with water and acidified and extracted with petroleum ether. After the solution was dried and the solvent distilled off, the residue was directly analyzed by gas chromatography. The structures of the isolated products were determined by NMR and IR spectra and elemental analysis. The data are shown in Table VIII.

Registry No.—$R^1SR^2{=}CR^3R^4$ (R^1 = Et, R^2 = R^4 = H, R^3 = SEt), 14044-67-8; $R^1SR^2C{=}CR^3R^4$ (R^1 = R^3 = R^4 = Me, R^2 = H), 52101-04-9; $R^1SR^2C{=}CR^3R^4$ (R^3 = R^4 = Me, R^1 = Et, R^2 = H), 27482-14-0; $R^1SR^2C{=}CR^3R^4$ (R^1 = R^4 = Me, R^1 = Et, R^3 = H), 42954-19-8; $R^1SR^2C{=}CR^3R^4$ (R^2 = R^3 = H, R^1 = Et, R^4 = Me), 36784-55-1; $R^1SR^2C{=}CR^3R^4$ (R^3 = R^4 = Me, R^1 = *i*-Pr, R^2 = H), 63196-95-2; $R^1SR^2C{=}CR^3R^4$ (R^2 = R^3 = Me, R^1 = *i*-Pr, R^4 = H), 63269-82-9; $R^1SR^2C{=}CR^3R^4$ (R^3 = R^4 = Me, R^1 = *t*-Bu, R^2 = H), 63196-96-3; $R^1SR^2C{=}CR^3R^4$ (R^2 = R^3 = R^4 = H, R^1 = Ph), 1822-73-7; methyl diazoacetate, 6832-16-2; dimethyl diazomalonate, 6773-29-1; 2,3-dihydro-6-methyl-4*H*-thiapyran, 13042-79-0; 2,3-dihydro-1,4-dithiin, 23230-01-5; thiophene, 110-02-1; phenylethylthioacitylene, 14476-62-1; methylethylthioacetylene, 13597-15-4; 1,2-bisethylthioacetylene, 54045-21-5; phenyldiazomethane, 766-91-6; diphenyldiazomethane, 883-40-9; *tert*-butyl allylsulfide, 37850-75-2; chloroform, 67-66-3; allyl vinyl sulfide, 41049-25-6; dichlorocarbene, 1605-72-7; 1-phenylthio-2-methyl-1-propene, 13640-71-6; 1-sec-buthylthio-2-methyl-1-propene, 63196-68-9; 1-allylthio-2-methyl-1-propene, 63196-69-0.

References and Notes

(1) Paper 21 of The Chemistry of Carbene Series: W. Ando, A. Sekiguchi, and T. Migita, *Chem. Lett.*, 779 (1976).
(2) W. Ando, H. Higuchi, and T. Migita, *J. Chem. Soc., Chem. Commun.*, 523 (1974).
(3) W. Ando, K. Nakayama, K. Ichibori, and T. Migita, *J. Am. Chem. Soc.*, **91**, 5164 (1969).
(4) W. Ando, T. Yagihara, S. Kondo, K. Nakayama, H. Yamato, S. Nakaido, and T. Migita, *J. Org. Chem.*, **36**, 1732 (1971).
(5) C. Kaiser, B. M. Lester, C. L. Zirkle, A. Burnger, C. S. Davis, T. J. Delia, and L. Zirngible, *J. Med. Pharm. Chem.*, **5**, 1243 (1962).
(6) W. E. Parham, L. Christensen, and S. H. Groen, *J. Org. Chem.*, **29**, 2211 (1964).
(7) W. E. Parham, S. Kajigaeshi, and S. H. Groen, Bull. Chem. Soc. Jpn., **45**, 509 (1972).
(8) W. Ando, H. Fujii, T. Takeuchi, H. Higuchi, Y. Saiki, and T. Migita, *Tetrahedron Lett.*, 2117 (1973).
(9) W. Ando, T. Yagihara, and T. Migita, *Tetrahedron Lett.*, 1975 (1969).
(10) W. Ando, T. Yagihara, S. Tozune, and T. Migita, *J. Am. Chem. Soc.*, **91**, 2786 (1969).
(11) W. Ando, T. Yagihara, S. Tozune, and T. Migita, *Tetrahedron Lett.*, 1979 (1969).
(12) W. Ando, T. Yagihara, S. Tozune, I. Imai, J. Suzuki, T. Toyama, S. Nakaido, and T. Migita, *J. Org. Chem.*, **37**, 1721 (1972).
(13) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", Cornell

University Press, Ithaca, N.Y., 1969, p 87.
(14) W. Ando, M. Yamada, E. Matsuzaki, and T. Migita, *J. Org. Chem.*, **37**, 3791 (1972).
(15) W. E. Parham and S. H. Groen, *J. Org. Chem.*, **29**, 2214 (1964); **30**, 7285 (1965); **31**, 1694 (1966).
(16) M. Makosza and M. Wawrzyniewicy, *Tetrahedron Lett.*, 4659 (1969).
(17) N. E. Searle, "Organic Synthesis", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 424.
(18) R. A. Moss and U. H. Doering, *J. Am. Chem. Soc.*, **93**, 954 (1971).
(19) L. I. Smith and K. L. Howard, "Organic Synthesis", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 351.
(20) H. J. Boostra, L. Bradsma, A. M. Wiegman, and J. Arens, *Recl. Trav. Chim. Pays-Bas*, **78**, 252 (1952).
(21) A. H. Ford-Moore, R. A. Peters, and R. W. Wakelin, *J. Chem. Soc.*, 1754 (1949).
(22) W. Windus and D. R. Shildneck, "Organic Synthesis", Collect. Vol. II, Wiley, New York, N.Y., 1950, p 345.
(23) L. A. Cohen and J. A. Steele, *J. Org. Chem.*, **31**, 2333 (1966).
(24) W. E. Parham, J. Heberling, and H. Wynberg, *J. Am. Chem. Soc.*, **77**, 1169 (1955).
(25) L. Brandsma, H. E. Wijers, and C. Jonker, *Recl. Trav. Chim. Pays-Bas*, **83**, 208 (1964).

Synthesis of 1,2,3,5-Oxathiadiazole 2-Oxides from Amidoximes and Thionyl Chloride and the Mechanism of Their Thermally Induced Fragmentation and Rearrangement to Carbodiimides[1]

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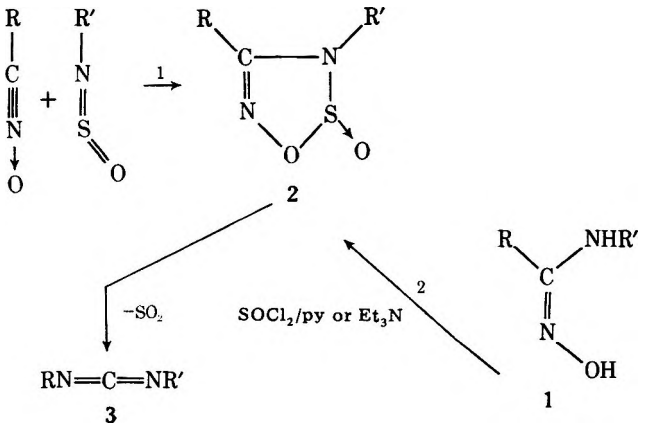
Received March 22, 1977

3,4-Disubstituted 1,2,3,5-oxathiadiazole 2-oxides **2** are prepared in good yields by cyclization of *N*-alkyl- and *N*-arylamidoximes **1** with thionyl chloride in the presence of triethylamine. The reaction provides a convenient route to heterocycles **2** as an alternative to the cycloaddition of *N*-sulfinylamines to nitrile oxides. 4-Aryl substituted heterocycles **2** decompose under mild thermal conditions to sulfur dioxide and carbodiimides **3**. Kinetic evidence as well as the failure to detect unstable intermediates by trapping experiments suggests that the conversion of **2** into **3** is a one-step process where the fragmentation and rearrangement occur concertedly via a single transition state.

The synthesis of 3,4-disubstituted 1,2,3,5-oxathiadiazole 2-oxides **2**, heterocycles of some interest as fungicides[3] and precursors of carbodiimides **3**, has been described by 1,3-dipolar cycloaddition of *N*-sulfinylamines to nitrile oxides[3,4] (route 1). Of the alternative entry to heterocycles **2** from amidoximes **1** and thionyl chloride in the presence of a tertiary



amine (route 2), a single example has been so far described[4b] in order to confirm the structure of the product **2** (R = *p*-$NO_2C_6H_4$, R′ = *p*-MeC_6H_4) obtained from the cycloaddition reaction.

As route 2 appeared a promising alternative to route 1, we have examined the cyclization of a number of *N*-alkyl- and *N*-arylamidoximes with thionyl chloride in order to define the scope and limitations of this reaction. We have then employed the easy thermal fragmentation of various oxathiadiazole 2-oxides for the preparation of carbodiimides and investigated the kinetics of the reaction as well as attempted trapping experiments in order to gain some insight into its mechanism.

Results and Discussion

Synthesis of Heterocycles 2. The cyclization of amidoximes **1a–r** with thionyl chloride in the presence of triethylamine occurred readily in methylene chloride below room temperature to give the corresponding 3,4-disubstituted 1,2,3,5-oxathiadiazole 2-oxides (**2a–r**) (Table I). Structural proof of new compounds was based on spectral data (IR, NMR,[5] and MS). Compounds **2a–k** and **2q** were isolated in good yields (70–90%), whereas other products were obtained in much lower yields or could not be isolated. For **2m–p** this can be explained by the observation (IR at 2140 cm^{-1}) that these compounds rearranged into the corresponding carbodiimides when the reaction mixture was allowed to warm up to room temperature. The low yield of **2l** was due to both its partial conversion to *N*-*tert*-butyl-*N*′-phenylcarbodiimide (**3g**) and to some reluctance of *N*-*tert*-butylbenzamidoxime (**1l**) to undergo the cyclization (see footnote *j* of Table I). Also **2r** was obtained in very low yield from *N*-*tert*-butyltrimethylacetamidoxime (**1r**) under the standard conditions (−15 or 0 °C, 1 h at room temperature), but its thermal stability allowed the reaction temperature to be raised to 10 °C, and the yield increased to an acceptable value (60%).

The yields were not optimized nor were the effects of changing solvent or the tertiary amine investigated in detail. However, it was observed that almost identical results were obtained when the cyclization of *N*-phenylbenzamidoxime (**1i**) was carried out in benzene solvent instead of methylene chloride and/or by using pyridine in place of Et_3N (Table I, footnote *h*).

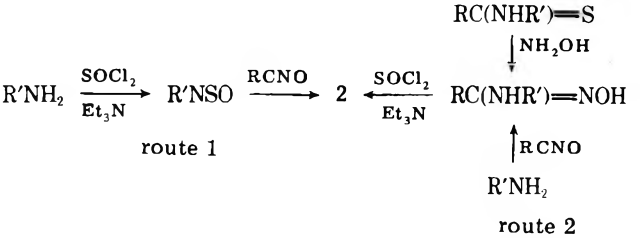
From the examples reported in Table I it appears that the cyclization of amidoximes with thionyl chloride can be conveniently employed for the synthesis of heterocycles **2** in a number of cases. This reaction offers several advantages with respect to the nitrile oxide–*N*-sulfinylamine cycloaddition (route 1), since: (i) it circumvents the preparation of *N*-sulfinylamines; (ii) it does not suffer from side reactions[4c] such as dimerization and isomerization of nitrile oxides,[6] and decomposition of *N*-sulfinylamines by moisture and air[7]; (iii) it occurs at low temperature, which is an important factor in view of the thermal instability of heterocycles **2**; (iv) it employes stable and easily available starting materials: *N*-sub-

Table I. 1,2,3,5-Oxathiadiazole 2-Oxides[a] 2 from Reaction of Amidoximes 1 and $SOCl_2$–Et_3N[b] in CH_2Cl_2

Compd 2	Registry no.	R	R′	Temp,[c] °C	Yield,[d] %	Crystn Solvent[e]	Mp,[f] °C	IR,[g] cm^{-1}
a	63105-00-0	*m*-ClPh	Ph	−10	84	Bz–PE	87–88	1360, 1210
b	63105-01-1	*p*-ClPh	Ph	−10	84	Bz–PE	87–88	1370, 1210
c	63105-02-2	*p*-CH_3Ph	Ph	−15	70	Bz–PE	93–94	1370, 1210
d	65105-03-3	*p*-CH_3OPh	Ph	−15	70	Bz–PE	91–92	1365, 1205
e	3815-53-0	Ph	*p*-CH_3OPh	−15	83	E–PE	93–94[i]	1370, 1205
f	63105-04-4	Ph	*p*-CH_3Ph	−15	82	E–PE	74–75	1365, 1205
g	63105-05-5	Ph	*p*-ClPh	−15	84	Bz–PE	82–83	1365, 1210
h	63105-06-6	Ph	*m*-ClPh	−15	85	Bz–PE	60–61	1360, 1210
i[h]	3815-50-7	Ph	Ph	−15	78	E–PE	74–75[i]	1370, 1210
j	63105-07-7	Ph	CH_3	−15	78	E–PE	58–59	1360, 1195
k	63105-08-8	CH_3	Ph	−15	80	E–PE	38–40	1370, 1205
l	63105-09-9	Ph	$(CH_3)_3C$	0	25[j]	E–PE	83–85	1370, 1205
m	63133-66-4	Mesityl	Ph	−15	*k*		*k*	1370, 1200
n	63133-67-5	Ph	Mesityl	0	24	PE	99–101	1365, 1205
o	63133-72-2	Mesityl	Mesityl	−5	*k*		*k*	1370, 1200
p	63105-10-2	2,4-$(CH_3)_2$Ph	Ph	−15	20	E–PE	64–65	1350, 1205
q	63105-11-3	2,6-Cl_2Ph	Ph	0	92	E–PE	92–93	1350, 1210
r	63105-12-4	$(CH_3)_3C$	$(CH_3)_3C$	10	60		*l*	1370, 1200

[a] Satisfactory analytical values for all new compounds (±0.3% for C, H, N, S). [b] Mole ratio amidoxime–$SOCl_2$–Et_3N 1:5:2.5. [c] Reaction temperature followed by warming to room temperature (1 h). [d] Based on the material recovered before recrystallization. [e] In acetone–carbon dioxide bath; Bz = benzene; PE = petroleum ether; E = ethyl ether. [f] Although determined in a preheated bath, the observed melting points may be lower than the actual values because of the thermal instability of the products. [g] In CCl_4–CS_2; attributable to [OS(O)N], see F. Wudl and T. B. K. Lee, *J. Am. Chem. Soc.*, **95**, 6349 (1973). [h] Obtained in 70–75% yield by using benzene solvent or benzene and $SOCl_2$–pyridine at 0 °C. [i] Reference 4a. [j] Allowed to stand at room temperature for 3 h; unreacted amidoxime was recovered. [k] Not determined because the product partly decomposed to carbodiimide at room temperature; identified by IR and TLC (silica, benzene). [l] Mass spectrum M^+ 218; oil impure of traces of carbodiimide.

stituted amidoximes can be prepared from two different routes, viz. from thioamides and hydroxylamine[8] or nitrile oxides and amines.[9] Finally it may be observed that the costs of the processes 1 and 2 are comparable, since they use the

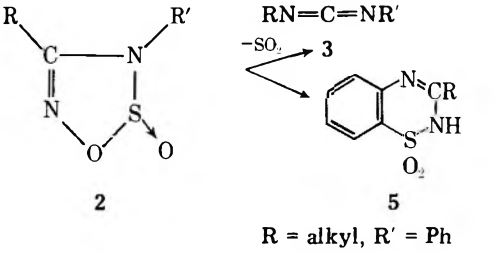


same commercial materials, although in a different succession of steps.

While the mechanism of the cyclization of amidoximes with $SOCl_2/Et_3N$ is unknown, its ready occurrence is consistent with the stereochemistry recently assigned to the most stable form of *N*-monosubstituted benzamidoximes in solution[10] and solid state,[11] viz. the *Z* configuration about the C=N bond (OH cis to NHR′) and the s-trans conformation about the amidic nitrogen (H of NHR′ faces the OH group). From the results of compounds **2l** and **2r**, the reaction appears somewhat retarded when the size of the groups R and R′ are increased. This parallels the observation[10] that bulky groups R and R′ give rise to a partial conformational change on the NHR′ group; this leads to the presence of the s-cis form which constitutes evidently an unfavorable arrangement for cyclization.

Thermal Decomposition of Heterocycles 2. A. Preparation of Carbodiimides 3. 3,4-Disubstituted 1,2,3,5-oxathiadiazole 2-oxides **2** have been reported to fragment at or just above their melting points to give carbodiimides **3** and sulfur dioxide when R is an aryl group[4] and/or undergo ring enlargement to 1,2,4-benzothiadiazine 1,1-dioxides[12] (**5**) when R is an alkyl and R′ an aryl group.

Our results on the thermal fragmentation of 4-aryl-1,2,3,5-oxathiadiazole 2-oxides (**2a–j** and **2l–q**) confirm the expectations based on previous findings[4] and give details on



R = alkyl, R′ = Ph

the preparation of a number of carbodiimides **3a–k** (Table II). The carbodiimides **3** yields were satisfactory (70–80%) with the exception of *N*-methyl-*N*′-phenylcarbodiimide (**3f**), whose low yield[13] is probably due to a considerable tendency to polymerize.[14] This demonstrates that the preparative value of this reaction depends on the stability of the carbodiimide at the temperature required for the fragmentation of its precursor. Carbodiimides which partly decompose on distillation were conveniently identified after conversion to the corresponding ureas **4**. In the same way, all compounds **3** of Table II could have been employed in situ for other reactions, their impurities being some polymeric material which, however, could be easily removed by dissolving the carbodiimide in a proper solvent, such as petroleum ether, and filtration.

For most of the heterocycles **2** the pyrolysis was carried out at 100–125 °C for 10–30 min. However, the two 4-mesityl derivatives **2m** and **2o** and the 4-(2,4-dimethylphenyl) derivative **2p** converted into the corresponding carbodiimides **3h, 3i,** and **3j** already at room temperature. This prevented the isolation of **2m** and **2o** from the originating reaction mixture of amidoximes **1h** and **1i** with thionyl chloride (see previous section and footnote *k* of Table I). Evidently, other factors being equal, the ease of conversion **2** → **3** depends on the migratory aptitude of R from carbon to nitrogen,[15] which appears to be favored when R is an aryl group with electron-donating substituents and inhibited when R is an alkyl group, particularly methyl. The latter observation accounts for the failure to obtain the carbodiimide **3f** from **2k** (R = CH_3, R′ = Ph)[13] and in general for the preferential formation of benzothiadiazines **5** when R is an alkyl group.[12]

Table II. Carbodiimides[a] 3 from the Thermolysis of 1,2,3,5-Oxathiadiazole 2-Oxides 2

Compd 3	Registry no.	Precursor 2	R	R′	Time, min	Temp, °C	Yield, %	Bp (mm) or mp, °C	IR (CCl_4), cm^{-1}	Urea 4, mp, °C	Registry no.
a	63105-13-5	a	*m*-ClPh	Ph	20	120	70[b]	*c*	2140	185–186	2008-71-1
a		h	Ph	*m*-ClPh	20	110	70[b]	*c*	2140	185–186	
b	53288-64-5	b	*p*-ClPh	Ph	15	120	80[b]	135–138 (0.2)	2140	240 dec	1967-26-6
b		g	Ph	*p*-ClPh	20	100	80[b]	*c*	2140	240 dec	
c	19244-07-6	c	*p*-CH_3Ph	Ph	20	100	85[b]	*c*	2140	217–218	4300-33-8
c		f	Ph	*p*-CH_3Ph	20	120	80[b]	*c*	2140	217–218	
d	3815-60-9	d	*p*-CH_3OPh	Ph	10	100	80[b]	*c*	2140	193–194	3746-53-0
d		e	Ph	*p*-CH_3O-Ph	30	125	80[b]	*c*	2140	193–194	
e	622-16-2	i	Ph	Ph	30	120	75	121–122 (0.5)	2140	239–240	102-07-8
f	4172-91-2	j	Ph	CH_3	30	110	20[b]	*d*	2140	150–151	1007-36-9
g	2219-34-3	l	Ph	$(CH_3)_3C$	15	100	88[b]	73–75 (760)	2120	167–168	15054-54-3
h	60986-29-0	m	Mesityl	Ph		*e*	82	145–158 (0.4)[c]	2150	236–237	2904-67-8
h		n	Ph	Mesityl	30	105	80	*c*	2150	236–237	
i	63105-14-6	o	Mesityl	Mesityl		*f*	77	41–41.5 (PE)	2160	310	6095-81-4
j	63105-15-7	p	2,4-$(CH_3)_2$-Ph	Ph	20	55	60[f]	oil[c]	2140	219–220	13140-55-1
k	63105-16-8	q	2,6-Cl_2Ph	Ph	30	115	89	46–47 (PE)	2160	240–241	63105-17-9

[a] All compounds 3 and the corresponding ureas 4 gave satisfactory analytical data (±0.3% for C, H, and N). [b] Determined after conversion to the corresponding urea by acid-catalyzed hydration (see Experimental Section). [c] Partly decomposed on distillation, giving material boiling in a large range of temperature. A pure sample was obtained by column chromatography (silica, benzene, or petroleum ether–methylene chloride 2:1). [d] Not isolated in a pure state. [e] At room temperature without isolation of the oxathiadiazole *S*-oxide (see Table I, footnote *k*); yields refer to the initial amount of amidoxime. [f] Obtained in 79% yield following the conditions of footnote *e*.

The selective thermal breakdown to carbodiimides and the mild conditions required appears to be a characteristic of 3,4-diaryl-1,2,3,5-oxathiadiazole 2-oxides **2**, since structurally related five-membered heterocycles behave differently. For instance, 3,4-diaryl-1,2,4-oxadiazolin-5-ones fragment at 260 °C into carbon dioxide and benzimidazoles,[16] whereas 1,5-diaryltetrazoles give mixtures of benzimidazoles and carbodiimides by loss of nitrogen at 200 °C.[17]

If we now look at the overall process **1** → **3**, we can conclude that the key step of this conversion is the formation of the heterocycle **2**, which activates the amidoxime **1** for the dehydration and rearrangement processes. The thermodynamic stability of the departing sulfur dioxide molecule is probably the driving force of the breakdown process. Similar examples of activation of hydroxamic acid derivatives through cyclic or open-chain intermediates include the thermal conversion of benzohydroxamic acids to isocyanates through their esters (Lossen rearrangement)[18] or through 1,3,2,4-dioxathiazole 2-oxides[19] and of amidoximes to carbodiimides by benzenesulfonyl chloride through the *O*-benzenesulfonyl ester[20] or by phosphorus oxychloride through a postulated phosphazole intermediate.[21]

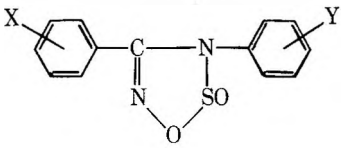
B. Mechanism of the Thermal Conversion 2 → 3. It has already been suggested[4a] that the thermolysis of heterocycles **2** to carbodiimides **3** is a concerted reaction, so that the loss of sulfur dioxide is concomitant with the migration of R from carbon to nitrogen. In order to gain further insight into the mechanism of the reaction, we have studied the kinetics of the thermal decomposition of 3,4-diaryl-1,2,3,5-oxathiadiazole 2-oxides (**2a–i**) and carried out proper experiments in order to exclude more justifiably the presence of unstable intermediates.

The reactions of **2a–i** were followed to at least 2 half-lives and were found to be of first-order throughout. In reactions allowed to proceed for infinite time, the values of conversion into carbodiimide varied from 80 to 95% (Table III), the lower yields being found in the slowest runs where the extent of polymerization of the carbodiimide became significant. Reactions at different initial concentrations of **2** gave reproducible first-order rate constants which exclude intermolecular processes or catalytic phenomena. The results of Table III illustrate the substituent effect on the reaction rate, which in fact appeared to be affected in opposite ways by substitution in the 3-phenyl (*N*-Ph) and 4-phenyl (*C*-Ph) ring. A plot of log *k* against σ^+ values[22] for substituents X in *C*-Ph fitted in a good straight line with negative slope ($\rho^+ = -1.92$, $r = 0.992$), whereas the plot against σ values[22] produced a less satisfactory correlation ($\rho = -3.04$, $r = 0.962$). The accelerating effect by electron-donating substituents X in the migrating aryl group R as well as its magnitude compare quite well to those observed in classical [1,2] shifts from carbon to nitrogen, such as in benzamides (Hofmann degradation $\rho = -2.5$),[23] in benzohydroxamic acid esters (Lossen rearrangement $\rho = -2.6$),[23] and in acetophenone oximes (Beckmann rearrangement $\rho = -1.95$, $\rho^+ = -1.70$).[23,24] On the other hand, a good correlation with a positive slope ($\rho = 0.61$, $r = 0.992$) was found to hold between log *k* and σ values for substituents Y in *N*-Ph, a result which points out that the reaction is retarded by electron-releasing, and accelerated by electron-withdrawing, substituents Y.

In Table IV are reported the data aiming to elucidate the effects of the solvent and temperature on the rate of decomposition of the representative compound 3,4-diphenyl derivative **2i**. The rate constant determined in four solvents of markedly different character changes little with the polarity of the solvent; the value in nitrobenzene ($\epsilon = 34.8$) was only about double that in chlorobenzene ($\epsilon = 5.62$). From the rate constants measured at different temperatures in chlorobenzene solvent the following activation parameters were calculated: $\Delta G^{\ddagger} = 27.9$ kcal mol^{-1}, $E_a = 28.1$ kcal mol^{-1}, $\Delta S^{\ddagger} = -1.4$ eu.

These kinetic results are consistent with a single-step mechanism and it is suggested that the [1,2] aryl shift[25] from carbon to the electron-deficient nitrogen[26] occurs intramolecularly in concert with the loss of sulfur dioxide in the transition state **a** (Scheme I). Owing to the simultaneous electron redistribution, the transition state **a** must possess little polarity, a characteristic which accounts for the slight dependence of the rate on the polarity of the solvent. The participation of the migrating aryl group in the transition state explains the substantial effect of substituents X on rate[27] and accounts for the low temperature of decomposition,[28] a fact

Table III. Rate Constants for the Thermal Decomposition of 3,4-Diaryl-1,2,3,5-oxathiadiazole 2-Oxides 2 in Chlorobenzene at 100 °C



2

Compd 2	X	Y	10^2 [2][a]	10^4k, s^{-1}	$t_{1/2}$, min	λ (ε),[b] cm^{-1}	Yield,[c] %
a	*m*-Cl	H	2.471	0.565		1360 (26.5)	
			4.910	0.570		1360	78
				mean 0.568	203		
b	*p*-Cl	H	2.685[d]	1.36		2140 (187.5)	81
			2.685[d]	1.36		1360 (27.8)	
			8.079	1.39		1370	
				mean 1.37	84		
c	*p*-CH_3	H	0.441	12.0		2140 (164.5)	81
			1.319	11.6		2140	
				mean 11.8	9.8		
d	*p*-CH_3O	H	0.403	83.5		2140 (158.5)	98
			1.207	82.0		2140	
				mean 82.8	1.4		
e	H	*p*-CH_3O	0.464	2.78		2140 (158.5)	82
			7.495	3.03		1365 (18.9)	97
				mean 2.91	40		
f	H	*p*-CH_3	0.446	2.94		2140 (164.5)	90
			1.324	2.88		2140	
				mean 2.91	40		
g	H	*p*-Cl	0.382	5.40		2140 (187.5)	96
			1.151	5.41		2140	
				mean 5.41	21		
h	H	*m*-Cl	5.442[d]	6.52		1360 (2(.5)	
			5.442[d]	6.47		2140 (186.7)	
			16.32	6.58		1360	92
				mean 6.52	18		
i	H	H		3.61[e]	32		

[a] At room temperature. [b] Analytical wavelength, molar extinction coefficient in parentheses (1-mm NaCl cell). [c] Of carbodiimide; determined from the absorbance at 2140 cm^{-1} after 5 or 6 half-lives. [d] Single run followed at two wavelengths. [e] Extrapolated from the Arrhenius parameters (Table IV).

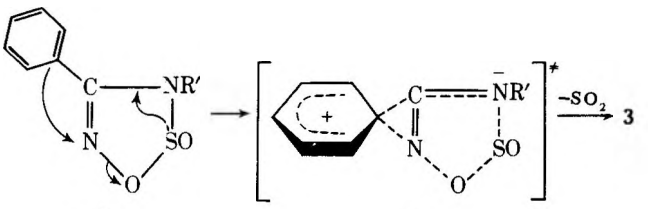
Table IV. Rate Constants[a] for the Thermal Conversion of 3,4-Diphenyl-1,2,3,5-oxathiadiazole 2-Oxide (2i) to Diphenylcarbodiimide (3e) in Various Solvents

Solvent[b]	Temp, °C	10^4k, s^{-1}	$t_{1/2}$, min	Yield,[c] %
Chlorobenzene (5.62)	70	0.134[d]	861	95
	86	0.823[d]	140	90
	90	1.28[d]	90	96
	110	9.90[d]	12	93
o-Dichlorobenzene (9.93)	86	0.966	119	92
Nitrobenzene (34.8)	86	2.21	52	92
Me_2SO (46.6)	86	6.6[e]	18	80

[a] Average of three runs with a standard error of ±2%; initial concentrations of **2i**: 0.004–0.02 M in chlorobenzene and dichlorobenzene [λ (ε), 2140 (187), 1-mm NaCl cell]; 0.009–0.04 M in nitrobenzene and Me_2SO [λ (ε), 2140 (182, 230), 0.5-mm NaCl cell]. [b] Dielectric constants in parentheses (ref 33). [c] Of carbodiimide **3e** (see footnote c of Table III). [d] The activation parameters calculated from these rate constants were: E_a = 28.1 ± 0.1 kcal mol^{-1}, $\Delta S^{\ddagger}$ (90 °C) = −1.4 ± 0.3 eu, $\Delta H^{\ddagger}$ (90 °C) = 27.4 ± 0.1 kcal mol^{-1}, $\Delta G^{\ddagger}$ (90 °C) = 27.9 ± 0.1 kcal mol^{-1}. [e] Inaccurate because of the slow reaction of **3e** with Me_2SO: J. G. Moffatt, *J. Org. Chem.*, **36**, 1909 (1971).

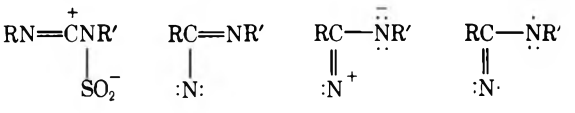
which is reflected in the moderate value of the activation energy (28 kcal mol^{-1}). Finally, the small negative entropy value (−1.4 eu), which is well comparable with those recorded for the Beckmann[24] and Curtius[29] rearrangements, is consistent with the transition state a, whereas a large positive value would be expected for the rate-limiting formation of an open-chain intermediate.[29]

Scheme I



2 a

In line with the kinetic data, trapping experiments failed to reveal the presence of open-chain intermediates. In fact, the amount of carbodiimide **3e** from the thermolysis of 3,4-diphenyl 1,2,3,5-oxathiadiazole 2-oxide (**2i**) was practically independent of the solvent employed[30] (Tables IV and V), whereas lower and/or variable yields were expected if intermediates **6** or **7** were formed, since it seems unlikely[25c,31] that



6 7a 7b 7c

they should not be at least partially trapped by any of the solvents employed. Moreover, while benzimidazoles, diagnostic for azomethine nitrene **7a**, are formed from the fragmentation of 3,4-diaryl-1,2,4-oxadiazolin-5-ones[32] and 1,5-diaryltetrazoles,[14] the presence of 2-phenylbenzimidazole was not detected by VPC of the reaction mixture from the thermolysis of **2i** in cyclohexane.

Table V. Thermal Fragmentation of 3,4-Diphenyl-1,2,3,5-Oxathiadiazole 2-Oxide (2i) in Various Solvents

Solvent	Time, h	Carbodiimide 3e, %[a]
None[b]		75
Cyclohexane	48	76
Anisole	24	81 (34)
Acetonitrile	20	79 (4)
Benzene (DMADC)[c]	24	70

[a] Number in parentheses refers to the amount of **3e** isolated as *N,N'*-diphenylurea. [b] See Table II. [c] Plus 15 molar excess with respect to **2i** of dimethyl acetylenedicarboxylate (DMADC).

In conclusion, the implication of our kinetic results and our failure to detect any unstable intermediates is that the decomposition of the heterocycles **2** to carbodiimides **3** and sulfur dioxide most probably occurs by a concerted process.

Experimental Section[33]

Reagents and Solvents. Thionyl chloride, amines, and solvents for preparative experiments were distilled or recrystallized before use. Triethylamine and pyridine were distilled twice over potassium hydroxide pellets. The petroleum ether corresponds to fraction bp 40–60 °C. Solvents for kinetic experiments were purified by proper procedures[34] and were distilled twice over anidrone just prior to use.

Amidoximes. These compounds were prepared by addition of amines to nitrile oxides. Details on the preparation of amidoximes **1b, 1f, 1t, 1i, 1j, 1m, 1n,** and **1q** have already been reported.[10] For the other compounds the reaction mixtures (CCl_4, 5 molar excess of amine) were allowed to stand at room temperature for 24–36 h. The excess of amine and by-products deriving from self-reaction of the nitrile oxide was removed by chromatography (silica), eluent benzene; the amidoxime was then recovered almost pure by elution with benzene–ethyl ether (9:1 or 9:2). After recrystallization from benzene–petroleum ether, unless not otherwise noted, all compounds gave satisfactory analytical data and IR spectra (CCl_4–C_2Cl_4–CS_2), showing the characteristic bands at 3600 (OH), 3400 (NH), ~3300 br (OH), and 1630 cm^{-1} (C=N): **1a** (R = *m*-ClPh, R' = Ph), mp 131–132 °C; **1c** (R = *p*-CH_3Ph, R' = Ph), mp 124–125 °C; **1d** (R = *p*-CH_3OPh, R' = Ph), mp 121–122 °C; **1e** (R = Ph, R' = *p*-CH_3OPh), mp 160–162 °C; **1h** (R = Ph, R' = *m*-ClPh), mp 129–130 °C (from ethanol); **1k** (R = CH_3, R' = Ph), mp 117–118 °C (from benzene); **1l** [R = Ph, R' = $(CH_3)_3C$], mp 129–130 °C (from methanol); **1o** (R = R' = mesityl), mp 198–200 °C; **1p** [R = 2,4-$(CH_3)_2$Ph, R' = Ph], mp 163–164 °C; **1r** [R = R' = $(CH_3)_3C$], mp 134–135 °C (from ethanol).

1,2,3,5-Oxathiadiazole 2-Oxides 2. The cyclizations were carried out in a four-neck 1-L flask equipped with a stirrer, a thermometer, an addition funnel, and a gas outlet tube protected with a $CaCl_2$ valve. The solution of the amidoxime 1 (18–30 mmol) and 2.5 molar excess of triethylamine in 250–300 mL of methylene chloride was cooled at the required temperature (Table I) in the reaction flask. To this mixture was added with efficient stirring over a 15-min period a 5 molar excess of thionyl chloride in 20 mL of methylene chloride. The mixture was allowed to warm to room temperature (1 h) and then 250 mL of a 10% solution of $NaHCO_3$ in water was added with vigorous stirring and cooling. The heterogeneous mixture was stirred for an additional 30-min period and then allowed to stand until the two phases were well separated. The organic phase was washed with cold water and dried over $CaSO_4$. Evaporation of the solvent under reduced pressure at room temperature gave an oil which solidified on treating with petroleum ether and cooling in an acetone–carbon dioxide bath. In the case of compounds **2m, 2o,** and **2p** the oil residue showed the presence of a considerable amount of carbodiimide (IR absorption at 2140 cm^{-1}). Details of the experimental conditions and properties of compounds **2** are given in Table I.

Thermolysis of 1,2,3,5-Oxathiadiazole 2-Oxides 2 to Carbodiimides 3. A. Preparative Scale. A 25-mL thick wall vial was charged with 2.0 g of **2** and connected to a vacuum system. When the vacuum was regulated at 100–120 mmHg, the vial was carefully placed in a preheated oil bath. This produced an almost instant melting of the solid material and an intense gas evolution, which ceased within a few minutes. Heating under slight vacuum was continued for an additional period (Table II). After cooling the vial to room temperature, proper tests (TLC and IR) on the oil residue showed the total disappearance of **2** (absence of the 1360–1370-cm^{-1} band) and the formation of **3** (IR absorption at 2140–2160 cm^{-1}). All carbodiimides **3** were identified after conversion to the corresponding ureas **4** by heating the oil residue on a steam bath (1 h) with 25 mL of 20% HCl. The N,N'-disubstituted ureas **4**, which simply crystallized on cooling, exhibited the expected IR (Nujol) bands [3300 (NH) and 1650 cm^{-1} (CONH)] and gave satisfactory analytical data. Comparisons with authentic samples were also made.

B. Trapping Experiments. Solutions of 3,4-diphenyl 1,2,3,5-oxathiadiazole 2-oxide (**2i**) (1.5–2.0 g) in the selected solvent (40 mL) were refluxed with exclusion of the moisture till the total disappearance on TLC. The solvent was evaporated under reduced pressure and the residue was chromatographed (silica, benzene) to give the carbodiimide **3e** and then the corresponding urea (eluent, benzene–ethyl ether 1:1) (Table V).

C. Kinetic Measurements. The reactions were initiated by adding a weighed amount (0.02–0.2 g) of the selected compound **2** in a small thin-wall vial to the preheated solvent (20–50 mL) which was contained in a kinetic flask placed in a thermostatted oil bath. Aliquots were removed at intervals and quenched by cooling in liquid nitrogen. The kinetics were followed spectroscopically by monitoring the carbodiimide at 2140 cm^{-1} or the unreacted oxathiadiazole 2-oxide at 1360 cm^{-1} or both compounds. In the first case, in order to have measurable absorbance values (1- or 0.5-mm NaCl cells), the aliquots were diluted with the same solvent employed for the reaction. In the second case, the solvent of the aliquots was removed under vacuum at room temperature and the residue dissolved in carbon tetrachloride for the IR measurements. Normally, 10–15 readings were taken for a given reaction, which was followed to at least 2 half-lives. First-order rate constants were calculated from linear plots of ln C_t vs. time (C_t, concentration of **2**) or more simply of ln A_t at 1360 cm^{-1} vs. time. For reactions followed through the 2140-cm^{-1} band, the C_t values were calculated from $(C_0 - x)$, where C_0 was the initial concentration of **2** and x the concentrations of the carbodiimide calculated from the measured absorbances by the Lambert–Beer law. Control experiments showed: (i) the stability of the carbodiimide for at least 2 half-lives of a given reaction; (ii) the occurrence of the Lambert–Beer law at the analytical wavelengths in the range of concentrations employed.

The activation parameters were calculated by standard method:[35] E_a from the linear plot of ln k vs. $1/T$ (Table IV), $\Delta S^{\ddagger}$ from log A (13.0 s^{-1} at 90 °C), $\Delta H^{\ddagger}$ from the approximation $\Delta H^{\ddagger} = (E_a - RT)$, and $\Delta G^{\ddagger}$ from $\Delta H^{\ddagger} - T\Delta S^{\ddagger}$.

Acknowledgment. This research was entirely carried out at the C.N.R. Laboratory of Ozzano Emilia, which is gratefully acknowledged for the financial support to one of us (A.D.). We are grateful to Miss Patrizia Giorgianni (C.N.R. Laboratory) for the able technical assistance in kinetic experiments.

Registry No.—**1a,** 63163-64-4; **1b,** 28051-07-2; **1c,** 57984-77-7; **1d,** 60404-64-0; **1e,** 52395-23-0; **1f,** 36954-50-4; **1g,** 57767-05-2; **1h,** 63133-68-6; **1i,** 3488-57-1; **1j,** 28267-98-3; **1k,** 5661-30-3; **1l,** 20002-26-0; **1m,** 3023-19-6; **1n,** 36954-51-5; **1o,** 16031-60-0; **1p,** 63133-69-7; **1q,** 63133-70-0; **1r,** 63133-71-1; $SOCl_2$, 7719-09-7; H_2NR' (R' = Ph), 62-53-3; H_2NR' (R' = *p*CH_3OPh), 104-94-9; H_2NR' (R' = *m*-ClPh), 108-42-9; H_2NR' (R' = *t*-Bu), 75-64-9; H_2NR' (R' = mesityl), 88-05-1; O=N≡CR (R = *m*-ClPh), 13820-15-0; O=N≡CR (R = *p*CH_3Ph), 13820-14-9; O=N≡CR (R = *p*-CH_3OPh), 15500-73-9; O=N≡CR (R = Ph), 873-67-6; O=N≡CR (R = CH_3), 7063-95-8; O=N≡CR (R = mesityl), 2904-57-6; O=N≡CR [R = 2,4-$(CH_3)_2$Ph], 63105-18-0; O=N≡CR (R = *t*-Bu), 27143-81-3.

References and Notes

(1) Presented in part at the 7th International Symposium on Organic Sulfur Chemistry, Hamburg, West Germany, July 12, 1976.
(2) (a) University of Ferrara; (b) C. N. R. Laboratory.
(3) E. E. Schmitt, U.S. Patents 3 118 902 and 3 118 903 (1964); *Chem. Abstr.*, **60,** 1069 1h and 10692b (1964).
(4) (a) P. Rajagopalan and H. U. Daeniker, *Angew. Chem., Int. Ed. Engl.*, **2,** 46 (1963); P. Rajagopalan and B. G. Advani, *J. Org. Chem.*, **30,** 3369 (1965); (b) F. Eloy and R. Lenaers, *Bull. Soc. Chim. Belg.*, **74,** 129 (1965); (c) P. Beltrame and C. Vintani, *J. Chem. Soc. B*, 873 (1970).
(5) The ^1H NMR spectrum ($CDCl_3$, Me_4Si) of 3-mesityl-4-phenyl derivative **2n** showed the following features: three methyl signals at δ 2.06, 2.18, and 2.23, two broad signals at δ 6.75 and 6.83, and a multiplet centered at δ 7.25. The magnetic nonequivalence of the two *o*-methyls and the two *m*-hydrogens of the mesityl ring indicates that these groups are diastereotopic owing to the presence of center(s) of asymmetry in the molecule. This stereochemical problem is now under investigation.
(6) C. Grundmann and P. Grunanger, "The Nitrile Oxides", Springer-Verlag, New York, N.Y., 1971, Chapter 4.
(7) G. Kresze, A. Maschke, R. Albrecht, K. Bederke, H. P. Patzschke, H. Smalla, and A. Trede, *Angew. Chem., Int. Ed. Engl.*, **1,** 89 (1962); G. Kresze and W. Wucherpfenning, *ibid.*, **6,** 149 (1967).

(8) H. Muller, *Ber. Dtsch. Chem. Ges.*, **19**, 1669 (1886); P. Chabrier and S. H. Renard, *Bull. Soc. Chim. Fr., Doc.*, 272 (1949); R. N. Hurd and G. De La Mater, *Chem. Rev.*, **61**, 45 (1961).
(9) Reference 6, p 161.
(10) O. Exner, V. Jehlička, A. Dondoni, and A. C. Bolcelli, *J. Chem. Soc., Perkin Trans. 2*, 567 (1974); A. Dondoni, L. Lunazzi, P. Giorgianni, and D. Maciantelli, *J. Org. Chem.*, **40**, 2979 (1975).
(11) A. Dondoni, G. Gilli, and M. Sacerdoti, *J. Chem. Soc., Perkin Trans. 2*, 1036 (1976).
(12) F. Eloy, *Helv. Chim. Acta*, **48**, 380 (1965).
(13) The Carbodiimide **3f** was obtained from 3-methyl-4-phenyl-1,2,3,5-oxathiadiazole 2-oxide (**2j**), since the 3-phenyl-4-methyl derivative **2k** gave mainly tarry material which, however, was not further examined for the presence of the 1,2,4-benzothiadiazine 1,1-dioxide.[12]
(14) H. G. Khorana, *Chem. Rev.*, **53**, 145 (1953); S. R. Sandler and W. Karo, "Organic Functional Group Preparations", Vol. 2, Academic Press, New York, N.Y., 1972, Chapter 9.
(15) In a [1,2] shift to an electron-deficient center, the migratory aptitude of a group R is aryl > alkyl > H and this "expresses the familiar order of carbonium ion stabilization". See J. B. Hendrickson, D. J. Cram, and G. S. Hammond, "Organic Chemistry", 3rd ed, McGraw-Hill, New York, N.Y., 1970.
(16) T. Bacchetti and A. Alemagna, *Gazz. Chim. Ital.*, **91**, 1475 (1961), and previous papers on this series.
(17) P. A. S. Smith and E. Leon, *J. Am. Chem. Soc.*, **80**, 4647 (1958); J. Vaughan and P. A. S. Smith, *J. Org. Chem.*, **23**, 1909 (1958).
(18) L. Bauer and O. Exner, *Angew. Chem., Int. Ed. Engl.*, **13**, 376 (1974).
(19) (a) E. Burk and D. Carlos, *J. Heterocycl. Chem.*, **7**, 177 (1970); (b) J. E. Franz and H. K. Pearl, *J. Org. Chem.*, **41**, 1297 (1976). Evidence has been recently provided[19b] showing that in addition to the concerted mechanism previously postulated[19a] the formation of isocyanate from 1,3,2,4-dioxathiazole 2-oxides may occur by a multi-step process involving an intermediate nitrile oxide. For leading references on nitrile oxide–isocyanate isomerization see ref 6 and A. Dondoni, G. Barbaro, A. Battaglia, and P. Giorgianni, *J. Org. Chem.*, **37**, 3196 (1972); C. Grundmann, P. Kochs, and J. R. Boal, *Justus Liebigs Ann. Chem.*, **761**, 162 (1972).
(20) J. H. Boyer and P. J. A. Frints, *J. Org. Chem.*, **35**, 2449 (1970).
(21) J. Garapon and B. Sillion, *Bull. Soc. Chim. Fr.*, 2672 (1975); J. Garapon, B. Sillion, and J. M. Bonnier, *Tetrahedron Lett.*, 4905 (1970).
(22) L. P. Hammett, "Physical Organic Chemistry", 2nd ed, McGraw-Hill, New York, N.Y., 1970, p 356.
(23) J. Hine, "Physical Organic Chemistry", McGraw-Hill, New York, N.Y., 1962, Chapter 15.
(24) D. E. Pearson, J. F. Baxter, and J. C. Martin, *J. Org. Chem.*, **17**, 1511 (1952).
(25) (a) Review on [1,2] shifts: G. W. Wheland, "Advanced Organic Chemistry", 3rd ed, Wiley, New York, N.Y., 1960, Chapter 12; (b) G. L'abbé, *Chem. Rev.*, **68**, 345 (1968); (c) W. Lwowski, *Angew. Chem., Int. Ed. Engl.*, **6**, 897 (1967); (d) H. Meier and D. P. Zeller, *ibid.*, **14**, 32 (1975); (e) ref 18.
(26) For a concise and exhaustive description of the mechanism of the suprafacial thermally allowed [1,2] shift to an electron-deficient center, see G. Klopman in "Chemical Reactivity and Reaction Paths", G. Klopman, Ed., Wiley, New York, N.Y., 1974, Chapter 4, p 96.
(27) The *C*-Ph substituent effect is very similar to those of the classical examples of [1,2] shifts cited in ref 23 and 24 and which are currently considered to occur with phenyl participation in the transition state. Moreover, an identical trend with that reported here has been taken as evidence for concerted thermolysis of triarylmethyl azides, in contrast to the photochemical reaction where substituents have little, if any, effect and which probably involves a discrete nitrene intermediate [W. H. Saunders, Jr., and E. A. Caress, *J. Am. Chem. Soc.*, **86**, 861 (1964)]. By contrast, in the thermal fragmentation of 2,5-diaryltetrazoles to 1,3-nitrile imines, a case of decomposition of a heterocyclic system without aryl migration, the *C*-Ph substituent effect is very small ($\rho = -0.23$) [S. Y. Hong and J. E. Baldwin, *Tetrahedron*, **24**, 3787 (1968)]. For a survey on this subject see O. P. Strausz, J. W. Lown, and H. E. Gunning, *Compr. Chem. Kinet.*, **5**, Chapter 5 (1972).
(28) Structurally related systems, i.e., 3,4-diaryl-1,2,4-oxadiazolin-5-ones[13] and 1,5-diaryltetrazoles,[14] which at least partly decompose by mechanisms where there is no anchimeric assistance by the migrating aryl group, fragment at much higher temperatures.
(29) G. L'abbé and g. Mathys, *J. Org. Chem.*, **39**, 1778 (1974); G. L'abbé, G. Mathys, and S. Toppet, *ibid.*, **39**, 3449 (1974).
(30) Also the thermolysis of the 3-mesityl-4-phenyl derivative **2n** in benzene gave a yield (75%) of carbodiimide **3h** similar to that obtained without solvent (Table II). In benzene, however, there was also isolated a product (5%), mp 239–244 °C, whose structure is still under investigation.
(31) D. S. Breslow, M. F. Sloan, N. R. Newburg, and W. B. Renfrow, *J. Am. Chem. Soc.*, **91**, 2273 (1969); W. Lwowski, "Nitrenes", Interscience, New York, N.Y., 1970.
(32) J. H. Boyer and P. J. A. Frints, *J. Heterocycl. Chem.*, **7**, 59 (1970); J. Sauer and K. K. Mayer, *Tetrahedron Lett.*, 325 (1968).
(33) All temperatures are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrometer which was also employed for measuring IR absorptions in kinetic experiments. NMR spectra were recorded with a JEOL 60-MHz instrument in CCl_4 or $CDCl_3$ with Me_4Si as an internal standard. Mass spectra were obtained on a Varian MAT 111 low-resolution mass spectrometer. TLC were done on silica gel plates (IB2-F from Backer Chemical Co.) using benzene or mixtures of benzene–ethyl ether as eluent. Microanalyses were performed by F. B. Strauss Microanalytical Laboratory, Oxford, England.
(34) J. A. Riddick and E. E. Toops, Jr., *Tech. Org. Chem., 2nd Ed.*, **7** (1967); D. Martin and H. G. Hauthal, "Dimethyl Sulphoxide", translated by E. S. Halberstadt, Van Nostrand, Wokingham, England, 1975.
(35) S. Glasstone, K. J. Laidler, and H. Eyring, "The Theory of Rate Processes", McGraw-Hill, New York, N.Y., 1941, Chapter 6.

Condensation of Aldehydes with Methylimidazo[1,2-*a*]pyridines

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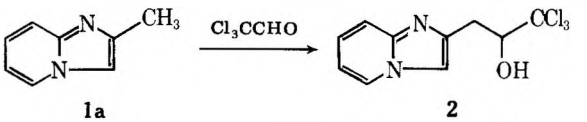
Received April 5, 1977

The reactions of various methylimidazo[1,2-*a*]pyridines (1) with acetaldehyde and chloral follow the usual course of electrophilic substitution at the 3 position, contrary to an earlier report of condensation at a methyl group. Initially formed adducts **6a–c** and **8** give secondary products, **5a–c**, **7a–c**, and **9**. Unusual IR, UV, and ^{1}H NMR spectral properties of the dichloro ketone **9** and the aldehyde **12**, which was formed by treating the chloral adduct **8** with strong base, are discussed.

The reported reaction[1] of the methyl group in 2-methylimidazo[1,2-*a*]pyridine (**1a**) with chloral to give the condensation product **2** must proceed via the anion **3**. Facile formation of such an anion, however, is incompatible with our finding that 7-methylimidazo[1,2-*a*]pyridine, which is expected to give a more stable anion (see **4**), does not readily give such an anion as shown by its failure to be oxidized to the aldehyde by selenium dioxide.[2] Further, reactions of imidazo[1,2-*a*]pyridine with other electrophilic reagents[3] generally occur at position 3. The reactivity of the methyl group in compound **1**, and concomitant correctness of structure **2**, therefore become questionable. The condensation of acetaldehyde with various methylimidazo[1,2-*a*]pyridines as



1a **2**

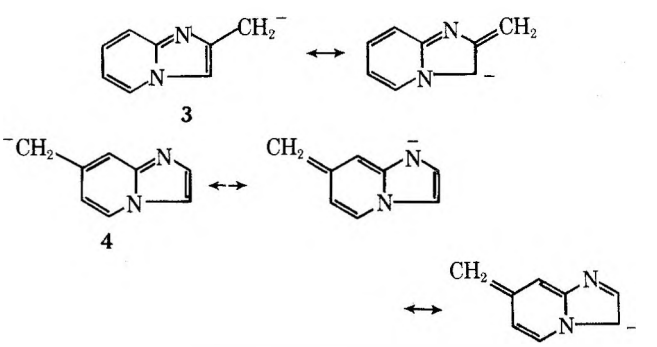
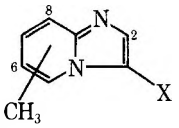
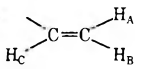
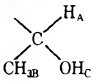
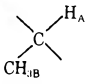


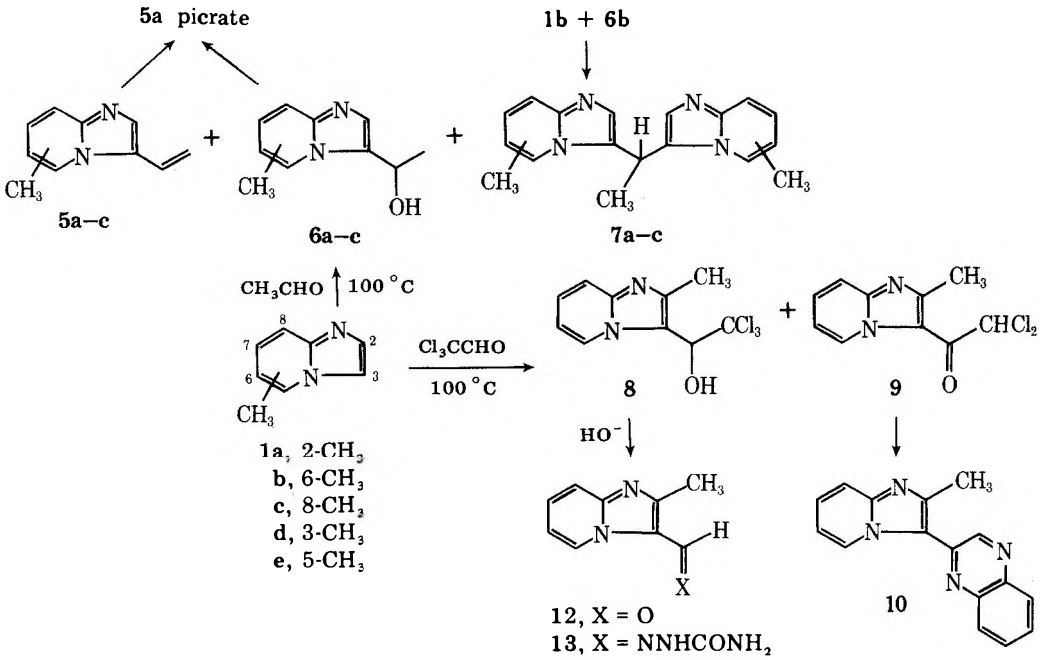
Table I. ^{1}H NMR Chemical Shifts (δ, ppm) of Some Imidazo[1,2-*a*]pyridines in $CDCl_3$[a]



			Registry no.	CH_3	H-2	H-3	H-5	H-6	H-7	H-8	H-A	H-B	H-C
X = H	2-CH_3	1a	934-37-2	2.42		7.27	7.97	6.64	7.04	7.48			
	6-CH_3	1b	874-38-4	2.27	7.54	7.45	7.85		6.95	7.49			
	8-CH_3	1c	874-10-2	2.63	7.62	7.56	7.98	6.66	6.94				
X = 	2-CH_3	5a	63076-78-8	2.56			8.17	6.84	7.16	7.56	5.60	5.45	6.87
	6-CH_3	5b	63076-66-4	2.32	7.71		7.89		6.99	7.49	5.68	5.29	6.76
	8-CH_3	5c	63076-67-5	2.62	7.77		8.03	~6.78	~7.00		5.75	5.34	~6.81
X = 	2-CH_3	6a	30489-51-1	2.08			8.49	6.71	7.08	7.40	5.23	1.63	4.42
	6-CH_3	6b	63076-68-6	2.32	7.10		8.16		6.99	7.35	5.09	1.70	4.23[c]
	8-CH_3	6c	63076-69-7	2.50	7.01		8.23	6.68	6.95		5.06	1.66	4.40
X = 	2-CH_3[b]	7a	63076-70-0	2.20			8.52	6.80	7.10	7.52	4.77	1.62	
	6-CH_3	7b	63076-71-1	2.26	7.46		7.64		7.03	7.47	4.70	1.92	
	8-CH_3	7c	63076-72-2	2.63	7.52		7.69	6.62	6.97		4.71	1.94	

[a] Relative to internal Me_4Si. Typical coupling constants: $J_{5,6} = 6$; $J_{6,7} = 6$; $J_{7,8} = 8$–10 Hz. For X = vinyl: $J_{A,B} \sim 1$; $J_{A,C} = 17$-18; $J_{B,C} = 12$ Hz. For X = $CH(OH)CH_3$: $J_{A,B} = 6$ Hz. For X = $CHCH_3$: $J_{A,B} = 7$ Hz. [b] Chemical shifts obtained from spectrum of a mixture containing compound **5a**. [c] Disappears upon addition of D_2O.

Scheme I



well as that of chloral with 2-methylimidazo[1,2-*a*]pyridine are the subject of this paper.

Results and Discussion

Condensation with Acetaldehyde. Prolonged heating of a mixture of 2-, 6-, or 8-methylimidazo[1,2-*a*]pyridine (**1a, b,** or **c**) with excess acetaldehyde at 100 °C gives in each case, besides starting material, three products. Their structures, established by mass spectral, ^{1}H NMR (see Table I), and elemental analyses, are **5a–c**, **6a–c**, and **7a–c** (see Scheme I). Compounds **5a–c**, low-melting, hygroscopic solids, were analyzed as picrates. ^{1}H NMR spectra show that reaction has not occurred at the CH_3 groups and that a vinyl substituent[4] has been introduced in the five-membered ring. Since the 2-CH_3 compound **1a** gives **5a**, substitution must have taken place at position 3.

Mass spectra of compounds **6a–c** indicate facile loss of water (base peak, $M^+ - 18$) and ^{1}H NMR spectra support these structures.[5] Further, compound **6a** gives the same picrate as the vinyl compound **5a**. Since loss of water from the α-ethanol compounds (**6a–c**) is relatively facile even under neutral conditions (cf. formation of the vinyl compounds **5a–c** during the aldehyde condensation), dehydration under acid conditions is expected.

Structures **7a–c** were established as follows. While mass spectra of the starting materials **1a–c** do not show peaks attributable to loss of a CH_3 group, the very intense base peak ($M^+ - 15$) in the spectrum of compound **7b** indicates that one CH_3 group is readily lost. Formation of a dipicrate from compound **7b** demonstrates the presence of two noninteracting imidazopyridine ring systems. An integrated ^{1}H NMR spectrum of compound **7b** shows that two 6-methylimidazo[1,2-*a*]pyridine moieties are present for one $CHCH_3$ group, but the position of substitution cannot unambiguously be established from this spectrum, since the chemical shift of the peak assigned to H-5 appears at sufficiently high field to fall in the region where H-3 usually absorbs. That structure **7b** is indeed correct is shown by the ^{1}H NMR spectrum of the

Table II. ^{1}H NMR Chemical Shifts[a] (δ, ppm) of Picrates of Some Imidazo[1,2-*a*]pyridines in Me_2SO-d_6

	H-2,3	H-5	H-6	H-7,8	picrate-H
7b	8.08	8.72		7.95	8.61
1b	8.32, 8.20	8.77		7.91	8.63
5a		8.95	7.54	7.97	8.60

[a] Relative to internal Me_4Si. Chemical shifts of other protons: **7b**, 1.87 (d, J = 7, CH_3), 2.45 (s, CH_3), 5.19 (q, CH); **1b**, 2.45 (s, CH_3); **5a**, 2.61 (s, CH_3), 5.80 (d, J = 12), 5.92 (d, J = 18), 7.12 (q) for vinyl group.

protonated compound, i.e., the dipicrate (see Table II). The spectrum now shows a low-field singlet that can only be due to H-5 and has a chemical shift similar to those of H-5 in the picrates of the parent **1b** and the 2,3-disubstituted compound **5a**.

When the acetaldehyde condensation with 3- and 5-methylimidazo[1,2-*a*]pyridine (**1d** and **e**) was attempted, no reaction occurred. While this was expected for the 3-CH_3 compound **1d**, the lack of reactivity of the 5-CH_3 compound **1e** must be attributed to steric hindrance, the peri effect well-known in other multiple ring systems. It should be noted that compound **1e** does react with other electrophilic reagents, such as nitric acid[6] and bromine,[3a] to give 3-substituted products. These reactions, however, are in general very much more facile, require short reaction times, and take place at less than or at room temperatures.

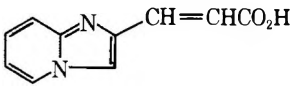
Thus, the reaction of acetaldehyde with imidazo[1,2-*a*]-pyridines proceeds by substitution at the 3 position to give adducts **6**, which can subsequently either form the vinyl compounds **5** by loss of water or condense with another molecule of starting materials (**1**) to give compounds **7**. When a mixture of compounds **6b** and **1b** is heated at 95 °C overnight, compound **7** is indeed formed. Alternate formation of compounds **7** from the vinyl compounds **5** and **1** cannot be excluded.

The Chloral Reaction. When 2-methylimidazo[1,2-*a*]-pyridine (**1a**) was treated with chloral as reported[1] (see, however, Experimental Section), two products were obtained. One of them forms a hydrochloride salt which shows the same melting behavior and analysis as reported[1] for compound **2**·HCl, and is stable toward refluxing ethanolic HCl. Its mass spectrum, however, does *not* contain peaks attributable to $M^+ - OH$ or $M^+ - H_2O$, which are mandatory[7] for structure **2**. This compound has in fact structure **8** (see Scheme I), and the other product has structure **9**.

The ^{1}H NMR spectrum (see Table III) of the adduct **8** clearly indicates that reaction has taken place at the 3 position. The considerably greater deshielding of H-5 in the adduct relative to the starting material **1a** is in accord with anisotropic effects of 3-substituents on H-5. The absence of deshielding of the CH_3 group implies restricted rotation of the $-CH(OH)CCl_3$ group.

Structure **9** is derived from the adduct **8** by loss of HCl followed by tautomerization. Formation of a quinoxaline derivative (**10**) establishes the presence of the $COCHCl_2$ group. Comparison of its ^{1}H NMR spectrum with that of imidazo-[1,2-*a*]pyridine-3-carboxaldehyde[8] shows that the $COCHCl_2$ group is indeed attached at the 3 position. All relevant protons are deshielded as compared to those of both the adduct **8** and the starting material **1a**, in accord with the presence of the strongly electron-withdrawing group. Other spectral properties of compound **9** are discussed below.

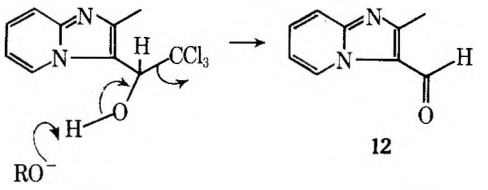
Lombardino[1] reported that treatment of the chloral adduct (**2**) with base, followed by acid, affords the acrylic acid **11**. In



11

our hands, the chloral adduct (with established structure **8**), when subjected to the described severe conditions, gives a compound which has the same melting point and ultraviolet absorption maxima[9] as reported for compound **11**. Its analysis, however, differs from that reported by the elements of CO, and its structure is **12**·HCl. The free base **12** gives a positive Tollens' test, forms a semicarbazone **13**, and displays a ^{1}H NMR spectrum (see Table III) that now approximates that of imidazo[1,2-*a*]pyridine-3-carboxaldehyde except for replacement of the H-2 singlet by a three-proton CH_3 singlet.

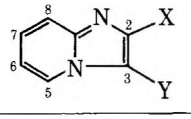
The reaction of the adduct **8** with strong base is envisioned to proceed by abstraction of a proton from the OH group and cleavage as shown. Formation of this product appears to de-

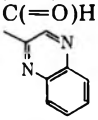


12

pend on the conditions used. Thus, trichloromethylphenylcarbinol, when boiled with water gives phenylhydroxyacetic acid, but when boiled with saturated potassium hydroxide solution, chloroform, benzaldehyde, and mandelic acid are formed.[11] Hydrolysis with dilute base of other trichloromethylcarbinols leads to hydroxyacetic acids,[12] which can only be converted to aldehydes by oxidation.[13] In our hands appreciably more aldehyde (75 vs. 43%) was obtained in very concentrated solution than in more dilute solution. For the latter conditions, concurrent formation of 3-imidazo-[1,2-*a*]pyridylhydroxyacetic acid, which could not be isolated

Table III. ^{1}H NMR Chemical Shifts[a] (δ, ppm) of Some Imidazo[1,2-*a*]pyridines in $CDCl_3$



		Registry no.	H-5	H-6	H-7	H-8	X	Y
1a,	X = CH_3; Y = H		7.97	6.64	7.04	7.48	2.42	7.27
8,	X = CH_3; Y = $CH(OH)CCl_3$	63076-73-3	9.07	6.78	7.16	7.35	2.32	5.66
9,	X = CH_3; Y = $C(=O)CHCl_2$	63076-74-4	9.79	7.18	7.66[b]	7.66[b]	2.92	6.85
	X = H; Y = $C(=O)H$[c]		9.60	7.11	7.55	7.81	8.33	9.95
12,	X = CH_3; Y = $C(=O)H$	30384-93-1	9.59	7.11	7.55	7.71	2.75	10.08
10,	X = CH_3; Y = 		9.84	7.00	7.40	7.71	2.90	9.28 (s)[d] 8.15, 7.91[e]

[a] X and Y substituents give sharp singlets, except as noted; H-5 and H-8 are doublets showing further fine splitting; H-6 is a triplet; H-7 is an unsymmetrical quartet. [b] Overlapping multiplets. [c] Taken from ref 8. [d] In quinoxaline itself, δ H-2 and H-3 = 8.73, δ H-5 and H-8 = 8.06, δ H-6 and H-7 = 7.67 ppm.[10] [e] Centers of A_2B_2 multiplets.

Table IV. Ultraviolet Data for Imidazo[1,2-*a*]pyridines[a] in 95% Ethanol and Ethanolic Hydrochloric Acid[b]

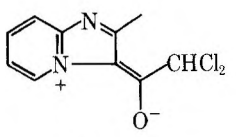
12 or 12·HCl[c,d,f]	12·HCl + HCl	9	9 + HCl[f]	8·HCl[f]	8·HCl + HCl
323 (9.7) ↓↓		338 (11.7) ↓↓	278 (7.0)	283 (5.8)	280 (7.4)
~300[e] (7.0) ~same	283 (7.5)	297 (5.7) → 281			
255 (25.5) ↓		261 (16.0) ↓	253 (7.8)		
248 (21.1) ↓	247 (12.0)	255 (15.2) ↓	247[e] (6.9)		
~242[e] (15.9) ~same	242[e] (11.1)	248[e] (12.6) ↓240[e]	240[e] (5.7)	231 (24.9)	
217 (20.0) ↓	220[e] (16.5)	219 (16.7) ↑	219 (18.6)	224 (21.7)	222 (27.2)
214 (18.4) ~same	213 (19.3)	216 (16.8) ↑	214 (21.9)	220[e]	219 (27.2)

[a] λ_{max}, nm ($\epsilon \times 10^{-3}$). [b] Ca. 2×10^{-2} N HCl. [c] Arrows indicate changes in extinction coefficient when 1 drop 0.1 N HCl is added to the solutions in the cells to give ca. 7.5×10^{-4} N HCl. [d] Reported for 11·HCl, λ_{max}, nm ($\epsilon \times 10^{-3}$): 324 (8.1); 300 (6.7); 256 (20.8); 248 (17.2). [e] Shoulder. [f] Registry no.: 12·HCl, 63076-75-5; 9·HCl, 63076-76-6; 8·HCl, 63076-77-7.

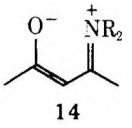
under the work-up conditions used, would explain the much lower yield.

Spectral Properties

Infrared. The carbonyl group of the dichloro ketone **9** absorbs at 1625 cm^{-1}, considerably beyond the lower limit observed for aromatic ketones (1700–1680 cm^{-1}).[14] Since an α-chloro group increases the frequency, the expected range is nearer 1720–1700 cm^{-1}. The low-frequency absorption indicates a weaker carbonyl double bond due to significant contribution of the resonance form **9a** to the ground state of the molecule. Equally unusual absorption of the aldehyde **12** at 1625 cm^{-1} is interpreted in the same manner. An analogy is found in β-amino-α,β-unsaturated ketones which absorb 20–80 cm^{-1} lower than expected and for which resonance structure **14** has been evoked.[15]



9a



14

Ultraviolet. The identity of the spectra of the aldehyde **12** and its salt (see Table IV) indicates complete, or nearly complete, dissociation of the pyridinium salt, which in turn corroborates the notion of charge separation in the neutral molecule that would lead to a lowering of the pK_a.

The spectra of the aldehyde **12** and the dichloro ketone **9** are similar. Complex changes observed in the spectra of both compounds when acid is added are interpretable in terms of the equilibria shown below. An immediate drop in the extinction coefficients of several bands (indicated by arrows in Table IV) caused by the addition of acid indicates protonation (equilibrium 1, Scheme II). The observation that the spectrum of compound **9** continues to change with time, while that of **12** remains the same, is attributed to more facile hemiacetal formation[16] (equilibria 2 and 4) of the dichloro ketone. The concentration of neutral hemiacetal must be very low, since

Scheme II

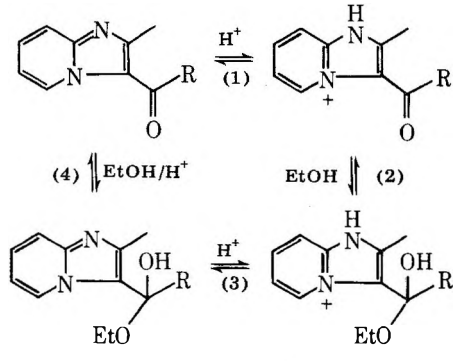


Table V. ^1H NMR Chemical Shifts (δ, ppm) of Imidazo[1,2-*a*]pyridines In Various Solvents[a]

	CH_3	H-5	C–H[b]	
		Me_2SO-d_6		
1a·HCl	2.91	9.39		
8·HCl	3.08	9.74	6.44	
9·HCl	3.37	10.11	7.90	
12·HCl	3.20	9.98	10.57	
		TFAA		
1a	2.66	8.60		
8·HCl	2.74	9.42	5.88	
9	3.18	10.06	6.85	
12	3.06	9.92	10.28	
		D_2O		
1a·HCl	2.95	8.97		
8·HCl	3.15	9.65		
9·HCl	3.18	9.66	6.78	low
	3.50	10.25	7.68	high
12·HCl	3.35	10.09	10.58	
		EtOH		
9	2.92	9.72	7.18	
12	2.72	9.51	10.06	
		EtOH/HCl		
8	2.76	9.44		
9	3.10	9.93	7.34	low
	2.79	9.41	6.38	high
12	2.97	9.78	10.30	low
	2.70	8.91		high

[a] Relative to external Me_4Si in Me_2SO-d_6 and D_2O, internal Me_4Si in TFAA and EtOH. [b] These are the chemical shifts of the substituent protons, i.e., –CH(OH)CCl_3, –COC**H**Cl_2, and –C**H**O of compounds **8**, **9**, and **12**, respectively.

its pK_a is expected to be near that (ca. 6)[3a] of alkyl-substituted imidazo[1,2-*a*]pyridines. Further addition of acid causes an immediate pronounced change in the spectra (only protonated species present). Both spectra now continue to change with time, so that the rate of acid-catalyzed hemiacetal formation of the aldehyde (**12**) has become sufficiently enhanced to be observable. Since no further changes occur when more acid is added, the spectra then are of the species involved in equilibrium 2. Three of the absorption bands are at wavelengths similar to bands found in the protonated chloral adduct **8** and can therefore be assigned to the protonated hemiacetals.[17] The remaining bands can then be attributed to protonated aldehyde and ketone.

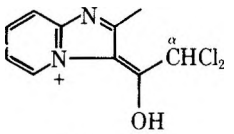
^1H NMR. The dichloro ketone **9** is also subject to hydration. A spectrum of its salt, **9**·HCl, in D_2O (see Table V) exhibits two sets of peaks, while that of the aldehyde **12**·HCl is normal. Of the several possible interpretations, i.e., presence of impurity, tautomerism (N, O, or C protonation), and partial hydration, the last is shown to be correct. The presence of an isomeric

Table VI. Analytical Data for Some Imidazo[1,2-*a*]pyridines

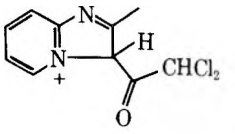
Compd			Calcd %				Found %			
Formula	No.[c]	Mp, °C	C	H	N	Cl	C	H	N	Cl
$C_{10}H_{10}N_2 \cdot C_6H_3N_3O_7$	**5a**·pic[a]	198.5–199.5					49.47	3.40	17.97	
	5b·pic	225–226	49.61	3.36	18.09		49.79	3.46	18.01	
	5c·pic	171–173					49.83	3.61	17.66	
$C_{10}H_{12}N_2O$	**6b**	149–151	68.18	6.82	15.91		68.20	6.84	15.92	
	6c	124–125					67.98	6.86	15.86	
$C_{18}H_{18}N_4 \cdot 2C_6H_3N_3O_7$	**7b**·pic	260–261.5 dec	48.13	3.21	18.72		48.18	3.35	18.73	
$C_{18}H_{18}N_4$	**7c**	180–181	74.48	6.21	19.31		74.38	6.22	19.26	
$C_{10}H_9N_2OCl_3 \cdot {}^1/_4H_2O$	**8**	102[b]	42.25	3.35	9.86		42.30	3.10	9.57	
$C_{10}H_9N_2OCl_3 \cdot HCl$	**8**·HCl	246 dec[b]	37.97	3.16	8.86		37.99	3.35	8.56	
$C_{10}H_8N_2OCl_2$	**9**	102–104	49.38	3.29	11.52	29.22	49.40	3.32	11.51	29.03
$C_{10}H_8N_2OCl_2 \cdot HCl$	**9**·HCl	204 dec[b]	42.93	3.22	10.02		42.97	3.22	10.03	
$C_{16}H_{12}N_4$	**10**	178–179[b]	73.85	4.62	21.54		73.96	4.66	21.30	
$C_9H_8N_2O$	**12**	107–109.5	67.50	5.00	17.50		67.58	5.17	17.20	
$C_9H_8N_2O \cdot HCl$	**12**·HCl	252 dec[b]	54.96	4.58	14.25	18.07	55.17	4.77	14.25	17.92
$C_{10}H_{11}N_5O$	**13**	251–265 dec[b]	55.30	5.07	32.26		55.19	5.12	32.10	

[a] Picrate. [b] These compounds either darkened prior to melting or showed peculiar melting characteristics; see Experimental Section. [c] Registry no.: **5a**·pic, 63076-79-9; **5b**·pic, 63076-80-2; **5c**·pic, 63076-81-3; **7b**·pic, 63076-82-4; **10**, 63076-83-5; **13**, 63104-20-1.

impurity is ruled out by the finding that compound **9**·HCl shows only one set of peaks in either Me_2SO-d_6 or trifluoroacetic acid (TFAA). Tautomerism between N vs. O protonated species is a priori unlikely, since such proton transfer is usually so rapid that only an average spectrum of the two forms is observable in the NMR;[18] further, in the O-protonated species **9b** the α proton should exchange in D_2O and this



9b



9c

is not observed. If protonation on C, a much slower process, were occurring (see **9c**), an extra peak should appear in the TFAA solution spectrum (total of nine protons), and this is not the case. The great similarity of the chemical shifts of the less intense set to those of H-5 and CH_3 in the chloral adduct **8**·HCl supports the supposition of partial hydration. The more intense set absorbs at relatively lower field, in accord with the anticipated greater deshielding by the carbonyl group, and as observed in the $CDCl_3$ solution spectra of the free bases **8** and **9**.

The chemical shifts of the aldehyde **12**·HCl in Me_2SO-d_6 and TFAA differ from those in D_2O by no more than expected for solvent effects (cf. data for **8**·HCl). The spectra of the protonated dichloro ketone **9**·HCl in these solvents are also best interpreted in terms of the ketone rather than the hydrated structure.

The spectra of both free bases **9** and **12** in absolute ethanol are normal; addition of acid causes not only downfield shifts expected for protonation, but also the appearance of a second set of peaks at higher field which increases in intensity with time at the expense of the other set. The conclusion drawn from the ultraviolet spectra that hemiacetals[19] are formed is thus directly confirmed. The ratios of hemiacetals to unreacted compounds **9** and **12** are ~3, that of hydrate to unreacted compound **9** is ~0.3.

In conclusion, since only the ketone forms a hydrate, although aldehydes in general hydrate more readily than ketones, the neighboring dichloromethyl group appreciably enhances the susceptibility of the ketone toward nucleophilic attack. The lack of hydration, the relatively slow semicarbazone formation of the aldehyde **12**, as well as IR and ^1H NMR data of the free bases **9** and **12**, indicate significant contribution of the charge-separated resonance forms to the ground state of the molecules. Indeed, for these compounds the zwitterionic structure appears to be a better pictoralization.

Table VII. Conditions and Product Distribution of Acetaldehyde Condensation with Methylimidazo[1,2-*a*]pyridines (1)

Compd	(g)	Time, h	Yield, % 5	6	7
1a	(0.65)	18	40	47	13
1b	(1.0)	65	10	50	38
1c	(1.75)	40	8	21	27
1d	(1.96)	19			
1e	(2.77)	80		Traces	

Experimental Section

Woelm neutral alumina, Brockmann grade 3, was used for chromatography. Solutions were dried over anhydrous Na_2SO_4. Melting points are uncorrected. ^1H NMR spectra were recorded with a Varian HA-100 spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M instrument equipped with a solid sample injector; ionizing voltage was 73 eV. IR spectra were recorded of Nujol mulls with a Beckman AccuLab 1 instrument. UV spectra were taken with a Varian Techtron UV–vis spectrophotometer, Model 635. Elemental analyses were determined by either the Analytical Services Laboratory of the University of Alabama Chemistry Department or Atlantic Microlab, Inc., Atlanta, Ga. Analytical data are collected in Table VI.

Acetaldehyde Condensation with Methylimidazo[1,2-*a*]pyridines (1). Compounds **1** were purified by column chromatography on alumina with 50% $C_6H_6/CHCl_3$. Acetaldehyde was distilled just prior to use. A mixture of compound **1** and acetaldehyde (~15 equiv) was heated in a steam bath in a sealed tube and the reaction was monitored by TLC. In all cases except with compound **1a** starting material was still present when the reaction was stopped. Evaporation under reduced pressure left a brown liquid which was subjected to column chromatography. The **3-vinylimidazo[1,2-*a*]pyridines 5** and compounds **7** were eluted with 50% $C_6H_6/CHCl_3$, the **3-(1-hydroxyethyl)imidazo[1,2-*a*]pyridines 6** were eluted with $CHCl_3$. Conditions and product distribution are shown in Table VII. The yields are not of isolated pure compounds, since some overlap occurred in the chromatographic separations, but rather are meant to show approximate product distribution.

The hygroscopic vinyl compounds **5**, although pure according to TLC and ^1H NMR spectra, had wide melting ranges even after sublimation and were therefore converted into picrates. Typically, when a hot solution of picric acid (43 mg, 0.18 mmol) in EtOH (3 mL) was added to a hot solution of compound **5** (30 mg, 0.16 mmol), a quantitative yield of picrate was obtained. Analytical samples were prepared by two or three crystallizations from EtOH.

The hydroxy compounds **6b** and **6c** were further purified by sublimation [80–100 °C (0.025 Torr)] followed by two crystallizations from C_6H_6. When the hydroxy compound **6a** was treated with picric acid as above, a yellow solid, mp 193–194.5 °C, was obtained. Its ^1H NMR spectrum was identical with that of the picrate of compound **5a**, and a mixture melting point with pure compound **5a**·picrate (mp 198.5–199.5 °C) was 195–196 °C.

Compound **7b** was hygroscopic and was converted into its picrate. After crystallization from EtOH or DMF failed, crystallization was achieved by dissolving the compound (50 mg) in hot ethylene glycol (5 mL), filtering, and adding EtOH (4 mL). Compound **7c** was purified by two crystallizations from benzene. Compound **7a** was not obtained pure, but its formation was demonstrated by ^1H NMR spectral comparisons.

Alternate Formation of 1,1-Bis(6-methylimidazo[1,2-*a*]-pyrid-3-yl)ethane (7b). A mixture of the hydroxy compound **6b** (0.11 g, 0.6 mmol) and parent **1b** (0.10 g, 0.7 mmol) was maintained at 95 °C overnight. When fractionated by chromatography, compound **7b** (60 mg, ~30%) was obtained as shown by TLC and ^1H NMR spectral comparisons.

Reaction of 2-Methylimidazo[1,2-*a*]pyridine (1a) with Chloral. When Cl_3CCHO (Eastman, 12 mL) was added to compound **1a** (2.0 g, 15 mmol), a colorless solid separated and a light red solution was obtained. The deep red clear solution obtained on brief warming was heated the requisite 24 h on the steam bath,[1] although TLC indicated the absence of starting material after 1 h. Cooling gave a viscous gum that could not be induced to crystallize. Treatment with ice/water gave a mixture (pH 6) that was extracted with three 20-mL portions of $CHCl_3$ (pH then 5). The combined extracts were dried, stripped of solvent, and dried in vacuo (0.025 Torr) when a small amount of $Cl_3CCH(OH)_2$ sublimed. The residual thick oil was fractionated on 150 g of alumina with $CHCl_3$ to give needles of compounds **9**, mp 98–99.5 °C (0.62 g, 17%), trace amounts of other materials, and finally compound **8** as a glass (1.55 g, 37.5%). A second crop of compound **8** was obtained from the aqueous layer after treatment with $NaHCO_3$ and extracting with $CHCl_3$ (1.95 g, ~83% total). **Sublimation of 2-methyl-3-(2,2,2-trichloro-1-hydroxyethyl)imidazo-[1,2-a]pyridine (8)** led to extensive decomposition, but gave a small amount of fine, fluffy material (IR same as nonsublimed sample): mp softens and darkens ~92 °C, forms a glass ~102 °C, used for analysis.

The HCl salt of compound **8** had mp 248 °C dec (darkens ≳200 °C), lit.[1] mp 249.5–252.5 °C. An analytical sample, obtained by two crystallizations from EtOH/EtOAc, had mp 229 °C dec (darkens ≳220 °C), lit.[1] mp 240.5–241.5 °C, and after drying [4 h, 95 °C (0.025 Torr)] mp 246 °C dec (darkens ≳220 °C).

According to TLC, IR, and mp, compound **8**·HCl remained unchanged when treated with refluxing absolute EtOH/HCl for 24 h.

3-(2,2-Dichloroacetyl)-2-methylimidazo[1,2-*a*]pyridine (9) crystallized as colorless needles from hexane. Sublimation [95 °C (0.025 Torr)] afforded an analytical sample. Treatment of compound **9** with absolute EtOH/HCl and evaporating to dryness gave compound **9**·HCl. An analytical sample, obtained by two crystallizations from absolute EtOH/EtOAc, had mp 204 °C dec (darkens ~180 °C) and could be sublimed [90 °C (0.025 Torr)].

The salt, after heating with absolute EtOH/HCl for 5 days, had the same mp, IR, ^1H NMR, and mass spectra as the above sample.

2-Methyl-3-(2-quinoxalyl)imidazo[1,2-*a*]pyridine (10). Since after heating a mixture of compound **9** (50 mg, 0.2 mmol), *o*-phenylenediamine (23 mg, 0.21 mmol), and H_2O (3 mL) for 1 h on the steam bath much insoluble starting material remained, solution was affected by the addition of EtOH and heating was continued overnight. Treatment with aqueous NaOH (to pH 8) gave a yellow solid, **10**, which was filtered. TLC of the filtrate showed the presence of starting materials. The solid was extracted with hot hexane (30 mL) and the extract concentrated (2 mL) to give sturdy yellow needles, which after sublimation [100 °C (0.025 Torr)] had mp 178–179 °C (darkens ≳160 °C) (~8 mg, 15%).

Base Treatment of Compound 8: Formation of 3-Formyl-2-methylimidazo[1,2-*a*]pyridine (12). (1) When a solution of the crude second crop of compound **8** (1.95 g) in absolute EtOH (10 mL) was treated dropwise with aqueous NaOH (1.1 g in 2 mL), it turned dark red and heat was liberated. Brief warming on a steam bath induced a vigorous exothermic reaction and separation of NaCl. The mixture was then gently refluxed for 20 min, cooled, and filtered. The solid was washed with absolute EtOH, and the filtrate stripped of solvent to give a sticky solid that was extracted with three 10-mL portions of hot $CHCl_3$. The extracted material was subjected to chromatography on 120 g of alumina with 50% $C_6H_6/CHCl_3$. Early fractions yielded compound **12** (0.48 g, ~43%), mp 110–111 °C. An analytical sample, obtained by sublimation [80 °C (0.025 Torr)], gave a positive Tollens' test.

The HCl salt of compound **12**, twice crystallized from EtOH/EtOAc, had mp 252 °C dec (darkens ≳200 °C, lit.[1] for compound **11**·HCl, 252.5–254.5 °C) and could be sublimed [120 °C (0.025 Torr)].

(2) Base treatment, followed by acidification, under the reported conditions,[1] also afforded the HCl salt of compound **12** (55%) as established by TLC, mp, and IR spectral comparisons. A further crop, isolated as the free base, was obtained by chromatography of the material in the basified mother liquor (75% total).

3-Formyl-2-methylimidazo[1,2-*a*]pyridine Semicarbazone (13). The reaction of compound **12** (50 mg, 0.31 mmol) with semicarbazide hydrochloride (50 mg, 0.45 mmol) and NaOAc (75 mg, 0.91 mmol) in H_2O (5 mL) on the steam bath was followed by TLC. Reaction was complete after 1.5 h. Concentration to 2 mL caused the separation of pale yellow crystals, which were filtered and rinsed with H_2O to give 70 mg (100%). The product, after dissolution in EtOH (5 mL), addition of H_2O (2 mL), concentration to 2 mL, cooling, and filtering the precipitate, had mp 254–268 °C dec (softens 232 °C). The wide melting-point range implied that perhaps some HOAc salt contaminated the product. However, when it was treated with $NaHCO_3$ in EtOH/H_2O, no gas evolved and it then had mp 251–265 °C dec (softens 232 °C).

Acknowledgment. We wish to thank Diamond Shamrock Corporation for partial financial support.

Registry No.—**1a** HCl, 2549-26-0; **1d**, 5857-45-4; **1e**, 933-69-7; **6a** picrate, 63076-84-6; **11** HCl, 2717-93-3; acetaldehyde, 75-07-0; chloral, 75-87-6.

References and Notes

(1) J. G. Lombardino, *J. Org. Chem.*, **30**, 2403 (1965).
(2) E. S. Hand and W. W. Paudler, *J. Org. Chem.*, **40**, 2916 (1975).
(3) See, for example: (a) H. L. Blewitt, Ph.D. Thesis, Ohio University, Athens, Ohio, 1966; (b) E. S. Hand and W. W. Paudler, *J. Org. Chem.*, **41**, 3549 (1976), and references cited therein.
(4) C. J. Pouchert and J. R. Campbell, "The Aldrich Library of NMR Spectra", Vol. 4, Aldrich Chemical Co., Inc., Milwaukee, Wis., 1974, 17D.
(5) Cf. *sec*-phenethyl alcohol ^1H NMR spectrum: ref 4, Vol. 5, 1C.
(6) Unpublished results. Cf. L. Almirante, A. Mugnaini, N. De Toma, and W. Murmann, *Boll. Chim. Farm.*, **110**, 322 (1971); *Chem. Abstr.*, **75**, 151727s (1971).
(7) See, for example, S. R. Shrader, "Introductory Mass Spectrometry", Allyn and Bacon, Boston, Mass., 1971.
(8) W. W. Paudler and H. G. Shin, *J. Org. Chem.*, **33**, 1638 (1968).
(9) The extinction coefficients, however, differ appreciably (see Table IV).
(10) P. J. Black and M. L. Heffernan, *Aust. J. Chem.*, **18**, 707 (1965).
(11) Citation in Beilstein **6**, 476: Savariau, *C. R. Acad. Sci.*, **146**, 297 (1912).
(12) H. Pauly and H. Schanz, *Ber. Dtsch. Chem. Ges.*, **56**, 979 (1923).
(13) Reference 12; L. N. Ferguson, *Chem. Rev.*, **38**, 227 (1946).
(14) L. J. Bellamy, "The Infrared Spectra of Complex Molecules", Wiley, New York, N.Y., 1954.
(15) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace, *J. Am. Chem. Soc.*, **71**, 3337 (1949).
(16) Possible alternate hydrate formation is considered to be unimportant on the basis of ^1H NMR data (see below).
(17) Acetal formation is unlikely, since the spectra were obtained in 95% ethanol.
(18) J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem., Suppl. 1*, 1 (1976).
(19) Since absolute ethanol was used in the ^1H NMR experiments, formation of acetals cannot rigorously be excluded.

Addition Reaction of β-Imino- and β-Oxodithiocarboxylic Acids with Methyl Propiolate and with Strongly Electrophilic Olefins

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Received February 22, 1977

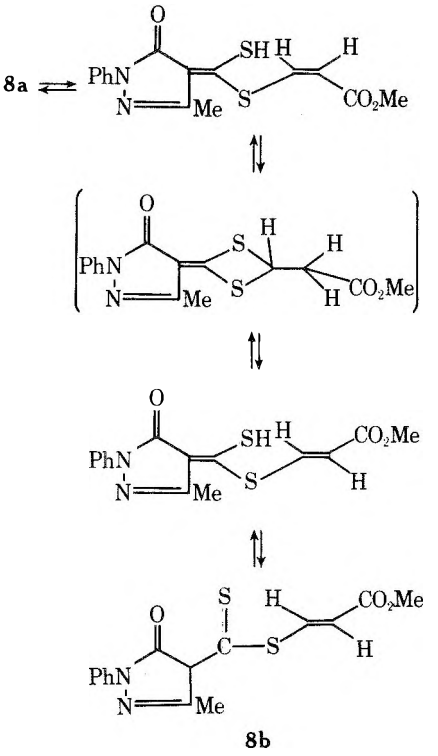
2-Iminocyclopentanedithiocarboxylic acid (1), 2-cyclohexyliminocyclopentanedithiocarboxylic acid (2), 2-oxocyclopentanedithiocarboxylic acid (3), and 3-methyl-5-oxo-1-phenyl-Δ^2-pyrazoline-4-dithiocarboxylic acid (4) reacted with methyl propiolate to give the cis adducts of normal ester type, **5, 6, 7,** and **8a**. Phenylacetylene and propargyl alcohol did not react with these acids. On dissolution in a solvent such as dimethyl sulfoxide, compound **8a** converted into the trans isomer **8b**. The acids **1–4** added only to the strongly electrophilic olefins. The iminodithio acids were much more reactive than the oxodithio acids in this addition reaction.

In the course of our studies of the dithio acids, 2-iminocyclopentanedithiocarboxylic acid (**1**), 2-cyclohexyliminocyclopentanedithiocarboxylic acid (**2**), 2-oxocyclopentanedithiocarboxylic acid (**3**), and 3-methyl-5-oxo-1-phenyl-Δ^2-pyrazoline-4-dithiocarboxylic acid (**4**)[2], we have now investigated the addition to methyl propiolate and to certain alkenes. Dithio acids **1, 2,** and **4** added to methyl propiolate simply on dissolution in a solvent; in the case of **3**, a small amount of a base such as triethylamine was necessary for the reaction to proceed (Scheme I). All the adducts assumed the cis configuration (see NMR data in the Experimental Section). Thus, the mode of the addition is the same as in the case of addition of thiols to carbon–carbon triple bond.[3] The new adduct esters obtained are listed in Table I. The acids **1–4** did not react with phenylacetylene and propargyl alcohol.

Among the adducts obtained, only **8a** rearranged to the trans isomer simply on dissolution in a solvent such as dimethyl sulfoxide. The transformation could be followed by the NMR spectra. It seems that the rearrangement occurs through the transient dithietan form shown (Scheme II), of the acids, only **4** is capable of forming a dithietane by addition to a carbonyl compound.[4]

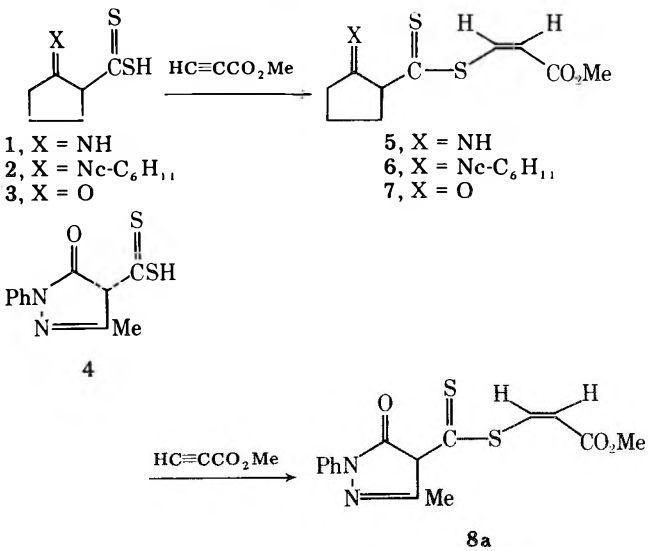
In reference to the above addition reaction, we have examined the addition of the acids, **1–4**, to olefins. Concerning the addition of dithioacids to olefins, dithiocarbamic acids with olefins[5] and *p*-benzoquinone[6] and dithioacetic acid with a variety of olefins[7] have been reported. It is stated that dithioacetic acid reacts with both electrophilic and nucleophilic olefins to give the corresponding ester type adducts (Schemes III and IV).

Scheme II



8b

Scheme I

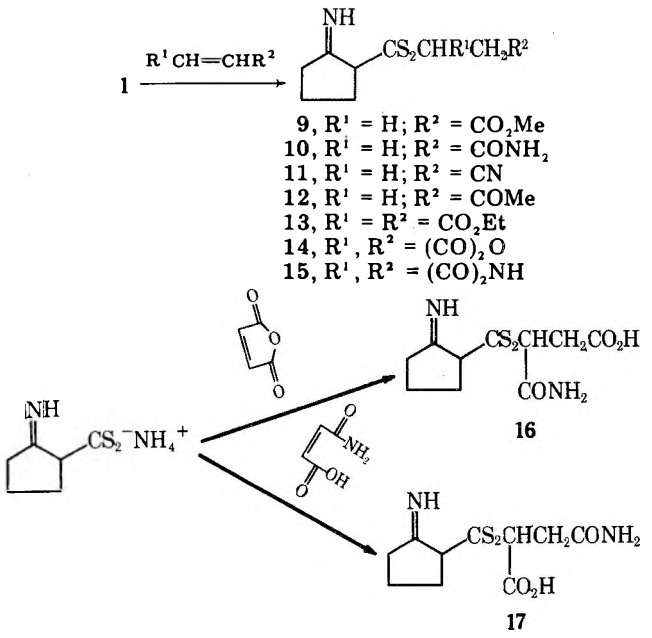


In our present experiment, it was found that the acids, **1–4,** differed from dithioacetic acid in that they reacted only with strongly electrophilic olefins to give the distinct crystalline adducts (Table II; Scheme V). The reaction was conducted in a solvent such as ethanol at room temperature. The presence of an excess of a base or an acid retarded the reaction. There was considerable difference in reactivity between the iminodithio acids and the oxodithio acids. The latter acids, **3** and **4,** were much less reactive and reacted only with maleic anhydride and maleimide.

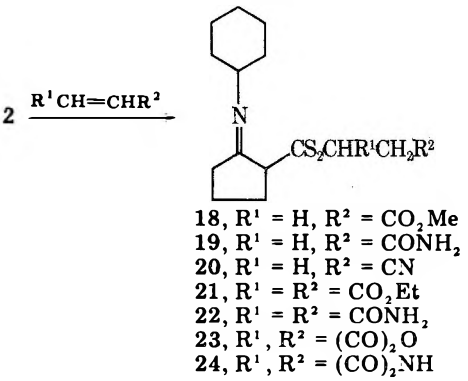
The β position of the olefins was the site of attack of the dithiocarboxyl group. It is of interest that tetracyanoethylene did not afford adducts with the dithio acids; instead, the same as those obtained on oxidation of the dithio acids were produced.[8] This behavior resembled the reaction of thiols with tetracyanoethylene.[9]

When the ammonium salt of acid **1** was subjected to reaction with maleic anhydride, adduct **16** was obtained rather than **14.** The ammonium salt reacted with maleic monoamide

Scheme III



Scheme IV



Scheme V

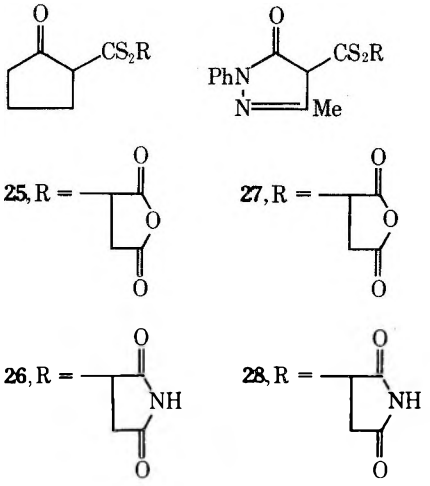


Table I. Adduct Esters 5–8[a]

Registry no.	Adduct ester	Yield, %	Mp, °C	Recryst. solvent
63018-07-5	**5**	82	240–241	DMF–EtOH
63018-06-4	**6**	39	130–131	DMF–EtOH
63018-08-6	**7**	79	113–115	DMF–EtOH
63018-09-7	**8a**	80	170–171	Dioxane
63058-89-9	**8b**		156–158	Me_2SO

[a] Satisfactory analytical data (±0.3% for C, H, N, S) were reported for all compounds listed in this table.

Table II. Adduct Esters 9–28[a]

Registry no.	Starting olefin[b]	Registry no.	Adduct ester	Yield, %[c]	Mp, °C	Recryst. solvent
96-33-3	Methyl acrylate	6301810-0	**9**	77	71–72	EtOH
79-06-1	Acrylamide	63058-86-6	**10**	65	175 dec	EtOH–DMF
107-13-1	Acrylonitrile	63018-11-1	**11**	45	104–106	EtOH–DMF
78-94-4	Methyl vinyl ketone	63018-12-2	**12**	98	122–123	EtOH–DMF
141-05-9	Diethyl maleate (diethyl fumarate)	63018-13-2	**13**	39 (72)	108–109	EtOH–DMF
108-31-6	Maleic anhydride	63018-14-4	**14**	75	136–137[d]	EtOH–C_6H_6
541-59-3	Maleimide	63018-15-5	**15**	93	200–201[e] dec	EtOAc–C_6H_6
	Maleic anhydride	63018-16-6	**16**	70	189[f]	DMF–H_2O
557-24-4	Maleic monoamide	63018-17-7	**17**	40	147–148[g]	MeOH
	Methyl acrylate	63018-18-8	**18**	46	75–76	EtOH
	Acrylamide	63018-19-9	**19**	64	117–119	EtOH–DMF
	Acrylonitrile	63018-20-2	**20**	58	89–90	EtOH
	Diethyl maleate (diethyl fumarate)	63018-21-3	**21**	35 (55)	70–71	EtOH–C_6H_6
928-01-8	Maleic diamide	63018-22-4	**22**	64	267–268[h]	DMF–H_2O
	Maleic anhydride	63018-23-5	**23**	89	145–146[i]	EtOAc–C_6H_6
	Maleimide	63018-24-6	**24**	99	203–204	
	Maleic anhydride	63018-25-7	**25**	60	198–200	EtOH
	Maleimide	63018-26-8	**26**	30	144–145	EtOH–H_2O
	Maleic anhydride	63018-27-9	**27**	93	186–189	
	Maleimide	63018-28-0	**28**	84	181–182	

[a] Satisfactory analytical data (±0.3% for C, H, N, S) were reported for all compounds listed in this table. [b] Olefins which did not react are: 1-hexene, cyclohexene, methyl crotonate, methyl methacrylate, mesityl oxide, citraconic anhydride, crotonaldehyde, cinnamaldehyde, methyl cinnamate, styrene, crotononitrile, methacrylonitrile, tetracyanoethylene, vinyl acetate, vinyl *n*-butyl ether, vinyl bromide, trichloroethylene, and tetrachloroethylene. [c] By using free dithiocarboxylic acids except for **16** and **17**. [d] Rapid heating, 152–156 °C. [e] Rapid heating, 214–216 °C dec. [f] Rapid heating, 200–202 °C. [g] Rapid heating, 156–157 °C. [h] Rapid heating, 277–280 °C. [i] Rapid heating, 161–163 °C.

to give the isomeric adduct **17**. The reaction of the ammonium salt of acid **1** with maleic anhydride thus seems to involve initial attack of the dithiocarboxyl group, followed by ammonolysis of the anhydride. Structure **16** is based on the close correspondence of the chemical shift for the $SCH(CONH_2)$ peak (δ 4.87 dd) in **16** and the corresponding peak (δ 4.90 dd) in the spectrum of **22**. The isomeric structure **17** then follows for the product from maleamic acid.

All the adducts obtained were identified on the basis of IR, NMR, and UV spectra together with elemental analyses (see Experimental Section). The adduct esters of acid **1** with methyl propiolate and olefins showed UV absorptions at ca. 310 and ca. 380–390 nm, which were in good agreement with the spectra of methyl and carboxymethyl 2-iminocyclopentanedithiocarboxylates (ca. 312 and 384 nm).[10]

Experimental Section

Ammonium 2-iminocyclopentanedithiocarboxylate was prepared by modification of previously described method.[11] A mixture of cyclopentanone (25 g, 0.30 mol), carbon disulfide (30 g, 0.39 mol), and 70 mL of aqueous ammonia (28%) was stirred below 0 °C for ca. 8 h. The yellow solid product was collected, washed with ether, and dried over $CaCl_2$; yield ca. 26 g (50%). The crude ammonium salt of **1** was recrystallized from EtOH; mp 135–137 °C dec (lit.[11] mp 135–137 °C dec).

2-Iminocyclopentanedithiocarboxylic Acid (1). The crude ammonium salt of **1** was dissolved in water. The solution was cooled in ice, and 2 N HCl was added to the solution. The yellow solid material separated from the solution was collected, washed with water, and dried over $CaCl_2$. The crude **1** was saturated with MeOH at 40–50 °C, and the solution was filtered. To the filtrate was added water (a quarter of the volume of the filtrate), and the solution was allowed to stand below 10 °C. The yellow solid was collected, washed with H_2O–EtOH (1:1), and dried over $CaCl_2$; mp 106–108 °C dec (rapid heating) and 99–101 °C dec (slow heating) (lit.[11] mp 101–102 °C dec and 96 °C dec).

2-Cyclohexyliminocyclopentanedithiocarboxylic acid (2) was prepared as previously reported.[12]

2-Oxocyclopentanedithiocarboxylic acid (3) was prepared by modification of a previously described method.[4] A mixture of sodium hydride (2 g, 50% oil dispersion) in THF (10 mL) and carbon disulfide (3.2 g, 0.042 mol) was stirred below 0 °C. To the mixture was added cyclopentanone (3 g, 0.036 mol) and then dropwise water (0.7 mL, 0.039 mol) in THF (10 mL). After an additional 30 min of stirring EtOH was added. The mixture was acidified with dilute acetic acid and kept overnight in an ice box. The orange solid product was collected, washed with water and EtOH, and dried; yield ca. 4 g (70%). The crude acid was recrystallized from EtOH; mp 91–92 °C (lit.[4] mp 90–91 °C).

3-Methyl-5-oxo-1-phenyl-Δ²-pyrazoline-4-dithiocarboxylic acid (4) was prepared as previously reported.[2]

***cis*-2-Methoxycarbonylvinyl 2-Iminocyclopentanedithiocarboxylate (5).** To a solution of acid **1** (0.4 g, 0.0025 mol) in EtOH (20 mL) was added methyl propiolate (0.22 g, 0.0026 mol). The mixture was kept overnight at room temperature. The yellow solid product was collected, washed with EtOH, dried, and recrystallized: IR (KBr) 3060 w (=CH), 1692 vs (C=O), 1627 vs cm^{-1} (C=C); UV max (EtOH) 307 (log ε 4.06), 383 nm (4.49); NMR (Me_2SO-d_6) δ ca. 1.90 (2 H, m, 4-H_2), ca. 2.80 (4 H, m, 3-, 5-H_2), 3.74 (3 H, s, CH_3), 6.31 (1 H, d, J = 11 Hz, CHCO), 8.85 (1 H, d, J = 11 Hz, SCH), 9.77 br, 11.40 br (each 1 H, s, tautomeric 2-NH_2).

***cis*-2-Methoxycarbonylvinyl 2-Cyclohexyliminocyclopentanedithiocarboxylate (6).** To a solution of acid **2** (0.5 g, 0.0021 mol) in EtOH (80 mL) was added methyl propiolate (0.18 g, 0.0021 mol). The mixture was left at room temperature for several days until the whole turned red and then kept for 2 days at ca. −18 °C in a refrigerator. The ocher yellow solid product was collected, washed with EtOH, dried, and recrystallized: IR (KBr) 2985 m (=CH), 1709 vs (C=O), 1595 br cm^{-1} (C=C); UV max (EtOH) 245 (log ε 3.60), 261 (3.70), 340 (4.33), 412 nm (4.46); NMR ($CDCl_3$) δ 1.15–2.10 (12 H, m, 4-,2′-3′-,4′-,5′-,6′-H_2), 2.55–3.00 (5 H, m, 3-,5-H_2 and 1′-H), 3.67 (3 H, s, CH_3), 5.93 (1 H, d, J = 11 Hz, CHCO), 8.63 (1 H, d, J = 11 Hz, SCH), ca. 13.10 br (1 H, s, tautomeric 2-NH).

***cis*-2-Methoxycarbonylvinyl 2-Oxocyclopentanedithiocarboxylate (7).** To a mixture of acid **3** (0.97 g, 0.0061 mol), methyl propiolate (0.53 g, 0.0063 mol), and dioxane (6 mL) was added triethylamine (0.04 g) at 0 °C. After an additional cooling for 30 min, the mixture was kept overnight in an ice box. To this was gradually added water, and the orange-red solid product was collected, washed with MeOH, dried, and recrystallized: IR (KBr) 3000 m (=CH), 1693 vs (C=O), 1585 vs cm^{-1} (C=C); UV max (EtOH) 260 (log ε 3.56), 322 sh (4.17), 350 (4.24), 380 nm (4.35); NMR (Me_2CO-d_6) δ ca. 2.90 (7 H, m, 1-H and 3-,4-,5-H_2), 3.80 (3 H,, s, CH_3), 6.40 (1 H, d, J = 11 Hz, CHCO), 8.65 (1 H, d, J = 11 Hz, SCH).

***cis*-2-Methoxycarbonylvinyl 3-Methyl-5-oxo-1-phenyl-Δ²-pyrazoline-4-dithiocarboxylate (8a).** To a solution of acid **4** (0.5 g, 0.002 mol) in EtOH (60 mL) was added methyl propiolate (0.18 g, 0.0021 mol). The mixture was kept overnight at room temperature. The yellow needles were collected, washed with EtOH, dried, and recrystallized: IR (KBr) 3030 w (=CH), 1696 vs (C=O), 1592 vs cm^{-1} (C=C and C_6H_5); UV max (EtOH) 248 (log ε 4.03), 266 sh (3.98), 336 (4.34), 390 nm (4.16); NMR (Me_2SO-d_6) δ 2.60 (3 H, s, 3-CH_3), 3.70 (3 H, s, OCH_3), 6.25 (1 H, d, J = 11 Hz, CHCO), 7.20–7.80 (5 H, m, C_6H_5), 8.54 (1 H, s, enol OH or enethiol SH), 8.85 (1 H, d, J = 11 Hz, SCH).

Isolation of *trans*-2-Methoxycarbonylvinyl 3-Methyl-5-oxo-1-phenyl-Δ²-pyrazoline-4-dithiocarboxylate (8b). 8a (0.5 g, 0.0015 mol) was dissolved in Me_2SO (14 mL) at 40 °C and filtered. The solution was warmed at 70 °C in a water bath for a few minutes and allowed to stand at room temperature for 24 h. The red precipitate [3,5-bis(3-methyl-5-oxo-1-phenyl-Δ²-pyrazolin-4-ylidene)-1,2,4-trithiole[8]] was filtered off and to the filtrate was added MeOH–H_2O (2:1). The yellow solid (0.2 g, 40%) was collected, washed with MeOH, and dried. From the filtrate the mixture of **8a** and **8b** was precipitated by adding water. The crude **8b** was recrystallized twice from Me_2SO to give yellow crystals of **8b**: IR (KBr) 3005 w (=CH), 1718 vs (C=O), 1590 vs cm^{-1} (C=C and C_6H_5); UV max (EtOH) 248 (log ε 4.20), 267 (4.22), 336 (4.44), 388 nm (4.25); NMR (Me_2SO-d_6) δ 2.60 (3 H, s, 3-CH_3), 3.75 (3 H, s, OCH_3), 6.37 (1 H, d, J = 16 Hz, CHCO), 7.20–7.80 (5 H, m, C_6H_5), 8.96 (1 H, d, J = 16 Hz, SCH), 9.75 (1 H, s, enol OH or enethiol SH).

2-Iminocyclopentanedithiocarboxylic Acid Esters (9–15). General Procedure. A mixture of acid **1** (1.59 g, 0.01 mol), olefin (0.01 mol), and EtOH (10–20 mL) was shaken at room temperature for 0.5–1.5 h and kept overnight in an ice box. The yellow solid product was collected, washed with EtOH, dried, and recrystallized.

2-Methoxycarbonylethyl 2-Iminocyclopentanedithiocarboxylate (9). IR (KBr) 1730 cm^{-1} (C=O); UV max (EtOH) 226 (log ε 4.61), 314 (4.72), 388 nm (4.93).

2-Carbamoylethyl 2-Iminocyclopentanedithiocarboxylate (10). IR (KBr) 3383 m, 3260, 3200 m (NH_2 and NH), 1638 vs, 1620 vs cm^{-1} (C=O and NH_2); UV max (EtOH) 218 (log ε 4.15), 315 (4.28), 388 nm (4.58); NMR (Me_2SO-d_6) δ 1.88 (2 H, quint, 4-H_2), 2.24 (6 H, m, 3-,5-H_2 and CH_2CO), 3.32 (2 H, t, SCH_2), 6.79 br, 7.28 br (each 1 H, s, $CONH_2$), 8.82 br, 10.86 br (each 1 H, s, tautomeric 2-NH_2).

2-Cyanoethyl 2-Iminocyclopentanedithiocarboxylate (11). IR (KBr) 2240 w, 2260 w cm^{-1} (C≡N); UV max (EtOH) 220 (log ε 3.93), 310 (4.04), 387 nm (4.34).

3-Oxobutyl 2-Iminocyclopentanedithiocarboxylate (12). IR (KBr) 1710 s cm^{-1} (C=O); UV max (EtOH) 315 (log ε 3.63), 387 nm (3.97).

1,2-Diethoxycarbonylethyl 2-Iminocyclopentanedithiocarboxylate (13). IR (KBr) 1720 vs, 1710 vs cm^{-1} (C=O); UV max (EtOH) 310 (log ε 3.59), 388 nm (3.94); NMR ($CDCl_3$) δ 1.28 (6 H, t, 2 × CH_3), 1.93 (2 H, m, 4-H_2), 2.73 (5 H, m, 3-,5-H_2 and 1-H), 3.05 (2 H, d, CH_2CO), 4.20 (2 H, quart, OCH_2), 4.27 (2 H, quart, OCH_2), 5.34 (1 H, t, SCH), 10.91 br (1 H, s, 2-NH).

3-(2,5-Dioxo)tetrahydrofuryl 2-Iminocyclopentanedithiocarboxylate (14). IR (KBr) 1860 sh, 1850 s, 1785 vs cm^{-1} (C=O); UV max (EtOH) 307 (log ε 3.81), 389 nm (4.23); NMR (Me_2SO-d_6) δ 1.90 (2 H, m, 4-H_2), 2.75 (4 H, m, 3-,5-H_2), 3.15–4.10 (2 H, m, CH_2CO), 5.40 (1 H, dd, SCH), 9.45 br, 10.75 br (eaeh 1 H, s, tautomeric 2-NH_2); *m/e* 257 (M^+).

3-(2,5-Dioxo)pyrrolidinyl 2-Iminocyclopentanedithiocarboxylate (15). IR (KBr) 3330 s, 3120 br (NH), 1765 m, 1736 w, 1705 vs, 1684 sh (C=O), 1635 m cm^{-1}; UV max (EtOH) 220 sh (log ε 3.93), 309 (4.05), 388 nm (4.51); NMR (C_5D_5N) δ 1.60 (2 H, quint, 4-H_2), 2.70 (4 H, m, 3-,5-H_2), 2.90–4.10 (2 H, m, CH_2CO), 5.00 br (1 H, s, NH), 5.93 (1 H, dd, SCH), 10.17 br, 11.50 br (each 1 H, s, tautomeric 2-NH_2).

1-Carbamoyl-2-carboxyethyl 2-Iminocyclopentanedithiocarboxylate (16). The ammonium salt of **1** (3 g, 0.017 mol) and maleic anhydride (1.7 g, 0.017 mol) were dissolved in DMF (30 mL) in an ice bath, and the mixture was kept at room temperature for 20 h. Water (200 mL) was added, and the mixture was kept for an additional 3 h. The solid product was collected, washed with water, dried, and recrystallized: IR (KBr) 3580 sh (OH), 3380 br, 3200 m (NH_2 and NH), 1705 vs, 1650 m cm^{-1} (C=O); UV max (EtOH) 310 (log ε 4.04), 382

nm (4.44); NMR (Me_2SO-d_6) δ 1.80 (2 H, quint, 4-H_2), 2.50–3.70 (6 H, m, 3-,5-H_2 and CH_2CO), 4.87 (1 H, dd, SCH), 7.20 br, 7.43 br (each 1 H, s, $CONH_2$), 9.23 br, 10.90 br (each 1 H, s, tautomeric 2-NH_2), 12.30 br (1 H, s, COOH).

2-Carbamoyl-1-carboxyethyl 2-Iminoeyclopentanedithiocarboxylate (17). A mixture of the ammonium salt of **1** (3 g, 0.017 mol), maleic monoamide (2 g, 0.017 mol), and DMF (70 mL) was kept at room temperature for 24 h. Ether was added to the oil which separated out. The resulting solid product was collected, washed with ether, dried, and recrystallized: IR (KBr) 3650 (s (OH), 3400 vs, 3375 vs, 3300 vs, 3230 s (NH_2 and NH), 1690 vs, 1640 vs cm^{-1} (C=O); UV max (EtOH) 311 (log ε 4.03), 381 nm (4.41); NMR (Me_2SO-d_6) δ ca. 1.70 (2 H, m, 4-H_2), ca. 2.70 (4 H, m, 3-,5-H_2), ca. 4.00 br (3 H, s, CH_2CO and COOH), 5.03 (1 H, t, SCH), 7.00 br, 7.47 br (each 1 H, s, $CONH_2$), 9.18 br, 10.93 br (each 1 H, s, tautomeric 2-NH_2); NMR (C_5D_5N) δ 3.70 (2 H, d, CH_2CO), 6.38 (1 H, t, SCH).

2-Cyclohexyliminocyclopentanedithiocarboxylic Acid Esters (18–24). General Procedure. A mixture of acid **2** (2.4 g, 0.01 mol), olefin (0.01 mol), and EtOH or EtOH–DMF (10–20 mL) was worked up according to the preparation of **9–15.**

2-Methoxycarbonylethyl 2-Cyclohexyliminocyclopentanedithiocarboxylate (18). IR (KBr) 1720 vs cm^{-1} (C=O); UV max (EtOH) 252 sh (log ε 3.84), 314 (3.90), 398 nm (4.18); NMR ($CDCl_3$) δ 1.44 (6 H, m, 3′-,4′-,5′-H_2), 1.84 (6 H, m, 4-, 2′-, 6′-H_2), 2.75 (6 H, m, 3-,5-H_2 and CH_2CO), 3.50 (3 H, m, 1′-H and SCH_2), 3.66 (3 H, s, CH_3), 12.50 br (1 H, s, tautomeric 2-NH).

2-Carbamoylethyl 2-Cyclohexyliminocyclopentanedithiocarboxylate (19). IR (KBr) 3380 s, 3305 sh, 3190 s (NH_2), 1653 vs, 1647 vs cm^{-1} (C=O and NH_2); UV max (EtOH) 227 sh (log ε 3.70), 315 (3.82), 398 nm (4.26).

2-Cyanoethyl 2-Cyclohexyliminocyclopentanedithiocarboxylate (20). IR (KBr) 2240 w cm^{-1} (C≡N); UV max (EtOH) 227 sh (log ε 3.74), 310 (3.87), 398 nm (4.26).

1,2-Diethoxycarbonylethyl 2-Cyclohexyliminocyclopentanedithiocarboxylate (21). IR (KBr) 1737 vs, 1725 vs cm^{-1} (C=O); UV max (EtOH) 311 (log ε 4.15), 399 nm (4.53).

1,2-Dicarbamoylethyl 2-Cyclohexyliminocyclopentanedithiocarboxylate (22). IR (KBr) 3380 s, 3300 sh, 3160 s (NH_2), 1650 vs cm^{-1} (C=O); UV max (DMF) 313 (log ε 4.00), 393 nm (4.46); NMR (Me_2SO-d_6) δ ca. 1.50 br (10 H, m, 2′-,3′-,4′-,5′-,6′-H_2), ca. 1.80 (2 H, m, 4-H_2), ca. 2.80 (5 H, m 3-,5-H_2 and 1′-H), 2.60–3.70 (2 H, m, CH_2CO), 4.90 (1 H, dd, SCH), 6.75 br (2 H, s, $CONH_2$), 7.17 br (2H, s, $CONH_2$), 12.50 (1 H, d, tautomeric 2-NH).

3-(2,5-Dioxo)tetrahydrofuryl 2-Cyclohexyliminocyclopentanedithiocarboxylate (23). IR (KBr) 1783 m cm^{-1} (C=O); UV max (EtOH) 309 (log ε 3.45), 400 nm (4.15); *m/e* 339 (M^+).

3-(2,5-Dioxo)pyrrolidinyl 2-Cyclohexyliminocyclopentanedithiocarboxylate (24). IR (KBr) 3160 m (NH), 1785 s, 1719 vs, 1708 vs cm^{-1} (C=O); UV max (EtOH) 225 sh (log ε 4.02), 309 (4.07), 398 nm (4.54).

3-(2,5-Dioxo)tetrahydrofuryl 2-Oxocyclopentanedithiocarboxylate (25). A mixture of acid **3** (1.6 g, 0.01 mol), maleic anhydride (1 g, 0.01 mol), and EtOH (10 mL) was warmed on a steam bath and then kept at room temperature for 2 h. The solid product was collected, washed with EtOH, dried, and recrystallized: IR (KBr) 1705 s, 1684 sh, 1671 vs cm^{-1} (C=O); UV max (EtOH) 320 (log ε 3.92), 370 nm (3.82); NMR (Me_2SO-d_6) δ 1.60–2.87 (7 H, m, 1-H and 3-,4-,5-H_2), 2.95–3.45 (2 H, m, CH_2COO), 4.82 (1 H, dd, SCH).

3-(2,5-Dioxo)pyrrolidinyl 2-Oxocyclopentanedithiocarboxylate (26). A mixture of acid **3** (1 g, 0.0062 mol), maleimide (1 g, 0.01 mol), and EtOH (15 mL) was worked up according to the preparation of **25:** IR (KBr) 3180 w (NH), 1784 w, 1700 vs cm^{-1} (C=O); UV max (EtOH) 318 (log ε 3.40), 374 nm (3.82); *m/e* 257 (M^+).

3-(2,5-Dioxo)tetrahydrofuryl 3-Methyl-5-oxo-1-phenyl-Δ^2-pyrazoline-4-dithiocarboxylate (27). A mixture of acid **4** (1.5 g, 0.006 mol), maleic anhydride (0.6 g, 0.006 mol), and EtOH (15 mL) was shaken at room temperature for 20 min. The solid product was collected, washed with benzene, and dried: IR (KBr) 1718 sh, 1705 vs, 1655 vs cm^{-1} (C=O); UV max (EtOH) 245 (log ε 4.41), 270 sh (4.19), 306 (4.30), 372 nm (4.49).

3-(2,5-Dioxo)pyrrolidinyl 3-Methyl-5-oxo-1-phenyl-Δ^2-pyrazoline-4-dithiocarboxylate (28). A mixture of acid **4** (1.5 g, 0.006 mol), maleimide (0.6 g, 0.006 mol), and EtOH (13 mL) was warmed on a steam bath and then shaken at room temperature for 10 min. The solid product was collected, washed with EtOH, and dried: IR (KBr) 3500 m (enol 5-OH), 3160 m(NH), 1777 s, 1718 vs, 1705 vs cm^{-1} (C=O); UV max (EtOH) 246 (log ε 4.10), 270 sh (3.85), 305 (3.90), 372 nm (4.24).

Acknowledgment. We thank Miss E. Ebisuya, Mr. A. Arashi, and Miss A. Kurashima for their assistance.

Registry No.—**1**, 18521-91-0; **1** NH_3, 36388-19-9; **2**, 54235-79-9; **3**, 57624-68-7; **4**, 57624-79-0; carbon disulfide, 75-15-0; cyclopentanone, 120-92-3; methyl propiolate, 922-67-2; 3,5-bis(3-methyl-5-oxo-1-phenyl-4^2-pyrazolin-4-ylidene)-1,2,4-trithiole, 61656-33-5; diethyl fumarate, 623-91-6.

References and Notes

(1) (a) Chiba University; (b) Josai University.
(2) P. Papini and M. Ridi, *Gazz. Chim. Ital.*, **89**, 526 (1959).
(3) See, for example, W. E. Truce in "The Chemistry of Organic Sulfur Compounds", Vol. 1, N. Kharasch, Ed., Pergamon Press, New York, N.Y., 1961, pp 112–120.
(4) T. Takeshima, N. Fukada, E. Okabe, F. Mineshima, and M. Muraoka, *J. Chem. Soc., Perkin Trans. 1*, 1277 (1975).
(5) (a) C. M. Buess, *J. Am. Chem. Soc.*, **77**, 6613 (1955); (b) N. Kreutzkamp and H. Peschel, *Arch. Pharm. (Weinheim, Ger.)*, **304**, 477 (1971); (c) H. Nagase, *Chem. Pharm. Bull.*, **22**, 505 (1974).
(6) R. L. N. Harris and L. T. Oswald, *Aust. J. Chem.*, **27**, 1309 (1974).
(7) S. Oae, T. Yagihara, and T. Okabe, *Tetrahedron*, **28**, 3203 (1972).
(8) T. Takeshima, N. Fukada, T. Ishii, and M. Muraoka, *J. Chem. Soc., Perkin Trans. 1*, 1706 (1976).
(9) W. J. Middleton, R. E. Heckert, E. L. Little, and C. G. Krespan, *J. Am. Chem. Soc.*, **80**, 2783 (1958).
(10) T. Takeshima, T. Miyauchi, N. Fukada, S. Koshizawa, and M. Muraoka, *J. Chem. Soc., Perkin Trans. 1*, 1009 (1973).
(11) T. Takeshima, M. Yokoyama, T. Imamoto, M. Akano, and H. Asaba, *J. Org. Chem.*, **34**, 730 (1969).
(12) T. Takeshima, N. Fukada, T. Miyauchi, M. Muraoka, T. Yamamoto, and T. Hayashi, *J. Chem. Soc., Perkin Trans. 1*, 914 (1974).

Intermediates in Nucleophilic Aromatic Substitution. 17.[1] Kinetics of Spiro Meisenheimer Complexes. Effect of Ring Size

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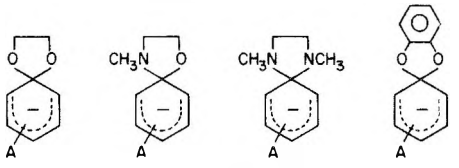
Received April 4, 1977

In the presence of base, 1-(3-hydroxypropoxy)-2,4,6-trinitrobenzene and 1-(3-hydroxypropoxy)-2,4-dinitrobenzene form the respective spiro Meisenheimer complexes with six-membered dioxane rings. On the other hand, 1-(4-hydroxybutoxy)-2,4,6-trinitrobenzene does not form a spiro complex but adds OH^- to the 3 position of the aromatic ring, whereas in the case of 1-(4-hydroxybutoxy)-2,4-dinitrobenzene spiro complex formation and OH^- attack on the aromatic ring appear to occur concurrently. Kinetic and equilibrium data on these reactions are reported. Spiro complex stability strongly decreases with increasing size of the spiro ring; this decrease is mainly due to a decrease in the rate of ring formation rather than ring opening, suggesting a complex-like transition state. The decrease in spiro complex stability with ring size is most pronounced with the 2,4,6-trinitrobenzene derivatives, least with the 2,4-dinitrobenzene derivatives, and intermediate with the 2,4-dinitronaphthalene derivatives known from the literature. This suggests that steric effects are important; in this comparison the changes from one system to another are mainly reflected in changes of the rate of ring opening rather than ring formation, suggesting a reactant-like transition state. A possible interpretation of this contradiction is that C–O bond formation and the turning of the o-nitro group(s) out of the plane of the aromatic ring have progressed to different degrees in the transition state. The question as to why spiro complex ring opening is much faster than methoxide ion departure from 1,1-dimethoxy Meisenheimer complexes is discussed. There are probably three factors which contribute; they are (a) difference in the basicity of the respective leaving groups, (b) relief of strain in the spiro complex, and (c) p–π overlap of the lone pairs of the nonleaving oxygen with the C–O bond being broken. Hydronium ion catalyzed spiro complex ring opening, on the other hand, proceeds at about the same rate as hydronium ion catalyzed methoxide ion in departure from 1,1-dimethoxy Meisenheimer complexes. Possible reasons are discussed.

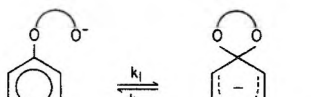
In our attempts to find model reactions which mimic C–O and C–N bond-forming and -breaking processes in S_NAr reactions we have studied the kinetics of the equilibrium formation of a number of spiro Meisenheimer complexes of the type **1–4**;[1,2] A represents activating substituents. In order to



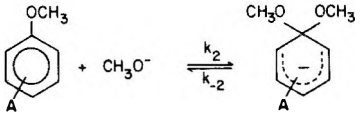
1 2d **2** 1,2c **3** 2b,2c **4** 2a

use these model reactions for the prediction of reactivities in *inter*molecular reactions, the intrinsic reactivity differences between inter- and intramolecular Meisenheimer complex forming reactions need to be known and understood.

It has commonly been observed that for nucleophiles of similar basicity the *intra*molecular addition is several orders of magnitude faster than *inter*molecular addition ($k_1 \gg k_2$, eq 1 and 2) and that the equilibrium constant for spiro com-



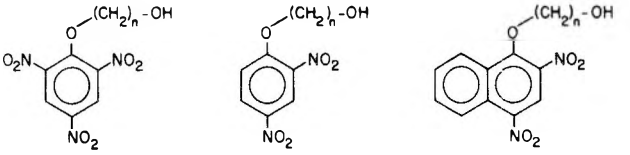
(1)



(2)

plex formation is several orders of magnitude higher than that for the intermolecular process ($K_1 \gg K_2$).[2,3] For example, for the spiro complex derived from 1-(2-hydroxyethoxy)-2,4,6-trinitrobenzene (**5a**) $k_1 \approx 4.8 \times 10^6\ s^{-1}$ [4] and $K_1 \approx 5.4 \times 10^7$ [4] in water, whereas for the formation of 1,1-dimethoxy-2,4,6-trinitrocyclohexadienate $k_2 = 17.3\ M^{-1}\ s^{-1}$ [5] and $K_2 = 1.7 \times 10^4\ M^{-1}$ [5] in methanol.[6] This greater facilitation of intramolecular reactions is consistent with general principles.[8,9]

Less well understood and perhaps contrary to expectation, ring opening of the (more stable) spiro complexes is considerably *faster* than methoxide ion departure from comparable complexes ($k_{-1} \gg k_{-2}$, typically by a factor of ~100 or more).[2,3] Since these observations referred to complexes with five-membered spiro rings of the type **1–4**, the first attempt to rationalize them was to invoke relief of steric strain in the five-membered ring.[3a] It appeared that a study of the effect of ring size on k_1 and k_{-1} might shed more light on this problem. Thus we set out to investigate spiro complex formation from the parent compounds **5b, 5c, 6b,** and **6c** and to compare them with **5a**[3a] and **6a**,[2e] respectively. When our study was already underway we learned that Crampton and Willison[3b] were investigating **7b** and **7c**, with a similar purpose

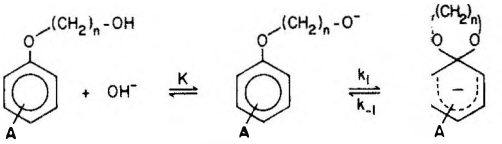


5a (n=2) **6a** (n=2) **7a** (n=2)
5b (n=3) **6b** (n=3) **7b** (n=3)
5c (n=4) **6c** (n=4) **7c** (n=4)

in mind. Some of our findings and conclusions reported here are similar to Crampton and Willison's,[3b] others deviate in important ways from theirs.

Results

Spiro complex formation occurs in two steps, where the first step is a rapid equilibrium, as shown in eq 3. When $n = 2$ spiro



(3)

complex formation is strongly favored over OH^- attack on the aromatic ring. However, when $n = 3$ or 4 spiro complex stability is much lower and the possibility that complexes such

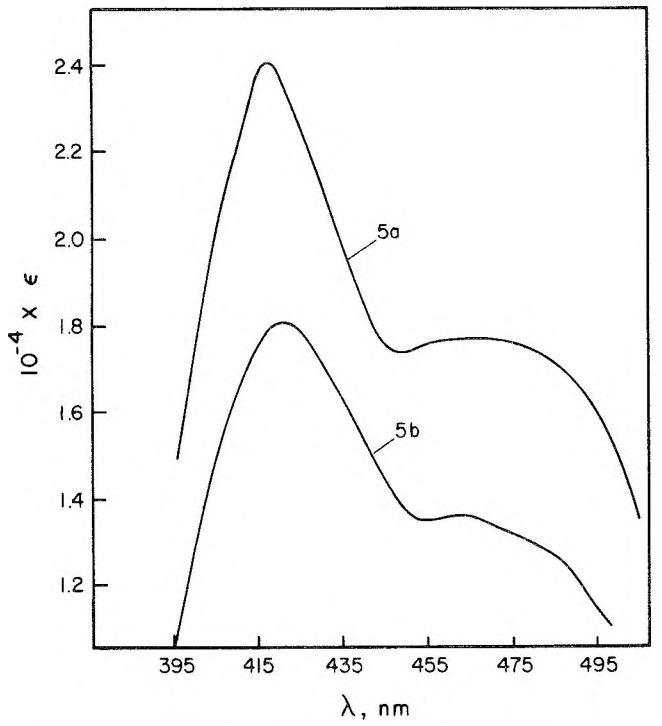
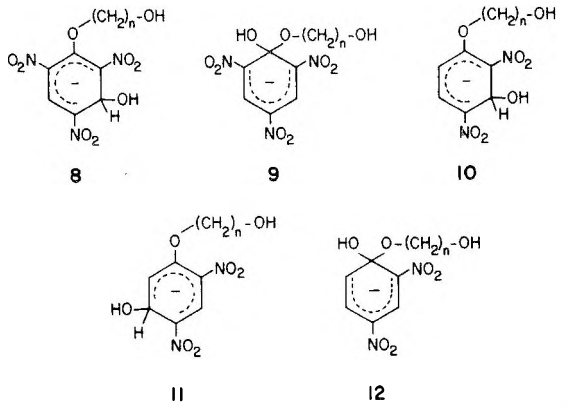


Figure 1. Spectra of the spiro complexes derived from **5a** (λ_{max} 416 nm, ϵ 24 000) and **5b** (λ_{max} 418 nm, ϵ 18 000[10]).

as 8–12 may be formed in competition with the respective spiro complex needs to be considered.



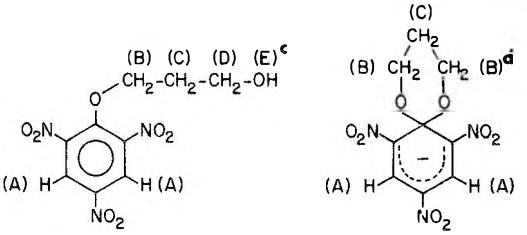
Another consequence of the lower spiro complex stability is that the parent substrate is present in significant concentration at equilibrium, which makes hydrolysis of the parent, to form picrate or 2,4-dinitrophenolate ion, respectively, an important side reaction.

1-(3-Hydroxypropoxy)-2,4,6-trinitrobenzene (5b). Addition of dilute NaOH to an aqueous solution of **5b** rapidly produces a short-lived species with a visible spectrum typical of Meisenheimer complexes. The color fades fairly rapidly due to conversion into picrate ion, which makes it necessary to record the spectrum in the stopped-flow spectrophotometer. The spectrum is shown in Figure 1; it is very similar to that of the spiro complex derived from **5a**[10] (also in Figure 1), suggesting that **5b** in fact forms a spiro complex.

^{1}H NMR data in Me_2SO-d_6, where the complex is much more stable than in aqueous solution, are also consistent with the structure of a spiro complex; they are summarized in Table I. It needs to be pointed out, however, that ^{1}H NMR proof in Me_2SO is not definite proof that the same complex also forms in aqueous solution, although it is very suggestive evidence.

Further evidence comes from kinetic measurements. Kinetics was studied in the stopped-flow apparatus, as a function

Table I. ^{1}H NMR Shift Data on 5b and Its Spiro Complex in Me_2SO-d_6[a,b]



H_A	9.13 (s, 2)	8.34 (s, 2)
H_B	4.31 (t, 2)	4.08 (t, 4)
H_C	1.87 (q, 2)	2.08 (q, 2)
H_D	3.50 (t, 2)	
H_E	3.87 (s, 1)	

[a] Chemical shifts (Me_4Si as internal standard); s = singlet, t = triplet, q = quintuplet; numbers in parentheses indicate relative intensities. [b] For NMR data in chloroform see ref 34. [c] Registry no., 56228-38-7. [d] Registry no., 63018-32-6.

Table III. Rate and Equilibrium Constants and Solvent Isotope Effects for the Reaction of NaOH with 5b in Water[a]

	15.1 °C	25.0 °C	35.1 °C
$Kk_1(H_2O)$, M^{-1} s^{-1}	11.2 ± 0.3	19.7 ± 0.1	36.3 ± 0.8
$k_{-1}(H_2O)$, s^{-1}	0.41 ± 0.04	0.87 ± 0.04	1.84 ± 0.1
$KK_1(H_2O)$, M^{-1}	27.3 ± 3.0	22.6 ± 1.1	19.7 ± 1.5
$Kk_1(D_2O)$, M^{-1} s^{-1}		26.6 ± 0.50	
$k_{-1}(D_2O)$, s^{-1}		0.69 ± 0.04	
$KK_1(D_2O)$, M^{-1}		38.6 ± 1.0	
$Kk_1(H_2O)/Kk_1(D_2O)$		0.74 ± 0.02	
$k_{-1}(H_2O)/k_{-1}(D_2O)$		1.26 ± 0.13	
$KK_1(H_2O)/KK_1(D_2O)$		0.585 ± 0.05	

[a] Kk_1 from slope of plot of $1/\tau$ vs. [NaOH]; k_{-1} from intercept of same plot; KK_1 from Kk_1/k_{-1}.

of [NaOH] at constant ionic strength, maintained by NaCl. Substrate concentration was always small compared to base concentration, thus assuring pseudo-first-order conditions. Based on the scheme of eq 3 the rates must obey:

$$\frac{1}{\tau} = \frac{Kk_1[\text{NaOH}]}{1 + K[\text{NaOH}]} + k_{-1} \quad (4)$$

where $1/\tau$ is the reciprocal relaxation time or pseudo-first-order rate constant for the approach to equilibrium.

Our data, collected in H_2O at three different temperatures, and in D_2O at one temperature, are summarized in Table II.[11] Plots of $1/\tau$ vs. [NaOH] (not shown) are linear, indicating that eq 4 simplifies to

$$1/\tau = Kk_1[\text{NaOH}] + k_{-1} \quad (5)$$

because of K[NaOH] $\ll 1$ even at the highest concentrations (0.4 M) used. From slopes and intercepts, the Kk_1 and k_{-1} values summarized in Table III are obtained.

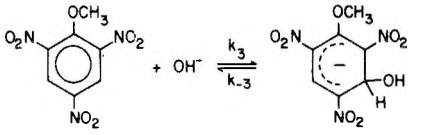
The linear concentration dependence of $1/\tau$ would, in principle, also be consistent with a reaction of OH^- with **5b** to form **8** (n = 3) or **9** (n = 3). Apart from the ^{1}H NMR evidence in favor of a spiro complex, **8** (n = 3) and **9** (n = 3) are unattractive alternatives for the following reasons. If the rate and equilibrium parameters referred to the formation of **8** (n = 3), they would be expected to be very similar to those for

Table VI. Rate and Equilibrium Constants and Solvent Isotope Effects of the Reactions of NaOH with 5c and with 2,4,6-Trinitroanisole in Water at 25 °C[a]

	5c[b]	TNA
$k_3(H_2O)$, M^{-1} s^{-1}	5.38 ± 0.50	7.37 ± 0.50
$k_{-3}(H_2O)$, s^{-1}	8.40 ± 0.30	8.90 ± 0.20
$K_3(H_2O)$, M^{-1}	0.64 ± 0.03	0.83 ± 0.04
$k_{-3}(D_2O)$, s^{-1}	5.50 ± 0.2	5.18 ± 0.15
$k_{-3}(H_2O)/k_{-3}(D_2O)$	1.53 ± 0.08	1.72 ± 0.08

[a] K_3 determined spectrophotometrically, with assumed ϵ 20 000 at 495 nm; k_{-3} from average of three $1/\tau$ values at [NaOH] = 0.01 to 0.06 M; k_3 from K_3k_{-3}. [b] Rate and equilibrium constant are believed to refer to formation of 8 (n = 4), hence the use of the symbols k_3 and k_{-3} instead of Kk_1 and k_{-1}, see text.

OH^- attack on the 3 position of 2,4,6-trinitroanisole (TNA), reaction 6. This is not the case. Kinetic and equilibrium data



(6)

for reaction 6 in H_2O and in D_2O, as a function of [NaOH], are summarized in Table IV,[11] whereas the rate and equilibrium constants calculated therefrom are in Table VI. We note that KK_1 = 22.6 for **5b** (Table III) is 27-fold larger than K_3 = 0.83 (eq 6) for TNA (Table VI), whereas k_{-1} = 0.87 for **5b** (Table III) is about ten times smaller than k_{-3} = 8.90 for TNA (Table VI). Furthermore, the different isotope effects on k_{-1} (**5b**) and k_{-3} (TNA) also indicate that we deal with different reactions; the value of $k_{-3}(H_2O)/k_{-3}(D_2O)$ = 1.72 (Table VI) is similar to the 1.70 for OH^- (OD^-) departure from the 4 position of the Meisenheimer complex derived from 1,3,6,8-tetranitronaphthalene,[12] whereas the value $k_{-1}(H_2O)/k_{-1}(D_2O)$ = 1.26 (Table III) is similar to 1.31 for ring opening of the spiro complex derived from **5a**.[3a]

9 (n = 3), though undoubtedly present at low concentrations as a precursor to picrate ion formation, cannot account for the kinetic and equilibrium parameters of complex formation either. This follows from the rate data on picrate ion formation, summarized in Table VII.[11] The pseudo-first-order rate constant (k_ψ) for picrate ion formation depends curvilinearly on [NaOH], as expected when there is an accumulating intermediate. If the data are analyzed by assuming that **9** (n = 3) is this accumulating intermediate, this requires that OH^- leaves **9** 12.4 times faster than $HOCH_2CH_2CH_2O^-$, which is contrary to the known tendency of alkoxide ions to be better leaving groups than OH^-.[7,13] Similar arguments exclude **9** (n = 4) and **12** (n = 3 or 4) in the systems described later in this paper and will not be repeated.

Analysis of the hydrolysis data according to

$$k_\psi = \frac{k_H[\text{NaOH}]}{1 + KK_1[\text{NaOH}]} \quad (7)$$

where k_H is the rate constant for hydrolysis of **5b** [equivalent to the rate constant of formation of **9** (n = 3)] leads, by way of an inversion plot ($k_\psi^{-1} = k_H^{-1}[\text{NaOH}]^{-1} + KK_1k_H^{-1}$), to k_H = 1.20 ± 0.12 M^{-1} s^{-1} and KK_1 = 17.2 ± 1.7 M^{-1}; this latter value is in fairly good agreement with KK_1 = 22.6 ± 1.1 (Table III) determined directly.

From the temperature dependence of Kk_1, k_{-1} and KK_1 (Table III) activation and thermodynamic parameters were calculated; they are summarized in Table VIII. For comparison purposes, analogous data were obtained for the spiro complex derived from **5a**, also included in Table VIII; the raw data for **5a** are in Table IX,[11] the rate and equilibrium constants in Table X,[11] whereas the experimental procedure is described in the Experimental Section.

Table VIII. Activation and Thermodynamic Parameters for Spiro Complex Formation

	5a[a]	5b[b]
$\Delta H^\ddagger(Kk_1)$, kcal/mol	4.3 ± 0.5	9.6 ± 0.5
$\Delta S^\ddagger(Kk_1)$, gibbs/mol	−17.4 ± 1.5	−20.4 ± 1.5
$\Delta H^\ddagger(k_{-1})$, kcal/mol	13.8 ± 1.0	12.1 ± 0.5
$\Delta S^\ddagger(k_{-1})$, gibbs/mol	−18.4 ± 3.0	−18.2 ± 1.5
$\Delta H°(KK_1)$, kcal/mol	−9.5 ± 0.5	−2.5 ± 1.0
$\Delta S°(KK_1)$, gibbs/mol	1.0 ± 1.5	−2.2 ± 3.0
$\Delta H^\ddagger(k_1)$,[c] kcal/mol	≈7.8	≈13.1
$\Delta H°(K_1)$,[c] kcal/mol	≈−6.0	≈1.0

[a] $\Delta H^\ddagger(Kk_1)$ and $\Delta H°(KK_1)$ determined from temperature dependence of Kk_1 and KK_1, respectively; $\Delta H^\ddagger(k_{-1})$ calculated as $\Delta H^\ddagger(Kk_1) - \Delta H°(KK_1)$; same holds true for entropies. [b] $\Delta H^\ddagger(Kk_1)$ and $\Delta H^\ddagger(k_{-1})$ determined from temperature dependence of Kk_1 and k_{-1}, respectively; $\Delta H°(KK_1)$ calculated as $\Delta H^\ddagger(Kk_1) - \Delta H^\ddagger(k_{-1})$; same holds true for entropies. [c] Estimated by assuming $\Delta H(K) \approx -3.5$ kcal/mol, see J. Murto, in "The Chemistry of the Hydroxyl Group", S. Patai, Ed., Interscience, Part 2, 1971, p 1087.

1-(4-Hydroxybutoxy)-2,4,6-trinitrobenzene (5c). The reaction of **5c** with NaOH also gives rise to a short-lived colored complex which is rapidly converted to picrate ion. Kinetic and equilibrium data obtained in the stopped-flow apparatus are summarized in Table V,[11] whereas in Table VI the rate and equilibrium constants are listed. We note that the equilibrium constant for complex formation is 0.64, which is very close to K_3 = 0.83 obtained for reaction 6; this suggests that the colored species formed in the reaction of **5c** with OH^- is 8 (n = 4) instead of the spiro complex. This conclusion is supported by the near identity of the reverse rate constant (8.4 s^{-1}) with k_{-3} = 8.9 s^{-1} for reaction 6.

The solvent isotope effect on the reverse reaction (1.53) is somewhat in between the one on k_{-3} in reaction 6 (1.72) and the one on k_{-1} for the ring opening of the spiro complexes derived from **5a** (1.31[3a]) and from **5b** (1.26), but closer to the one on k_{-3}. A possible interpretation of the intermediate value of the isotope effect is that there is a mixture of spiro complex with 8 (n = 4), but that k_{-1} and k_{-3} are close enough to prevent the detection of two separate kinetic processes.[14] This hypothesis is pure speculation at this point and shall not be discussed further.

1-(3-Hydroxypropoxy)-2,4-dinitrobenzene (6b). Due to the much lower reactivity of 2,4-dinitrobenzene derivatives, the reaction of NaOH with **6b** was studied in 52% Me_2SO–48% water; Me_2SO is known to favor Meisenheimer complex formation.[15] A visible spectrum, taken in the stopped-flow apparatus (not shown), is very similar to the one of the spiro complex derived from **6a**.[2d]

Kinetic and equilibrium data, obtained by the stopped-flow technique, are summarized in Table XI.[11] $1/\tau$ is independent of [NaOH], indicating that $Kk_1[\text{NaOH}] \ll k_{-1}$ so that eq 5 reduces to $1/\tau = k_{-1}$. Rate and equilibrium constants are summarized in Table XIV.

There is little doubt that the observed reaction is due to spiro complex formation; spiro complex formation is relatively more favored in 2,4-dinitrobenzene compared to 2,4,6-trinitrobenzene derivatives, because of less steric strain (see Discussion). As seen below this makes it even possible to see a spiro complex with **6c**.

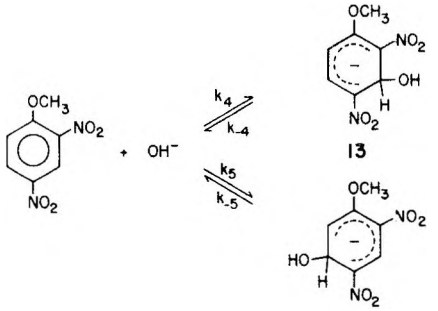
1-(4-Hydroxybutoxy)-2,4-dinitrobenzene (6c). In contrast to the cases discussed above, the reaction of **6c** with NaOH, studied in 52% Me_2SO–48% water and also in 60% Me_2SO–40% water, is characterized by *two* fast kinetic processes, followed by the usual much slower hydrolysis. Both

Table XIV. Rate and Equilibrium Constants of the Reactions of NaOH with 6b, 6c, and 2,4-Dinitroanisole (DNA) at 25 °C

	Kk_1,[a] $M^{-1}\,s^{-1}$	k_{-1}[b] s^{-1}	KK_1,[c] M^{-1}
6b (52% Me_2SO–48% H_2O)	0.26 ± 0.02	10.3 ± 0.3	0.025 ± 0.001
6c (52% Me_2SO–48% H_2O)	0.015 ± 0.0025 ($Kk_1 + k_4$)[d]	33 ± 3	4.5 ± 0.3 × 10^{-4} ($KK_1 + K_4$)[d]
6c (60% Me_2SO–40% H_2O)	0.094 ± 0.015 ($Kk_1 + k_4$)[d]	26 ± 1.3 $\Delta H^{\ddagger}$ = 10.1 ± 0.5 kcal/mol $\Delta S^{\ddagger}$ = −18.0 ± 1.5 gibbs/mol	3.6 ± 0.36 × 10^{-3} ($KK_1 + K_4$)[d]
DNA (60% Me_2SO–40% H_2O)	0.013 ± 0.003 (k_4)	(9.7 ± 1.2) (k_{-4}) $\Delta H^{\ddagger}$ = 13.2 kcal/mol $\Delta S^{\ddagger}$ = −9.5 gibbs/mol	1.3 ± 0.13 × 10^{-3} (K_4)

[a] Kk_1 obtained as $KK_1 \cdot k_{-1}$. [b] Average of $1/\tau$ values (Kk_1[NaOH] ≪ k_{-1}). [c] KK_1 determined from plot of OD/[parent]$_0$ vs. [NaOH], assuming ε 21 000. [d] Complex formation assumed to be mixture of spiro complex and **10**, see text. [e] Same as ref c, but ε 20 000.

Scheme I



rapid processes are associated with an increase in absorption in the range where Meisenheimer complexes typically absorb; this suggests that two different complexes are formed. Only the relaxation time of the fastest process could be evaluated with meaningful precision; the second process has a small amplitude and appears to be about ten times slower. The experimental data are summarized in Table XII;[-1] $1/\tau$ is independent of [NaOH],[16] indicating that complex formation is disfavored, as is borne out by the equilibrium measurements. Rate and equilibrium constants are summarized in Table XIV.

A comparison with the interaction of NaOH with 2,4-dinitroanisole (DNA) is helpful for the interpretation of our observation; this interaction also shows two rapid processes, in a similar time range as the reactions of **6c**. According to Hasegawa and Abe,[17] who report a spectral study in 98% Me_2SO–2% water, the two processes are best interpreted in terms of Scheme I where **13** is probably the complex which forms faster but where **14** is thermodynamically more stable. Just as for **6c**, kinetic and equilibrium data were only obtained for the faster of the two processes; they are collected in Table XIII,[11,16] whereas rate and equilibrium constants are in Table XIV.

In comparing the reactivity of **6c** with that of 2,4-dinitroanisole in 60% Me_2SO–40% water, we note that the rate and equilibrium constants for the two are similar (Table XIV), but the similarity is not as close as that between the reactions of **5c** and 2,4,6-trinitroanisole (Table VI). In particular the rate of complex formation for **6c** is almost sevenfold larger than that for 2,4-dinitroanisole, and the equilibrium constant almost threefold larger. A reasonable interpretation of these findings is that the fast process in the case of **6c** refers to the formation of a mixture of spiro complex and **10** (n = 4). Thus the measured equilibrium constant refers to $KK_1 + K_4$ (defined as in Scheme I) and the rate constant for complex formation to $Kk_1 + k_4$. Ordinarily the formation of two complexes should manifest itself by the observation of two separate relaxation processes. However, if k_{-4} and k_{-1} are very similar and $1/\tau$ is completely determined by the rate of complex dissociation, due to an equilibrium position disfavoring complex formation, the relaxation curves merge into a time function which appears to be one single exponential.[14]

Further support for the assumption that spiro complex formation is in part and perhaps mainly responsible for the observed reaction is that the activation parameters for complex dissociation are quite different for **6c** compared to those of 2,4-dinitroanisole (Table XIV).

Discussion

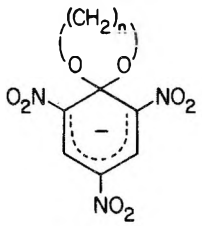
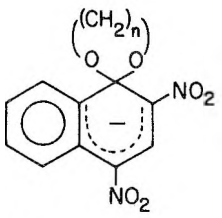
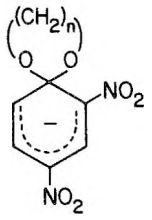
Spiro Complex Formation vs. OH^- Attack. For n = 3 we observe spiro complex formation for the 2,4,6-trinitrobenzene (**5b**) and 2,4-dinitrobenzene derivatives (**6b**), in agreement with Crampton and Willison's[3b] findings in the 2,4-dinitronaphthalene derivative (**7b**). Crampton and Willison[3b] also reported that spiro complex formation is the main interaction of **7c** with NaOH and that competition with OH^- attack on the aromatic ring is insignificant. This contrasts with our own conclusions in the 2,4,6-trinitrobenzene series where the main interaction of **5c** with NaOH is the formation of **8** (n = 4) and where there is no clear evidence that a spiro complex forms in detectable concentrations, and in the 2,4-dinitrobenzene series where our data suggest that **6c** forms a mixture of spiro complex with **10** (n = 4) and **11** (n = 4).

Absence of competing OH^- attack on the 3 position of **7c** is not surprising in view of the scarcity of reports about nucleophilic attack at the 3 position of 1-alkoxy-2,4-dinitronaphthalenes.[18] This is probably due to the absence of a nitro group para to the reaction site; nitro groups are known to have their greatest stabilizing influence on Meisenheimer complexes when in the para position.[15,19]

Effect of Ring Size on Spiro Complex Formation. Table XV summarizes kinetic and equilibrium parameters on the various spiro complexes. We note that in all three systems the effect of increasing ring size is to strongly decrease KK_1 and Kk_1, whereas k_{-1} is relatively little affected.[20] We agree with Crampton and Willison[3b] that the main effect on Kk_1 must be on the rate of the cyclization step (k_1), whereas K depends little on n.

In discussing the effect of ring size on rates of cyclizations it is usually recognized that there is an interplay of two main factors.[8,9,21] First, the formation of a ring results in the loss of rotational freedom and hence is accompanied by a decrease in entropy. With increasing chain length the loss in rotational freedom increases, which leads to increasingly more negative activation entropies. This is, for example, borne out by Illuminati's[20a] recent studies. The second factor is ring strain, which in cycloalkanes is known to decrease from three- to six-membered rings and then to increase with increasing ring size up to nine-membered rings.[22a,b] Recent data by Dale[22c] show that this is also true for oxygen containing rings; for

Table XV. Summary of Kinetic and Equilibrium Parameters on Spiro Complex Formation at 25 °C

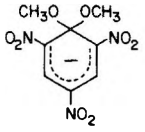
	Kk_1, M^{-1} s^{-1}	$\frac{Kk_1(n=2)}{Kk_1(n=3)}$	k_{-1}, s^{-1}	$\frac{k_{-1}(n=2)}{k_{-1}(n=3)}$	KK_1, M^{-1}	Solvent
						
$n = 2$[f]	7.25×10^5[a]	3.68×10^4	0.045[a]	0.052	1.6×10^7[a]	H_2O
$n = 3$[b]	1.97×10^1		0.87		2.26×10^1	H_2O
$n = 4$[b,g]	$\ll 10$				$\ll 1$	H_2O
						
$n = 2$[c]	9×10^4	5.30×10^4	2.3	2.70	3×10^4	H_2O
$n = 3$[d]	1.7		0.85		1.7	H_2O
$n = 4$[d]	0.6		0.64		0.7	H_2O
						
$n = 2$[e]	4.0×10^3	1.54×10^4	62	6.02	6.42×10^1	50% Me_2SO–50% H_2O
$n = 3$[b,h]	2.6×10^{-1}		10.3		2.5×10^{-2}	52% Me_2SO–48% H_2O
$n = 4$[b,i]	$\leq 1.5 \times 10^{-2}$		~33		$\leq 4.5 \times 10^{-4}$	52% Me_2SO–48% H_2O

[a] This work, at ionic strength 1.0 M; ref 3a reports $Kk_1 = 1.6 \times 10^6$ M^{-1} s^{-1}, $k_{-1} = 0.095$ s^{-1}, $KK_1 = 1.8 \times 10^7$ M^{-1}. [b] This work. [c] Reference 3a. [d] Reference 3b. [e] Reference 2d. [f] Registry no., 63058-85-5. [g] Registry no., 63018-33-7. [h] Registry no., 63018-34-8. [i] Registry no., 63018-35-9.

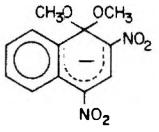
example, **15** is more strained than **16**. The strain factor is expected to be reflected in $\Delta H^{\ddagger}$.

15

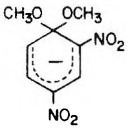
16



17



18



19

When comparing cyclizations of five- and six-membered rings, the latter are usually substantially slower,[8,9] just as in our cases, indicating that the smaller ring strain in the six-membered ring is over compensated by the more negative entropy. However, although $\Delta S^{\ddagger}$ for KK_1 is slightly more negative for the six-membered ring, **5a**, the difference between the two numbers is small and hardly distinguishable from experimental error. More significantly, however, $\Delta H^{\ddagger}$ for Kk_1 is about 5 kcal/mol more positive for the six-membered spiro complex, which suggests that ring strain is substantially *larger* in the *six*-membered rather than the five-membered ring. This probably arises from an unfavorable interaction of the spiro ring with the ortho nitro groups (steric compression) which, according to space filling molecular models, becomes worse as the ring size increases from five to six to seven (puckering of the ring). The consequence is to either increase steric strain directly, or to reduce resonance stabilization by the ortho nitro groups as they are moved out of the plane of the aromatic ring (indirect effect) or both. This is similar to Pietra's interpretation for the sulfur analogue spiro complexes.[23]

Intra- (k_{-1}) vs. Intermolecular (k_{-2}) Leaving Group Departure. Ring opening (k_{-1}) of the spiro complex from **5a** is about 82 times faster than methoxide ion departure from **17** ($k_{-2} = 5.51 \times 10^{-4}$ s^{-1} in water[24]), k_{-1} in the case of **7a** is about 580 times faster than methoxide ion departure from **18** ($k_{-2} = 3.95 \times 10^{-3}$ s^{-1} in methanol[25,26]), whereas k_{-1} for **6a** ($k_{-1} = 725$ s^{-1} in 2% Me_2SO–98% water[2d]) is about 17 times faster than methoxide ion departure from **19** ($k_{-2} = 42$ s^{-1} [26,27]). In their first attempt to rationalize these results, Crampton and Willison[3a] attributed the high rates of spiro complex ring opening to relief of steric strain. Later, based on their observation that in the 2,4-dinitronaphthalene series changing ring size mainly affects Kk_1 whereas k_{-1} hardly changes at all (Table XV), they concluded that the transition state for cyclization must already contain most of the strain present in the complex, so that an explanation of the high k_{-1} values in terms of strain relief no longer seemed justified.[3b] They offered an alternative explanation in terms of conformational differences about the C–O bonds in the spiro compared to 1,1-dimethoxy complexes. It was assumed that there is considerably more conformational freedom about the C–O bonds in the 1,1-dimethoxy complexes compared to the spiro complexes. In as much as this freedom is lost on passage to the transition state for C–O bond breaking, this would explain the lower rates.

It is difficult to assess the validity of this argument. If everything else were equal one would expect that this conformational effect should be reflected in more negative $\Delta S^{\ddagger}$ values for the 1,1-dimethoxy complexes. This is not borne out by the experimental data; in fact $\Delta S^{\ddagger}$ for methoxide ion departure from **17** is slightly *less* negative (−14.9 gibbs/mol in water[24]) than $\Delta S^{\ddagger}$ for spiro complex opening (−18.4 gibbs/mol for **5a**, −18.2 gibbs/mol for **5b**, Table VIII). Whether Crampton and Willison's conformational effect is perhaps masked by other effects, such as different solvation requirements in the transition state of spiro complex ring opening compared to 1,1-dimethoxy complex dissociation, or restriction in the rotation of the breaking C–O bond in the transition

state of spiro complex ring opening, cannot be decided on the basis of the data at hand.

Be it as it may, the faster rate with the spiro complex is an enthalpy effect ($\Delta H^{\ddagger}$ = 17.5 kcal/mol for **17**,[24] $\Delta H^{\ddagger}$ = 12.8 and 12.1 kcal/mol for **5a** and **5b**, respectively, Table VIII). We believe there are three factors which may all contribute to this effect. One of them is the lower pK_a of the OH group in **5a**, **6a**, and **7a** (p$K_a \leq 14.8$ based on pK_a of $CH_3OCH_2CH_2OH$[28]) compared to that of methanol (p$K_a \sim 15.5$ in water[28]). In view of our recent findings that the rate of alkoxide ion departure from 1,1-dialkoxy-2,4,6-trinitrohexadienate ions is roughly proportional to the acidity constant of the respective alcohols,[29] the above pK_a difference of $15.5 - \leq 14.8 = \geq 0.7$ could account for a factor of ≥ 5 in the accelerated spiro complex ring opening.

The second factor is relief of ring strain even though this was recently discounted by Crampton and Willison[3b] on the basis that the effect of ring size on k_{-1} is minimal in the 2,4-dinitronaphthalene series. This factor reveals itself when the effect of ring size on k_{-1} is compared among the three aromatic systems: $k_{-1}(n = 2)/k_{-1}(n = 3) = 0.052$ in the 2,4,6-trinitrobenzene system, 2.70 in the 2,4-dinitronaphthalene system, and 6.02 in the 2,4-dinitrobenzene system. This trend suggests that there are two opposing effects which influence these $k_{-1}(n = 2)/k_{-1}(n = 3)$ ratios. One of these effects could be the basicity of the leaving oxyanion, which might be expected to be somewhat higher when $n = 3$ than when $n = 2$, due to the attenuation of inductive effects. This would make the oxyanion for $n = 3$ a poorer leaving group and could account for $k_{-1}(n = 2)/k_{-1}(n = 3)$ ratios greater than one. The other effect is relief of strain (mainly with $n = 3$) which tends to make these ratios smaller than one and which is expected to be most pronounced in the most crowded 2,4,6-trinitrobenzene series.

A third factor, more speculative in nature, is that the most stable conformation about the C–O bonds in the 1,1-dimethoxy complexes is one where the lone pairs on the oxygen of the nonleaving methoxy group are *not* optimally aligned for p–π overlap in the transition state, whereas such alignment exists in the spiro complexes. This is similar to Crampton and Willison's suggestion at the end of their paper.[3b]

Structure of the Transition State. As pointed out before, the reduction in KK_1 with increasing ring size of the spiro complexes is mainly due to a large reduction in Kk_1 while k_{-1} changes relatively little with n (Table XV). As noted by Crampton and Willison[3b] this suggests a complex-like transition state.

On the other hand, a *reactant*-like transition state is suggested by a comparison of the effect of increasing bulkiness of the aromatic system on the $Kk_1(n = 2)/Kk_1(n = 3)$ and the $k_{-1}(n = 2)/k_{-1}(n = 3)$ ratios: the former change little when comparing the 2,4,6-trinitrobenzene, 2,4-dinitronaphthalene, and 2,4-dinitrobenzene series, the latter span a range of more than 100-fold (Table XV).

This kind of contradiction where different criteria suggest different transition state structures can often be resolved by assuming that different processes have made different progress in the transition state; i.e., it depends on one's definition of the reaction coordinate whether a transition state appears to be "early" or "late". An example somewhat similar to ours is the hydroxide ion addition to substituted benzaldehydes: changes in the equilibrium constants (by varying the substituents) are almost entirely reflected in changes of the forward rate constants (suggesting a product-like transition state), but the reactions are exothermic (suggesting a reactant-like transition state). This was interpreted by assuming that in the forward direction solvent reorganization lags behind C–O bond formation.[30] Other examples include Hupe and Jencks[31a] suggestion that desolvation of alkoxide ions has made more progress than C–O bond formation in the transition state of the reaction of alkoxide ions with esters, Sayer and Jencks[31b] suggestion that double bond formation and change of hybridization of carbon and nitrogen lag behind C–O bond cleavage and proton transfer in imine-forming elimination reactions, and the ionization of nitroalkanes in which rehybridization of carbon appears to lag behind proton removal and electron delocalization into the nitro substituent.[32]

In our own case the o-nitro group(s) is(are) probably turned out of the plane of the aromatic ring upon complex formation and it is conceivable that this process lags behind C–O bond formation. The difference in the bulkiness of the different aromatic systems would then be mainly felt when C–O bond formation has already made considerable progress, i.e., between the transition state and the complex. This would explain why the ratios $k_{-1}(n = 2)/k_{-1}(n = 3)$ but not $Kk_1(n = 2)/Kk_1(n = 3)$ are sensitive to the changes in bulkiness. In the absence of more evidence this interpretation is to be regarded as somewhat speculative.

Acid-Catalyzed Leaving Group Departure. It is interesting to compare the rate of the H^+-catalyzed ring opening of the spiro complex derived from **5a** ($k_{-1}^{H^+} = 2.2 \times 10^3\ M^{-1}\ s^{-1}$ [3a]) with that of H^+-catalyzed methoxide ion departure from **17** ($k_{-2}^{H^+} = 3.5 \times 10^3\ M^{-1}\ s^{-1}$ [29]). One obtains the ratio $k_{-1}^{H^+}/k_{-2}^{H^+} = 0.63$ which is in contrast to $k_{-1}/k_{-2} = 82$ for the *non*catalyzed reactions. This drastic change means that the factors which are responsible for the relatively much faster noncatalyzed spiro complex ring opening must be ineffective in the acid-catalyzed reaction or that a new, compensating factor plays a role in the acid-catalyzed leaving group departures, or both.

One (though probably minor) factor which was invoked as contributing to the large k_{-1}/k_{-2} ratio in the noncatalyzed reactions was the higher pK_a of methanol compared to the OH group in **5a**. This factor not only becomes ineffective in the acid-catalyzed reactions, but has even the opposite effect in that it slightly favors the departure of the more basic methoxide ion. This conclusion is based on our recent findings that the rate of H^+-catalyzed alkoxide ion departure from 1,1-dialkoxy-2,4,6-trinitrocyclohexadienates increases with increasing basicity of the alkoxide.[29]

The higher basicity of the methoxide ion could probably account entirely for the value of 0.63 in the $k_{-1}^{H^+}/k_{-2}^{H^+}$ ratio if protonation of the complex were the rate-determining step. On the other hand, if the mechanism of acid catalysis involved rapid equilibrium protonation followed by rate-limiting departure of the protonated leaving group, or, most likely,[3a,29] if the reaction is concerted, the basicity factor could only account for part of the change from $k_{-1}/k_{-2} = 82$ to $k_{-1}^{H^+}/k_{-2}^{H^+} = 0.63$.

Thus one is compelled to conclude that the other two factors believed to be partly responsible for the high k_{-1}/k_{-2} ratios in the noncatalyzed reaction, viz, relief of strain and alignment of the lone pairs for p–π overlap, are less effective in the acid-catalyzed reaction. This would imply that C–O bond breaking has made less progress in the transition state of the acid-catalyzed compared to the noncatalyzed reaction.

Experimental Section

Materials. 1-(3-Hydroxypropoxy)-2,4,6-trinitrobenzene (**5b**) was prepared by adding 9 mL of a 2.1 M sodium 3-hydroxypropoxide solution in 1,3-propanediol to 4 g of picryl chloride in 50 mL of 1,3-propanediol. The solution which immediately turned dark red was allowed to stand for 2 h and was then extracted with chloroform to remove unreacted picryl chloride. The reaction solution was then added to ice water and acidified to pH ~4. A yellow oil appeared which crystallized in the refrigerator, mp 50–52 °C,[33] ^{1}H NMR see Table I.

1-(4-Hydroxybutoxy)-2,4,6-trinitrobenzene (**5c**) was prepared by

a similar procedure, except that 1,3-propanediol was replaced by 1,4-butanediol, the picryl chloride was dissolved in a 1:1 mixture of 1,4-butanediol and *p*-dioxane, and the chloroform extraction was omitted. Mp 51–52 °C, ^{1}H NMR (Me_2SO-d_6) δ 8.99 (s, 2, ring protons), 4.16 (t, 2, α-CH_2), 1.70 (m, 4, β- and γ-CH_2), 3.37 (t, 2, δ-CH_2), 3.82 (s, 1, OH). **5c** decomposes over the time of about 2 weeks when stored in a desiccator.

1-(3-Hydroxypropoxy)-2,4-dinitrobenzene (**6b**) was prepared by adding 15 mL of a 2.6 M sodium 3-hydroxypropoxide solution in 1,3-propanediol to 7 g of 1-chloro-2,4-dinitrobenzene in 60 mL of 1,3-propanediol. After heating on a steam bath for 1 h the solution was poured onto 1 L of ice water and acidified. A yellow oil appeared which slowly crystallized; it was twice recrystallized from water: mp 55–56.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.82 (d, 1, aromatic 3 position), 8.43 and 8.60 (dd, 1, aromatic 5 position), 7.37 (d, 1, aromatic 6 position), 4.48 (t, 2, α-CH_2), 2.17 (q, 2, β-CH_2), 3.93 (t, 2, γ-CH_2), ~2 (broad, OH).

1-(4-Hydroxybutoxy)-2,4-dinitrobenzene (**6c**) was prepared from 1,4-butanediol by an analogous procedure as for **6b**, mp 41–42 °C, ^{1}H NMR ($CDCl_3$) δ 8.80 (d, 1, aromatic 3 position), 8.42 and 8.58 (dd, 1, aromatic 5 position), 7.30 (d, 1, aromatic 6 position), 4.35 (t, 2, α-CH_2), 2.0 (m, 4, β- and γ-CH_2), 3.78 (t, 2, δ-CH_2), ~2 (broad, OH).

2,4,6-Trinitroanisole and 2,4-dinitroanisole were available from previous studies.[27,35] Me_2SO (Baker Analyzed Reagent Grade) was used without further purification. D_2O (Mallinckrodt) was 99.8% pure.

Spectra. ^{1}H NMR spectra were taken at 60 MHz on a JEOL "Minimar" spectrometer. Visible spectra were obtained in a Durrum stopped-flow spectrophotometer or Cary 14 spectrophotometer (for **5a**).

Kinetic and Equilibrium Measurement. Except for the kinetics of picrate formation from **5b**, which was monitored on a Gilford 2000 kinetic spectrophotometer at λ 500 nm, all kinetic measurements were made on a Durrum stopped-flow spectrophotometer, at λ around 500 nm. In the case of **5a, 5b, 5c, 6b,** and 2,4,6-trinitroanisole good first-order plots were obtained and $1/\tau$ was easily evaluated; in the case of **6c** and 2,4-dinitroanisole the first part of the biphasic plots could still be evaluated relatively easily by known procedures,[14] since the time separation between the two processes was about a factor of 10.

In determining the $[OH^-]$ dependence of $1/\tau$ and of OD for **5a**, the OH^- concentration was calculated by solving eq 8 for $[OH^-]$:

$$K_w = \frac{\gamma_{H^+}\gamma_{OH^-}}{a_{H_2O}}[H^+][OH^-] = \frac{\gamma_{H^+}\gamma_{OH^-}}{a_{H_2O}}\frac{a_{H^+}}{\gamma_{H^+}}[OH^-] \qquad (8)$$

where a_{H^+} was measured by a Corning digital pH meter, γ_{H^+},[36a] $\gamma_{H^+}\gamma_{OH^-}/a_{H_2O}$,[36b] and K_w[37] are known at the employed temperatures and ionic strength.

Acknowledgment. Support of this work by Grant MPS 74-08379-A01 from the National Science Foundation is gratefully acknowledged.

Supplementary Material Available: Tables II, IV, V, VII, IX–XIII (10 pages). Ordering information is given on any current masthead page.

Registry No.—**5a,** 6478-31-5; **5c,** 63018-29-1; **6b,** 63018-30-4; **6c,** 63018-31-5; 2,4,6-trinitroanisole, 606-35-9; 2,4-dinitroanisole, 119-27-7; picryl chloride, 88-88-0; 1,3-propanediol, 504-63-2; 1,4-butanediol, 110-63-4; 1-chloro-2,4-dinitrobenzene, 97-00-7.

References and Notes

(1) Part 16: C. F. Bernasconi, C. L. Gehriger, and R. H. de Rossi, *J. Am. Chem. Soc.*, **98**, 8451 (1976).
(2) (a) C. F. Bernasconi and H.-C. Wang, *J. Am. Chem. Soc.*, **98**, 6265 (1976); (b) C. F. Bernasconi and F. Terrier, *ibid.*, **97**, 7458 (1975); (c) C. F. Bernasconi and C. L. Gehriger, *ibid.*, **96**, 1092 (1974); (d) C. F. Bernasconi and H. S. Cross, *J. Org. Chem.*, **39**, 1054 (1974); (e) C. F. Bernasconi and R. H. de Rossi, *ibid.*, **38**, 500 (1973).
(3) (a) M. R. Crampton and M. J. Willison, *J. Chem. Soc., Perkin Trans. 2*, 1681, 1686 (1974); (b) M. R. Crampton and M. J. Willison, *ibid.*, 155 (1976).
(4) Based on Crampton and Willison's results[3a] and assuming that the equilibrium constants for the deprotonation of 1-(2-hydroxyethoxy)-2,4,6-trinitrobenzene by OH^- is 0.3 M^{-1}.
(5) J. H. Fendler, E. J. Fendler, and C. E. Griffin, *J. Org. Chem.*, **34**, 689 (1969).
(6) The equilibrium and rate constants given are not strictly comparable for two reasons: (a) K_2 and k_2 were determined in methanol; in water they are expected to be at least threefold lower.[7] (b) More seriously, since the units of K_1 and K_2 and of k_1 and k_2 are not the same they cannot be directly compared. This problem can be avoided by defining the concentration in terms of mole fractions,[8] which necessitates a multiplication of K_2 and k_2 by the molarity of the solvent (55.5 for water). With these two corrections one obtains $k_2 \approx 320$ (still $\ll k_1$) and $K_2 \approx 3.15 \times 10^5$ (still $\ll K_1$).
(7) C. F. Bernasconi and R. G. Bergstrom, *J. Org. Chem.*, **36**, 1325 (1971).
(8) M. I. Page, *Chem. Soc. Rev.*, **2**, 295 (1973).
(9) See, e.g., B. Capon, *Q. Rev., Chem. Soc.*, **18**, 45 (1964).
(10) Since the spiro complex is not formed quantitatively, the extinction coefficients were calculated on the basis of the kinetically determined equilibrium constant of complex formation. Whether ϵ is, in fact, about 25% lower than in the case of **5a** as shown in Figure 1 or whether this reflects an experimental error in the equilibrium constant is difficult to decide.
(11) See paragraph concerning supplementary material at the end of this paper.
(12) J. H. Fendler, E. J. Fendler, and L. M. Casilio, *J. Org. Chem.*, **36**, 1749 (1971).
(13) C. F. Bernasconi and R. G. Bergstrom, *J. Am. Chem. Soc.*, **92**, 4682 (1970).
(14) C. F. Bernasconi, "Relaxation Kinetics", Academic Press, New York, N.Y., 1976, Chapter 9.
(15) For recent reviews, see (a) M. R. Crampton, *Adv. Phys. Org. Chem.*, 3, 211 (1969); (b) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).
(16) $1/\tau$ decreases by 10–20% with increasing [NaOH]. This is probably an artifact because of the difficulty in determining $1/\tau$ with high precision due to interference by the second process.
(17) Y. Hasegawa and T. Abe, *Bull. Chem. Soc. Jpn.*, **46**, 2756 (1973).
(18) F. Millot and F. Terrier, *Bull. Soc. Chim. Fr.*, 2692 (1969).
(19) See, e.g., (a) F. Terrier, A.-P. Chatrousse, and R. Schaal, *J. Org. Chem.*, **37**, 3010 (1972); (b) F. Millot and F. Terrier, *Bull Soc. Chim. Fr.*, 1823 (1974); (c) R. M. Murphy, C. A. Wulff, and M. J. Strauss, *J. Am. Chem. Soc.*, **96**, 2678 (1974); (d) J. H. Fendler, W. L. Hinze, and L.-J. Liu, *J. Chem. Soc., Perkin Trans. 2*, 1768 (1974).
(20) The slight difference in the solvent for $n = 2$ compared to $n = 3$ and 4 in the 2,4-dinitrobenzene derivatives has a negligible influence on the kinetic and equilibrium parameters and does not affect the conclusions.
(21) See, e.g., (a) G. Illuminati, L. Mandolini, and R. Masci, *J. Am. Chem. Soc.*, **97**, 4960 (1975); (b) A. C. Knipe and C. J. M. Stirling, *J. Chem. Soc. B*, 67 (1968).
(22) (a) J. Sicher, *Prog. Stereochem.*, **3**, 202 (1962); (b) E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1967, Chapter 7; (c) J. Dale, *Pure Appl. Chem.*, **25**, 469 (1971).
(23) R. Cabrino, E. Farina, F. Del Cima, and F. Pietra, *J. Chem. Soc., Perkin Trans. 1*, 2214 (1976).
(24) J. Murto and J. Vainionpää, *Suom. Kemistil. B*, **39**, 133 (1966).
(25) J. H. Fendler, E. J. Fendler, W. E. Byrne, and C. E. Griffin, *J. Org. Chem.*, **33**, 977 (1968).
(26) The rate is likely to be about the same in water.
(27) C. F. Bernasconi, *J. Am. Chem. Soc.*, **90**, 4982 (1968).
(28) P. Ballinger and F. A. Long, *J. Am. Chem. Soc.*, **82**, 795 (1960).
(29) C. F. Bernasconi and J. R. Gandler, in preparation.
(30) R. P. Bell and P. E. Sorensen, *J. Chem. Soc., Perkin Trans. 2*, 1594 (1976).
(31) (a) D. J. Hupe and W. P. Jencks, *J. Am. Chem. Soc.*, **99**, 451 (1977); (b) J. M. Sayer and W. P. Jencks, *ibid.*, **99**, 464 (1977).
(32) (a) F. G. Bordwell and W. J. Boyle, Jr., *J Am. Chem. Soc.*, **94**, 3907 (1972); (b) F. G. Bordwell and W. J. Boyle, Jr., *ibid.*, **97**, 3447 (1975); (c) A. J. Kresge, *Can. J. Chem.*, **52**, 1897 (1974); (d) R. Fuchs and E. S. Lewis in "Techniques of Chemistry", Vol. 6, Part 1, A. Weissberger, Ed., Wiley, New York, N.Y., 1974, Chapter 14.
(33) Drozd et al.[34] report mp 55 °C.
(34) V. N. Drozd, V. N. Knyazev, and V. M. Minov, *Zh. Org. Khim.*, **11**, 1135 (1975).
(35) C. F. Bernasconi, *J. Am. Chem. Soc.*, **93**, 6975 (1971).
(36) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions", Reinhold, New York, N.Y., 1950, (a) p 575; (b) p 598.
(37) "Handbook of Chemistry and Physics", 52nd ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1971–1972, p D-122.

Nucleophilic Addition of o-Tolyllithium Compounds to Di-*tert*-butyl Ketone. Thermal and Organolithium-Catalyzed Isomerization of o-Tolyldi-*tert*-butylcarbinol Rotamers

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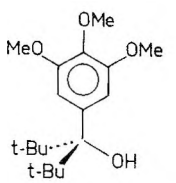
Received February 25, 1977

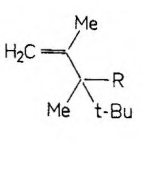
Addition of ring-substituted *o*-tolyllithium compounds to di-*tert*-butyl ketone gives rise to rotamers, syn- (sp) and anti-periplanar (ap) *o*-tolyldi-*tert*-butylcarbinols, the latter representing about 85–93% of the total, depending on the substituent. The ap isomer can be thermally isomerized to the sp form which, according to empirical force field calculations, is 6 kcal/mol more stable than the other. The IR and NMR spectra reveal marked similarities between the ap isomer and phenyldi-*tert*-butylcarbinol whereas the behavior of the hydroxyl group in the sp isomer is modified by the proximity of the *o*-methyl group. The enthalpy of activation for ap to sp rotation in dodecane varies from 25.1 to 26.6 kcal/mol whereas the activation entropy is −9 eu regardless of the substituent. The rotation rate of the parent compound is enhanced by a factor of about 10^5 by *n*-butyllithium in hexane, probably due to an increase in ground state strain in the lithium alkoxide ion pair. The mechanism of aryllithium addition to ketones is discussed: the formation of the ap alcohol is consistent with a four-center transition state with the aryl ring in the same plane as the carbonyl group and bisecting the *t*-Bu–C–*t*-Bu angle.

Restricted rotation about a single bond, other than a phenyl–phenyl bond, has been investigated primarily by the dynamic NMR method wherein barriers to rotation are measured by observing the temperature dependence of signals of protons which are exchanging environments. In this way barrier heights have been measured for rotation about a wide variety of bonds, including sp^3–sp^3 and sp^3–sp^2 carbon to carbon bonds.[1]

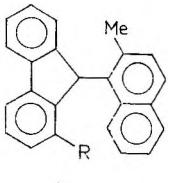
Recently, attention has been focused to some extent upon the isolation of rotamers, alternatively referred to as atropisomers or conformers. For this to be possible, two conditions at least must be satisfied. Firstly, the rotation energy barrier must be sufficiently high, about 15 kcal/mol or more, so that separation can be effected under normal experimental operating conditions, without significant isomerization. Further, the system must possess an asymmetric element which allows the differentiation of eventual rotational isomers. Thus, although the barrier to rotation about the phenyl to sp^3 carbon bond in 3,4,5-trimethoxypenyldi-*tert*-butylcarbinol (**1**) is high enough (about 20 kcal/mol),[1c,2] the rotamers are obviously identical, and rotation can only be discerned by NMR. The presence of two *tert*-butyl groups on an sp^3 carbon raises considerably the rotational energy barrier, as also occurs in the olefin **2** where $\Delta G^{\ddagger}$ goes from 9.1 to 11.2 to 15.4 kcal/mol for R = ethyl, isopropyl, and *tert*-butyl, respectively.[1e,3]



1



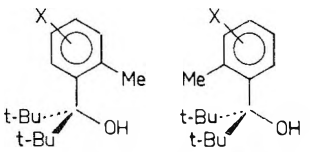
2



3 R = H
4 R = Me

Successful separation of rotamers has been achieved in the 9-arylfluorene series where not only are the barriers high, up to about 33 kcal/mol, but the introduction of an asymmetric element is straightforward.[4–7] Rotamers of 9-(2-methyl-1-naphthyl)fluorene (**3**) were partially separated by crystallization[7] and more recently **4** has been isolated in two crystalline forms.[5,8,9] It has been suggested[7] that the fact that two of the aryl groups bonded to the sp^3 carbon in question are bridged contributes to the enhancement of the energy barrier in such compounds and thus favors distinction between the two conformers. Mislow et al. have demonstrated,[10] however, that in suitably substituted triarylmethanes it is possible to isolate diastereomers with an interconversion barrier of some 30 kcal/mol, this interconversion occurring via a "one-ring flip" mechanism, which actually involves three simultaneous rotations about the phenyl to sp^3 carbon bonds.

Among systems containing three independent (i.e., not bridged) substitutents to an sp^3 carbon and where conformational isomerism involves, in principle, rotation about one bond only, the aryldi-*tert*-butylcarbinols offer the best prospects for the isolation of rotamers. We have shown[11] that the introduction of an *o*-methyl substituent into a system akin to alcohol **1** not only provides an asymmetric tag, but also increases the rotational energy barrier to about 29 kcal/mol ($\Delta G^{\ddagger}$), thus making the separation of rotamers **5** and **6** a relatively simple affair.



5 **6**

a : X = 4-OMe
b : 4-Me
c : 5-Me
d : H
e : 5-Cl
f : 3,4,5-Me_3

This system presents several features which make it interesting for further study. The NMR and IR spectra are sensitive to the environment of the OH group, the rotation rate of the less stable alcohol is easily measured by GLC, and the isomers are very different in their stability. The condensation of *o*-tolyllithium with di-*tert*-butyl ketone gives primarily the less stable isomer; in attempting to check our original interpretation of this phenomenon we were led to examine the stability of the alkoxides generated by treatment of the alcohols by *n*-BuLi and, incidentally, to observe a novel organolithium-catalyzed rotation process.

Finally, we propose a simple model for the transition state of nucleophilic addition of an aryllithium compound to a carbonyl group.

Results and Discussion

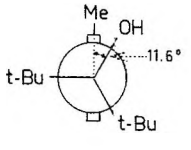
Aryldi-*tert*-butylcarbinols are most conveniently synthesized by the condensation of an aryllithium with di-*tert*-butyl ketone in diethyl ether at ambient temperature.[12] Normal work-up procedure (slow distillation at reduced pressure or preparative GLC on SE30 or Apiezon L at about 200 °C) led to the isolation of a stable alcohol **5** with appropriate IR and NMR spectral characteristics. When a crude reaction product

Table I. Spectroscopic Data for *o*-Tolyldi-*tert*-butylcarbinols, 5 and 6

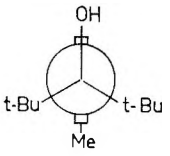
Compd	X	IR (CCl_4), cm^{-1}	NMR (CCl_4); ppm rel to internal Me_4Si						
			t-Bu (s, 18 H)	OH[a] (s, 1 H)	2-Me (s, 3 H)	Aromatic protons 3,4,5-H	6-H	$\Delta\nu$	X
5a	4-OMe	3643	1.09	1.73 (3.78)	2.56	6.52	7.34		3.72 (s, 3 H)
6a	4-OMe	3650, 3612	1.12	1.70 (4.29)	2.58	6.59	7.89	0.55	3.73 (s, 3 H)
5b	4-Me	3644	1.07	1.73 (3.82	2.56	6.89	7.28		2.30 (s, 3 H)
6b	4-Me	3650, 3613	1.11	1.69 (4.31)	2.57	6.86	7.84	0.56	2.25 (s, 3 H)
5c	5-Me	3643	1.13	1.77 (3.85)	2.57	6.89	7.28		2.30 (s, 3 H)
6c	5-Me	3649, 3613	1.12	1.72 (4.25)	2.57	6.86	7.80	0.52	2.30 (s, 3 H)
5d	H	3644	1.10	1.78 (3.84)	2.61	7.01	7.44		
6d	H	3650, 3613	1.13	1.75 (4.35)	2.62	7.01	8.01	0.57	
5e	5-Cl	3644	1.12	1.80 (4.13)	2.56	6.95	7.44		
6e	5-Cl	3649, 3611	1.12	1.85 (4.63)	2.57	6.98	8.00	0.54	
5f	3,4,5-Me_3	3641	1.11	1.78	2.51		7.11		2.16, 2.22 (6 H, 3 H)
6f	3,4,5-Me_3	3651, 3611	1.13	1.68	2.39		7.61	0.50	2.19, 2.27 (6 H, 3 H)

[a] Figures in parentheses are for Me_2SO solutions.

containing the 4-methoxy derivative **5a** was exposed for several weeks at summer room temperature (25 ± 5 °C), the alcohol **5a** was obtained in the form of well-defined triclinic crystals containing two molecules per unit cell. The complete crystallographic study, carried out by Hough,[13] gives full details of the molecular geometry, whose most important features are the angle between the plane of the aryl group and the C–O bond (11.6°) and the proximity of the o-methyl carbon to the carbinol oxygen atom (2.66 Å). This establishes unambigously that **5a** has the syn-periplanar (sp) conformation,[14] shown in **5A**. From the IR and NMR spectral similarities (Table I) it can be deduced that the other alcohols are of the same structural type as the 4-methoxy derivative.



5A

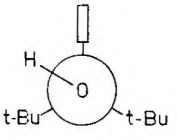


6B

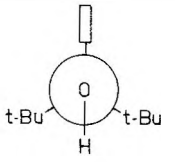
Whereas gas chromatography at the elevated temperatures required for such involatile compounds on regular 5-ft columns reveals only one product in the crude reaction mixture, it is possible by operating with very short, lightly loaded columns to reduce the oven temperature and the retention times to such an extent that the presence of a second product, **6**, of higher retention time than the stable isomer **5** becomes apparent. Moreover, this thermally unstable isomer proves to be the major component of the reaction mixture prior to distillation. This product can by isolated by adsorption chromatography on an alumina column packed in pentane or light petroleum; the stable isomer is eluted before the unstable one. Although it has not yet been possible to carry out a crystal study on this isomer, it is clear from spectral data and force-field calculations that it must have the anti-periplanar (ap) conformation,[14] **6B**.

Spectral Behavior. The NMR and IR spectra of the two conformers (Table I) are consistent with the structures assigned to the stable and unstable isomers, sp and ap, respectively. Thus, in Me_2SO the NMR absorption of the hydroxyl proton of alcohol **5** is at δ 3.78–3.85, whereas that of alcohol **6** is at δ 4.25–4.35, except for X = 5-Cl, where both values are substantially higher. A value of δ 4.16 has been reported for phenyldi-*tert*-butylcarbinol.[15b] Now, it is known that the downfield shift of the absorption of the hydroxyl proton in Me_2SO is related to the accessibility of the hydroxyl group;[15] the observed downfield shifts indicate then that the hydroxyl group is less accessible in **5** than in **6**.

The IR absorption of the OH stretch in isomer **5** is a narrow band (10^{-2}M solution in CCl_4) at 3643 cm^{-1} characteristic of free OH, whereas in the other isomer **6** there are peaks at 3612 and 3650 cm^{-1}. In this respect also, isomer **6** is rather similar to phenyldi-*tert*-butylcarbinol, which has bands at 3617 and 3644 cm^{-1}; the first of these was attributed to π-complexed OH,[16] but this implies a spatial relationship between the OH group and the aryl ring which was subsequently rejected.[15b] It is reasonable to attribute the two bands to conformations such as **6C** and **6D**.[15b] The absence of the low-frequency band in **5** corresponds then to the exclusion of conformation **C** due to the proximity of the o-methyl and the hydroxyl hydrogen atom which would arise therein.



6C



6D

Another feature of importance is the NMR shift of the ortho proton, which is about 0.55 ppm further downfield in isomer **6** than in the stable isomer **5**. A rather smaller difference, 0.22 ppm in the same direction, was found[2] between the two nonequivalent ortho protons in carbinol **1**. The nonequivalence of the ortho protons has been attributed to two competing effects:[1c] (i) the downfield shifts caused by the hydroxyl group, the syn ortho hydrogen being shifted about 0.6 ppm further than the anti; (ii) the downfield shift caused by overcrowding; the shift for the ortho hydrogen between the two *tert*-butyl groups is greater by 0.4 ppm. It seems likely that the very high downfield shift of the syn ortho hydrogen in alcohol **6** is due to an enhanced downfield contribution by the hydroxyl group, which will be much closer to this proton than it is in the phenyl, as opposed to o-tolyl, derivatives.

In conclusion, the spectral data are consistent with considerable steric hindrance by the o-methyl group of the hydroxyl group in the isomer **5** (sp), whereas isomer **6** (ap) resembles phenyldi-*tert*-butylcarbinol in that there is an accessible hydroxy function.

Estimation of the Ground-State Energies by Empirical Force-Field Calculations. Whereas most studies of restricted rotation about single bonds are concerned with conformers of similar energy, in the present case the thermal equilibrium between the ap and sp alcohols lies so heavily in

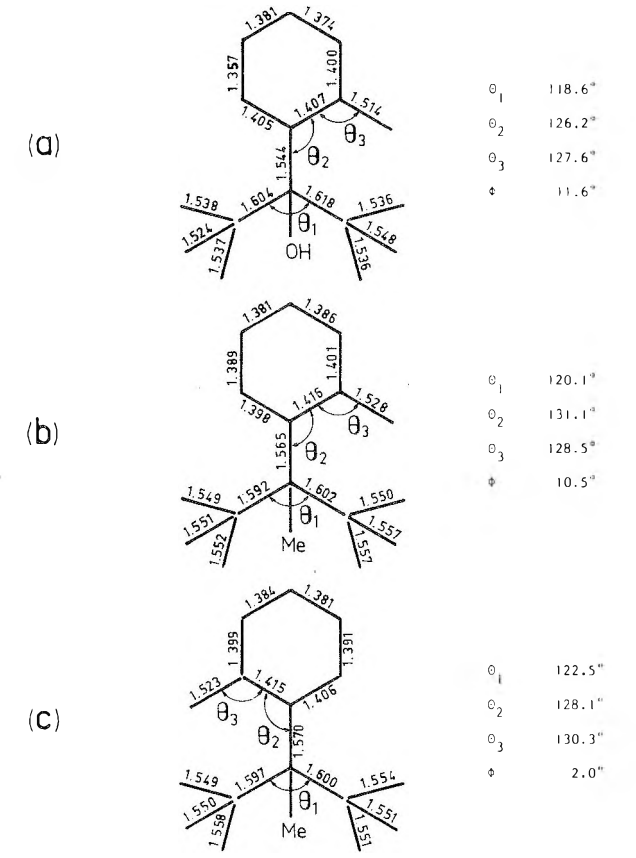
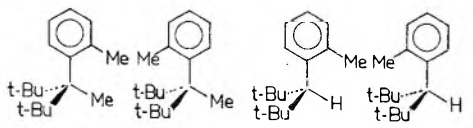


Figure 1. Molecular geometry of *o*-tolyldi-*tert*-butylcarbinols: (a) sp isomer from crystal data on **5a**; (b) force-field calculation on **5d** with OH replaced by Me; (c) force-field calculation on **6d** with OH replaced by Me. Φ is the angle between the benzene ring and the C–OH or C–Me bond. The layout of these structures is purely schematic and is designed to display the critical bond distances and angles.[26]

favor of the sp isomer that the ap isomer is not detectable by GLC (<0.1%); the energy difference between the conformers must then be at least 4–5 kcal/mol. A more precise estimate was obtained by empirical force field (molecular mechanics) calculations. This approach has been applied mainly to the calculation of the strain energies of saturated hydrocarbons, but has been extended to systems containing functional groups by Allinger, Boyd, Mislow, Schleyer, and others.[17]

Alcohols pose certain problems related to the nonspherical electron density distribution about the nucleus[18a] and have only recently been handled explicitly by the force-field approach.[18b] However, in cases where we are interested only in steric energy differences rather than in absolute values of the heat of formation, an OH group,[19] or even a tosylate[20] or a *p*-nitrobenzoate[21] group, can be treated as a hydrogen atom or a methyl group. A modified Boyd–Allinger force field for the treatment of benzenoid hydrocarbons is included in the Andose–Mislow program STRAIN which we used.[22]

Since we are concerned with conformation isomers in which the numbers of different bond and atom types are constant, the problem of determining the best values for group increments,[23] zero-point energy corrections,[24] etc., does not arise.



	5-Me	6-Me	5-H	6-H
Steric energy (kcal/mol)	40.1	46.7	14.1	20.0

Table II. Rate Constants (±1–3%) for the Rotation of (ap)-*o*-Tolyldi-*tert*-butylcarbinols 6 in Dodecane (10^4k, s^{-1})

Compd	95 °C	112 °C	130 °C	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
6a	0.847	4.24	18.3	25.1 ± 0.5	−9.3 ± 1.2
6b	0.779	3.78	16.9	25.2 ± 0.5	−9.3 ± 1.3
6c	0.603	3.04	13.6	25.5 ± 0.4	−9.0 ± 0.9
6d[a]	0.564	2.75	12.6	25.9 ± 0.4	−8.2 ± 0.9
6e	0.483	2.29	11.2	25.7 ± 0.4	−8.9 ± 1.0
6f	0.131	0.645	3.40	26.6 ± 0.6	−9.0 ± 1.5

[a] 0.126×10^{-4} s^{-1} at 80 °C (ref 11).

Errors could arise, however, from the tendency of Allinger's hydrogens to be too large and the carbons too small,[24] though, once again, such errors could be expected to cancel out.

The results show that the sp form **5** is approximately 6 kcal/mol more stable than the ap form **6**, whether the OH group is approximated by methyl (46.7 − 40.1 = 6.6 kcal/mol) or by hydrogen (20.0 − 14.1 = 5.9 kcal/mol).[25] Though there is no reason to expect the geometry of the hydrocarbons to reproduce that of the alcohols, it is nevertheless noteworthy that when OH is approximated by a methyl group the calculated geometry[26] of the sp form, **5**-Me, agrees reasonably well with the crystal data (Figure 1). There are, however, serious discrepancies when a hydrogen atom is used (not shown). The calculated geometry of the ap form, **6**-Me, is given for comparison. Outstanding features of both isomers are the very long carbon to *tert*-butyl bonds,[27,28] the very high angle, θ_1, subtended by the *tert*-butyl groups to the central carbon atom,[27,28] and the deformation of the two carbon to benzene bond angles,[29] θ_2 and θ_3. The dihedral angle, Φ, between the aryl ring and the C–O bond is closely similar to that found in 1-(4-methoxyphenyl)-2,2,6,6-tetramethylcyclohexanol[27] (12.9°); the molecular mechanics calculations offer no support for an angle of 45° we previously advanced on the basis of kinetic and model studies.[30] Complete rotation of the aryl group about the phenyl to sp^3 carbon axis in 10° steps revealed no minima other than those corresponding to the ap and sp conformations. The syn-planar conformation of **5**-Me (Φ = 0°) is, however, only 0.2 kcal/mol less stable than the sp conformation (Φ = 10.5°), indicating that interchange between the two sp forms must be very fast.

Substituent Effects Upon Thermal Isomerization Rates in Dodecane. It was anticipated that meta and para substituent effects on the rotation rate would be negligible, since the reaction involves no charged species. In fact, the substituent effects are small, but not insignificant, since the 4-OMe derivative is some 1.5 times more reactive than the parent alcohol and the 5-Cl derivative is 20% slower (Table II). The differences in reactivity are so small that linear free energy relationships are hardly meaningful; there is little to choose between σ ($\rho = -0.41$, $r = 0.940$) and σ^+ ($\rho = -0.24$, $r = 0.970$). The activation parameters are very similar from **6a** to **6e**, but $\Delta H^{\ddagger}$ tends to decrease with increasing electron donation, whereas no trend in the entropy term (−9 eu) is detectable.

The temperature dependence of the NMR spectrum of 9-chloro-9-mesitylfluorene was once attributed to ionization of the C–Cl bond, followed by recombination within a tight ion pair,[6] but this has been shown to be incorrect.[5] Clearly our data are consistent with no process in which ionic species are formed, but would be considered to support a radical mechanism if there were other evidence in its favor. We have found that o-tolyldi-*tert*-butylcarbinols *decompose* in a radical reaction to aryl *tert*-butyl ketones,[31] but at much higher temperatures ($k_1 = 0.4 \times 10^{-4}$ s^{-1} at 237 °C for the parent compound).[32] There is then no plausible mechanism for isomerization except rotation about the phenyl to sp^3 carbon

Table III. Equilibrium Constants (sp isomer, 5d) and Apparent Rate Constants (ap isomer, 6d) for the Equilibration of *o*-Tolyldi-*tert*-butylcarbinol by *n*-Butyllithium in *n*-Hexane at 25 °C

[*n*-BuLi], M	$K = [sp]_{eq}/[ap]_{eq}$	$10^3(k_A + k_S)$, s^{-1}	$10^3 k_A$, s^{-1}	$10^3 k_S$, s^{-1}
0.08	10.1			
0.16	6.88	2.78	2.43	0.35
0.48	3.44	3.86	2.99	0.87
0.80	2.27	5.62	3.90	1.72
1.12	1.78	7.65	4.90	2.75
1.60	1.57	9.65	5.90	3.75

axis accompanied, perhaps, by concerted movement of the *tert*-butyl groups.

Not unexpectedly, the prehnityl derivative **6f** is slower, by a factor of 6, than would be predicted on the basis of additivity of substituent effects, the difference appearing to reside entirely in the enthalpy term. The presence of four methyl groups on adjacent carbon atoms will tend to make the 2-methyl group more rigid. Opening of the C_1–C_2–Me angle will be more difficult and the barrier to rotation consequently higher. This point is illustrated by force-field calculations on aryldi-*tert*-butylethanes. In the prehnityl derivative the calculated C_1–C_2–Me angle is 124.8 (sp) and 125.0° (ap), whereas the corresponding values for **5**-Me and **6**-Me are 128.5 and 130.3°, respectively.

Alkoxide Rotation Catalyzed by *n*-Butyllithium in *n*-Hexane. In experiments designed to compare the stabilities of the alkoxides corresponding to **5d** and **6d** (see below), we observed that the rotation of the alkoxides proceeds much more rapidly than that of the alcohols. The alkoxide ion is generated by reaction of the alcohol with an organolithium compound. We would therefore expect the rotation rate of the ap and sp alcohols in *n*-butyllithium to be that of the corresponding alkoxide ions, AO^- and SO^-:

$$AO^- \underset{k_S}{\overset{k_A}{\rightleftharpoons}} SO^-$$

The rate of equilibration of the ap alcohol **6d**, $k_A + k_S$ proves, however, to be *n*-BuLi concentration dependent, as is the value of the apparent equilibrium constant, $K = k_A/k_S$ (Table III and Figure 2). These observations suggest that the alkyllithium is directly involved in the rotation process and that its role is not limited to mere proton abstraction. The rate constant for the ap → sp reaction in *n*-hexane, extrapolated to zero *n*-BuLi concentration, is approximately 2×10^{-3} s^{-1} at 25 °C. This is to be compared with the value of 1.08×10^{-8} s^{-1} calculated for the rotation of the ap alcohol **6d** in dodecane at 25 °C from data at higher temperatures. Tentatively, this rate increase, by a factor of approximately $10^{5.3}$, can be attributed to ground-state steric effects, as in the case of 9-X-9-mesitylfluorenes and related systems.[4,6,33] In these molecules steric interaction between X and the aryl group enhances the energy of the ground state when X increases in size from H to OH to Cl, but this interaction is absent in the transition state for rotation. Similarly, the effective size of the $-O^-Li^+$ ion pair will be greater than that of the hydroxyl group; the ground-state energies of the alkoxides must therefore be higher than those of the alcohols. In the rotation transition state the predominant steric interactions between *o*-methyl and *tert*-butyl groups are not modified by the change from –OH to $-O^-Li^+$; consequently the barrier to rotation will be lowered.

Rotation is known to be provoked by organolithium compounds in certain cases: optically active 3,3′-bithinpenyls are rapidly racemized by ethyllithium via an internally bridged dimetalated compound;[34] slow metalation of ap-9-(2-methoxy-1-naphthyl)fluorene leads to the more stable sp-9-(2-methoxy-1-naphthyl)fluorenide.[35] These reactions involve, however, C-metalation and are therefore not directly related to the present case. In the organolithium-catalyzed rotation of o-tolyldi-*tert*-butylcarbinols the role of the n-BuLi is twofold: firstly, it serves to generate the lithium alkoxide ion pair; secondly, excess *n*-BuLi enhances the rotation rate, probably by increasing the effective size of the reacting species by aggregation.

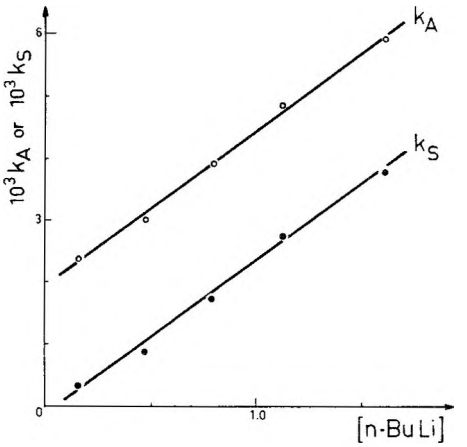


Figure 2. Rate constants for the equilibration of *o*-tolyldi-*tert*-butylcarbinols by *n*-butyllithium in *n*-hexane at 25 °C ($10^3 k$, s^{-1}).

The Transition State for the Addition of Aryllithium Compounds to Ketones. There is a small increase in the amount of the sp isomer **5** as we proceed from an electron-withdrawing substituent 5-Cl (7%) to an electron-donating substituent, 4-Me or 4-OMe (15%), but the addition process always favors formation of the less stable isomer (Table IV). We previously attributed this phenomenon to destabilization (of a product-like transition state) by steric interaction between the o-methyl and the incipient lithium alkoxide ion pair and its accompanying solvation shell.[11]

If the transition state is product-like we might expect the rotation of the ap alkoxide ion, prepared from the alcohol by treatment with an alkyllithium, to lead ultimately to a mixture with an ap/sp ratio similar to that of the addition reaction. Attempts to check this hypothesis in diethyl ether did not give satisfactory results, but treatment of either alcohol **5d or 6d** with *n*-butyllithium in *n*-hexane led to an equilibrium mixture, the apparent equilibrium constant for the reaction decreasing to 1.57 (38% of **6d** at equilibrium) for the highest concentration of *n*-BuLi used, 1.6 M (Table III). This is already much less than is found in the addition reaction, and extrapolation from data at higher concentrations indicates that, for equimolar *n*-BuLi and alcohol, the sp alkoxide is by far the most stable.[36] The alkoxide ions are therefore not valid models of the transition state for the addition of *o*-tolyllithium to di-*tert*-butyl ketone. We now propose a more satisfactory, though necessarily incomplete, interpretation.

Recent reviews on organolithium compounds[37] and on the addition of organometallic compounds to cyclic ketones[38] reveal two areas of uncertainty regarding the addition of an aryllithium to a ketone: (i) the identity of the kinetically active Li species and (ii) the geometry of the transition state.

(i) Fractional kinetic orders ($[RLi]^{1/n}$ where *n* is an integer) in organolithium reactions with various substrates have been interpreted in terms of polymer–monomer equilibria where the monomer is the kinetically active species,[39] but there is a growing awareness of the importance of the molecular aggregates[40] containing not only the organolithium, but also solvent molecules,[41] alkoxides,[42] and halides.[43] The ^7Li spectra of mixtures of phenyllithium and *p*-tolyllithium[44] indicate

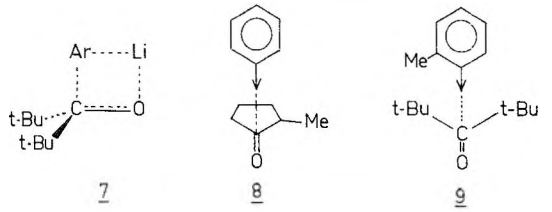
Table IV. Synthesis of *o*-Tolyldi-*tert*-butylcarbinols, 5-sp and 6-ap: Isomer Ratios and Yields

X	6/(6 + 5)[a]	% 5 (bp/mm; mp)	Registry no.	% 6[b] (mp)	Registry no.
4-OMe[f]	0.85 (0.96)	27[b,d] (–; 96)	63121-51-7	28–36 (62–63)	63121-53-9
4-Me[g]	0.85 (0.97)	60[c] (112/1.2; 58–59)	63076-53-9	50 (40–41)	63121-54-0
5-Me[g]	0.91 (0.98)	64[c] (106/0.8; 56–57)	63076-54-0	51 (40–42)	63121-55-1
H[h]	0.89 (0.98)	69[c] (116/2.0; 35)	63121-52-8	56–66 (–)	63162-57-2
5-Cl[i]	0.93 (0.99)	46[b,d] (–; 41)	63076-55-1	24 (47–48.5)	63121-56-2
3,4,5-Me_3[j]	0.84 (0.93)	44[b,e] (–; 129)	63076-56-2	52 (65–67)	63121-57-3

[a] Values in parentheses obtained when 1 mol/mol of TMEDA was added to the aryllithium. [b] By chromatography on Al_2O_3. [c] Distilled. [d] After 3 h at 112 °C. [e] After 10 h at 112 °C. [f] Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found for **5a**: C, 77.01; H, 10.63. **6a**: C, 77.35; H, 10.74. [g] Calcd for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found for **5b**: C, 81.74; H, 11.30. **6b**: C, 82.29; H, 11.04. **5c**: C, 82.18; H, 10.97. **6c**: C, 82.04; H, 11.15. [h] Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.08. Found for **5d**: C, 81.78; H, 10.96. **6d**: C, 81.79; H, 10.92. [i] Calcd for $C_{16}H_{25}OCl$: C, 71.49; H, 9.38; Cl, 13.19. Found for **5e**: C 71.92; H, 9.56; Cl, 13.37. **6e**: C, 71.12; H, 9.21; Cl, 13.29. [j] Calcd for $C_{19}H_{32}O$: C, 83.15; H, 11.02. Found for **5f**: C, 83.58; H, 11.38. **6j**: C, 83.51; H, 11.15.

that these compounds are monomeric in ether solution, though differential vapor pressure[45] and elullioscopic measurements[46] favor dimeric species. The kinetics of phenyllithium reactions with 1,1-diphenylethylene,[47] triphenylmethane,[48] and benzonitrile[49] are consistent with a scheme involving active monomer *and* dimer species in equilibrium; the reaction of aryllithium compounds with ketones has yet to be studied kinetically.

(ii) The very existence of the ap isomer **6** resolves one problem regarding the transition state. If we consider the simplest plausible model wherein the aryllithium monomer attacks the ketone via a four-center transition state **7**, there



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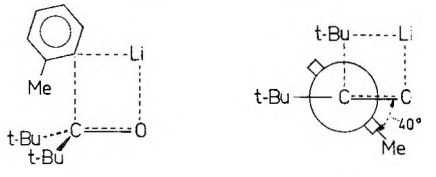
are two distinct ways in which the aryl group can be oriented: either in the plane which bisects the *t*-Bu–C–*t*-Bu angle, or orthogonal to the plane. In an attempt to explain the anomalous behavior of PhMgBr in its additions to 4-*tert*-butylcyclohexanone and 2-methylpentanone, Ashby[38] assumes that the plane of the entering phenyl group is orthogonal to that which bisects the C–CO–C angle, as in **8**. However, if this were so in the addition of o-tolyllithium to di-*tert*-butyl ketone, **9**, there would be no grounds for the formation of the ap alcohol **6**, since the *o*-methyl would always be situated between a *tert*-butyl group and the carbonyl oxygen and would inevitably give the sp isomer **5** only. We conclude, therefore, that the aryl group lies in the plane which contains the carbonyl group and is perpendicular to the C–CO–C system, as shown in **10**. Why then does the aryllithium attack in the observed



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manner to give the less stable isomer? The perturbation of the C_1–Li bond upon approach of the C=O bond requires that the lithium atom shift toward either C_2 or C_6. Our results would appear to indicate that the shift is toward C_6 rather than upward C_2, which bears the methyl group, and, furthermore, that this shift controls the orientation of attack, i.e., that the orientation is determined at an early stage of the approach, before repulsive interactions between the o-methyl and the *tert*-butyl groups become dominant. Both TMEDA and an electron-withdrawing substituent reduce the amount of sp isomer formed in the addition (Table IV), possibly enhancing charge separation in the C–Li bond and thus favoring an even earlier transition state.

Although the condensation of the aryllithium with di-*tert*-butyl ketone is generally the easier method, aryldi-*tert*-butylcarbinols have been prepared by reaction of *tert*-butyllithium with the aryl *tert*-butyl ketone.[2] We find that the addition of *tert*-butyllithium to o-tolyl *tert*-butyl ketone in diethyl ether at −40 °C gives no trace of the ap isomer **6d**; the only tertiary alcohol formed has the sp conformation. Spectral evidence[52] indicates that the dihedral angle between the carbonyl group and the aryl group is about 40° and that the carbonyl oxygen is close to the o-methyl group. The ketone molecule is therefore set up in a conformation which lends itself to preferential formation of the sp alcohol **5d** upon attack by *tert*-butyllithium via a four-center transition state depicted in **11**.

Experimental Section

The IR spectra were determined on a Perkin Elmer 225 grating instrument using 1-cm silica cells containing a 10^{-2} M solution of the alcohol in CCl_4. The NMR spectra were recorded on a Jeol HF60 instrument at 60 MHz with internal Me_4Si as reference. Melting points are uncorrected.

The "low temperature–low retention time" GLC technique previously[11] described was slightly modified. A 40-cm column of 1% SE30 on HMDS-washed Chromosorb 80/100 was used at temperatures between 100 and 115 °C with an inlet pressure of 1 atm; the injector temperature was 160 °C. Under these conditions the retention times ranged from 65 (**5d** at 100 °C) to 230 s (**6f** at 115 °C) and the extent of isomerization was in no case greater than 7% (**6a** at 115 °C).

Synthetic Procedures. Aryl bromides were obtained either commercially or by molecular bromination of substituted benzenes in methylene dichloride. In the case of 4-chlorotoluene this gave rise to a mixture of isomers (70/30) which were separated by GLC on Carbowax 20M; the most abundant isomer was identified as the required 2-bromo-4-chlorotoluene. Aryllithium compounds were prepared either directly by reaction of aryl bromide with lithium metal or indirectly by exchange between *n*-butyllithium and the aryl bromide. After addition of di-*tert*-butyl ketone the alcohols were isolated as described previously[11] for **5d** and **6d**. For small-scale preparations (**5e**) or when the product was involatile (**5a,f**) the sp alcohols were isolated by column chromatography after ap → sp isomerization at 112 °C for a suitable time; alcohol **5** was obtained in yields of 27–69% (Table IV, 3rd column).

Standard Procedure for the Determination of the 6/5 Isomer Ratio. *n*-Butyllithium in *n*-hexane (1.6 M, 2 mL, 0.0032 mol) was diluted with diethyl ether (10 mL). Under argon and at room temperature (20–22 °C) the aryl bromide (0.003 mol) was syringed in dropwise. After 15 min stirring, di-*tert*-butyl ketone (0.48 g, 0.0032 mol) was introduced in the same way. After a further 15 min the reaction was stopped by pouring the mixture into water; the organic phase was washed to neutrality and dried (Na_2SO_4). A sample of the crude product after removal of the solvent was taken for determination of the isomer ratio and the remainder was chromatographed on alumina (activity II–III) in light petroleum (35–60 °C) followed by

ether/light petroleum mixtures to isolate **6** in yields of 24–66% (Table IV, 5th column).

The **6/5** isomer ratio of the crude reaction product was determined by selective dehydration. Since the ap alcohol **6** is dehydrated some 10^4 times faster than the sp isomer **5**, a brief treatment with dilute H_2SO_4 destroys completely the former while the latter is untouched. Procedure was as follows: a solution of crude product (50–60 mg) with a suitable hydrocarbon standard (20 mg) in acetic acid (10 mL) was treated with 10 mL of a 2% v/v solution of H_2SO_4 in acetic acid at 25 °C. When the alcohol mixture is chromatographed on a standard column (SE30 10%, 5 ft × ⅛ in.) with a high injector (250 °C) and oven (200–220 °C) temperature the two alcohols emerge as a single peak. A sample taken at zero time gives the ratio of total alcohol to standard, while a sample taken after 10–15 half-lives of the ap alcohol gives the ratio of unreactive sp alcohol to standard, whence the **6/5** isomer ratio (Table IV).

Synthesis of 2-Methylpivalophenone. Alcohol **5d** (4 g) upon heating under reflux for 3 h at 240–260 °C decomposed to give, after purification on SE30 15% at 190 °C, the required ketone (2.36 g, 78% yield): IR (CCl_4) 1684 cm^{-1}; NMR (CCl_4), singlet (δ 1.19), 9 H of *tert*-butyl; singlet (δ 2.17), 3 H of 2-methyl; multiplet (δ 7.10), 4 aromatic H.

Addition of *tert*-Butyllithium to 2-Methylpivalophenone. *tert*-Butyllithium[53] was prepared by slow addition (1 h) of *tert*-butyl chloride (2.5 g, 0.03 mol) in diethyl ether (40 mL) to vigorously stirred finely chopped lithium (0.5 g, 0.07 g atom) in ether (30 mL) at −40 °C. At the same temperature, 2-methylpivalophenone (1.8 g, 0.01 mol) in ether (30 mL) was added during 30 min. The mixture was allowed to warm to room temperature overnight and was then worked up as usual. GLC analysis of the crude produce revealed only the secondary alcohol, o-tolyl-*tert*-butylcarbinol, and the sp isomer, **5d**. Chromatography on alumina in light petroleum followed by ether gave secondary alcohol (1.44 g, 63%) and **5d** (0.55 g, 23%).

Kinetic Procedures. The method used for the determination of alcohol rotation rates in dodecane was as described previously.[11]

Equilibration of Alcohols 5d and 6d Catalyzed by *n*-Butyllithium in *n*-Hexane. A thermostated 5-mL flask was fitted with a rubber septum cap pierced with two syringe needles so that it could be continuously flushed with argon. Into 5 mL of an *n*-butyllithium solution in *n*-hexane, stirred magnetically, was injected 15 μL of a solution of alcohol **5d** in the same solvent (150 mg in 100 μL; final alcohol concentration ca. 0.01 M). Samples (0.25 mL) were withdrawn by means of a syringe at approximately 5-min intervals and injected into ice-cooled water. Low-temperature GLC analysis of the organic phase revealed that the **5d/6d** ratio rose to a constant value after 5–10 min and did not vary significantly thereafter. Approximately the same ratio was found when the sp isomer **5d** was replaced by the ap isomer **6d**. The sum of the apparent forward and reverse rate constants, k_A and k_S, was obtained by following the rotation of alcohol **6d** during 3–4 reaction half-lives and plotting $\log([ap]_t - [ap]_{eq})$ against elapsed time. The standard deviation on $k_A + k_S$ is within ±5%; the equilibrium percentage of either isomer is reproducible to ±2%. Probable errors on k_S are greater than those on k_A and increase as k_S approaches zero.

Acknowledgments. We are indebted to Professor K. Mislow for access to the STRAIN program, to Dr. E. Hough for communication of crystallographic data prior to publication, and to P. Fellman for helpful discussions.

Supplementary Material Available. Calculated Cartesian coordinates for structures 5-Me, 5-H, 6-Me, and 6-H (4 pages). Ordering information is given on any current masthead page.

Registry No.—2-Methylpivalophenone, 2041-37-4; *tert*-butyllithium, 594-19-4.

References and Notes

(1) Leading references are: (a) G. J. Karabatsos and D. J. Fenoglio, *Top. Stereochem.*, **5**, 167 (1970); (b) B. Nilsson, P. Martinson, K. Olsson, and R. E. Carter, *J. Am. Chem. Soc.*, **96**, 3190 (1974); (c) J. M. A. Baas, J. M. van der Toorn, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **93**, 133 (1974); (d) J. E. Anderson, C. W. Doeke, and D. I. Rawson, *Tetrahedron Lett.*, 3531 (1975).
(2) R. E. Gall, D. Landman, G. P. Newsoroff, and S. Sternhell, *Aust. J. Chem.*, **25**, 109 (1972).
(3) P. D. Bartlett and T. T. Tidwell, *J. Am. Chem. Soc.*, **90**, 4421 (1968).
(4) Reviewed by: M. Oki, *Angew. Chem., Int. Ed. Engl.*, **15**, 87 (1976).
(5) W. T. Ford, T. B. Thompson, K. A. J. Snoble, and J. M. Timko, *J. Am. Chem. Soc.*, **97**, 95 (1975).
(6) E. A. Chandross and C. F. Sheley, *J. Am. Chem. Soc.*, **90**, 4345 (1968).
(7) T. H. Siddall and W. E. Stewart, *J. Org. Chem.*, **34**, 233 (1969).
(8) See also: M. Nakamura and M. Oki, *Tetrahedron Lett.*, 505 (1974).
(9) Triptycene rotamers have also been isolated: M. Oki and G. Yamamoto, *Chem. Lett.*, 45 (1972); G. Yamamoto and M. Oki, *J. Chem. Soc., Chem. Commun.*, 713 (1974).
(10) P. Finocchiaro, D. Gust, and K. Mislow, *J. Am. Chem. Soc.*, **96**, 3198 (1974).
(11) J. S. Lomas and J. E. Dubois, *J. Org. Chem.*, **41**, 3033 (1976).
(12) H. Tanida and H. Matsumura, *J. Am. Chem. Soc.*, **95**, 1586 (1973).
(13) E. Hough, *Acta Crystallogr.*, submitted for publication.
(14) "IUPAC Tentative Rules for the Nomenclature of Organic Chemistry, Section E. Fundamental Stereochemistry" *J. Org. Chem.*, **35**, 2849 (1970); R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, 5, 385 (1966).
(15) (a) R. J. Ouellette, D. L. Marks, and D. Miller, *J. Am. Chem. Soc.*, **89**, 913 (1967); (b) F. H. Hon, H. Matsumura, H. Tanida, and T. T. Tidwell, *J. Org. Chem.*, **37**, 1778 (1972).
(16) P. D. Bartlett, T. R. Steadman, T. T. Tidwell, and W. P. Weber, *Tetrahedron Lett.*, 2915 (1970).
(17) (a) N. L. Allinger, *Adv. Phys. Org. Chem.*, **13**, 1 (1976); (b) O. Ermer, *Struct. Bonding (Berlin)*, **27**, 161 (1976); (c) E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **95**, 8005 (1973).
(18) (a) M. A. Robb, W. J. Haines, and I. G. Csizmadia, *J. Am. Chem. Soc.*, **95**, 42 (1973); (b) N. L. Allinger and D. Y. Chung, *ibid.*, **98**, 6798 (1976).
(19) P. Müller and J. C. Perlberger, *J. Am. Chem. Soc.*, **97**, 6862 (1975).
(20) See, for example: D. Lenoir, D. J. Raber, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **96**, 2149 (1974).
(21) J. L. Fry, E. M. Engler, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **94**, 4628 (1972).
(22) J. D. Andose and K. Mislow, *J. Am. Chem. Soc.*, **96**, 2168 (1974); calculations were performed on an IBM 370 computer of the Centre National de la Recherche Scientifique.
(23) D. F. DeTar and C. J. Tenpas, *J. Am. Chem. Soc.*, **98**, 4567 (1976).
(24) S. Fitzwater and L. S. Bartell, *J. Am. Chem. Soc.*, **98**, 5107 (1976).
(25) We formerly attributed the lower reactivity of the sp isomer in part to steric hindrance to protonation of the hydroxyl group,[11] due to the proximity of the *o*-methyl group. In fact, we now find that the calculated difference in the steric energies of the alcohols is very nearly the same as that of the activation energies for dehydration, 5.6 kcal/mol. This means that if the transition states for dehydration of the isomeric alcohols are similar in energy, both being close to the common intermediate carbonium ion, then the difference in reactivity is completely explained by that of the ground-state energies of the two alcohols in question, without any other supplementary cause needing to be invoked. This point will be developed in a forthcoming article.
(26) Cartesian coordinates for these structures are given in the Supplementary Material.
(27) H. van Koningsveld, *Cryst. Struct. Commun.*, **3**, 491 (1973).
(28) H. B. Burgi and L. S. Bartell, *J. Am. Chem. Soc.*, 94 5236 (1972); G. Lepicard, J. Berthou, J. Delettré, A. Laurent, and J. P. Mornon, *C. R. Acad. Sci., Ser. C*, **276**, 575 (1973).
(29) As in 1,2,4,5-tetra-*tert*-butylbenzene, for example: A. van Bruijnsvoort, L. Eilermann, H. van der Meer, and C. H. Stam, *Tetrahedron Lett.*, 2527 (1968).
(30) J. S. Lomas and J. E. Dubois, *Tetrahedron Lett.*, 407 (1976).
(31) Analogous to the decomposition of tri-*tert*-butylcarbinol: J. E. Lomas and J. E. Dubois, *J. Org. Chem.*, **39**, 1776 (1974).
(32) J. S. Lomas and J. E. Dubois, unpublished data.
(33) A. Rieker and H. Kessler, *Tetrahedron Lett.*, 1227 (1969).
(34) R. Haakansson, *Chem. Scr.*, **2**, 109 (1972).
(35) M. Nakamura and M. Oki, *Chem. Lett.*, 671 (1975).
(36) Extrapolation of the linear least-squares correlation of the k_S data gives, in fact, $10^3 k_S = -0.13 \pm 0.20$ for a 90% confidence interval at [*n*-BuLi] = 0.01 M, the alcohol concentration. The upper limit gives a value of 30 for *K*, but the true value is probably higher.
(37) B. J. Wakefield, "The Chemistry of Organolithium Compounds", Pergamon Press, Elmsford, N.Y., 1974, pp 3–15.
(38) E. C. Ashby and J. T. Laemmie, *Chem. Rev.*, **75**, 521 (1975).
(39) For a complete discussion see ref 37, pp 14, 92, and ref 40–43.
(40) T. L. Brown, *J. Organomet. Chem.*, **5**, 191 (1966).
(41) P. D. Bartlett, C. V. Goebel, and W. P. Weber, *J. Am. Chem. Soc.*, **91**, 7425 (1969).
(42) L. F. Charbonneau and S. G. Smith, *J. Org. Chem.*, **41**, 808 (1976).
(43) D. P. Novak and T. L. Brown, *J. Am. Chem. Soc.*, **94**, 3793 (1972).
(44) J. A. Ladd and J. Parker, *J. Organomet. Chem.*, **28**, 1 (1971).
(45) P. West and R. Waack, *J. Am. Chem. Soc.*, **89**, 4395 (1967).
(46) G. Wittig, F. J. Meyer, and G. Lange, *Justus Liebigs Ann. Chem.*, **571**, 167 (1951); T. V. Talalaeva, A. N. Rodionov, and K. A. Kocheshkov, *Proc. Acad. Sci. USSR, Chem. Sect.*, **154**, 47 (1964); A. N. Rodionov, D. N. Shigorin, T. L. Talalaeva, G. V. Tsareva, and K. A. Kocheshkov, *Zh. Fiz. Khim.*, **40**, 2265 (1966).
(47) R. Waack and M. A. Doran, *J. Organomet. Chem.*, **29**, 329 (1971); *J. Am. Chem. Soc.*, **91**, 2456 (1969).
(48) P. West, R. Waack, and J. I. Purmort, *J. Am. Chem. Soc.*, **92**, 840 (1970).
(49) T. Holm, *Acta Chem. Scand.*, **23**, 833 (1971).
(50) NMR spectra of phenyllithium compounds[51] appear to show that all substituents other than CF_3 decrease the ionic character of the C–Li bond. The ordering of the substituents depends, however, upon which nucleus, ^7Li or ^1H, is considered and in neither case follows familiar σ or σ^+ values.
(51) J. A. Ladd and J. Parker, *J. Chem. Soc., Dalton Trans.*, 930 (1972).
(52) E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3754 (1955); K. S. Dhami and J. B. Stothers, *Can. J. Chem.*, **43**, 498 (1965).
(53) P. D. Bartlett and E. B. Lefferts, *J. Am. Chem. Soc.*, **77**, 2804 (1955).

Effect of Detergents on the S- to N-Acyl Transfer of S-Acyl-β-mercaptoethylamines

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Received March 23, 1977

The rate of S- to N-acyl transfer of S-octanoyl-β-mercaptoethylamine (OMA) is enhanced by hexadecyltrimethylammonium bromide (CTAB) micelles by 4.6-fold and slightly inhibited by the nonionic detergent Brij-35. The rate of the S to N transfer of S-acetyl-β-mercaptoethylamine (AMA) is unaffected by CTAB or Brij. Micelles of a negative detergent, sodium dodecyl sulfate, inhibit the rate of S to N transfer of AMA by 100-fold; the inhibition in the case of OMA is 5×10^3-fold. An increase in the apparent pK of the ammonium ion and a decrease in the conformational mobility of OMA are proposed to account for the observed results.

Micelles modify the rates and/or product distribution of a number of reactions in both aqueous and nonaqueous solvents (for recent reviews, see ref 1–3). The usefulness and limitations of the "micelle model" for the understanding of the catalytic mechanism of enzymes have been discussed.[1-3] Since distortion of a part of the substrate has been shown to be an important factor in some enzyme-catalyzed reactions,[4] it might be expected that micellar modeling of distortion would be more feasible in intra- rather than intermolecular reactions due to the high fluidity and mobility of micelles.[3]

This work is concerned with the effect of detergent on the S- to N-acyl transfer in mercaptoethylamines. The mechanism of this reaction is well known as a result of a number of studies.[5-10] In the early work of Martin and co-workers,[6] it was demonstrated that acyl transfer occurs via the formation of a cyclic intermediate of the type previously demonstrated for the S- to O-acyl transfer in the $CH_3COS(CH_2)_nOH$ series. Above pH 6, partitioning of the cyclic intermediate back to the starting thioester is negligible, resulting in the production of the amide as the only product.[11] The occurrence of a rate-limiting proton-transfer step was later proposed by Barnett and Jencks.[10] The fact that the rate of the S- to N-acyl transfer in mercaptoethylamine is insensitive to the addition of high salt concentration or of solvents like butanol[10] facilitates the analysis of the effect of detergent on this complex reaction; thus microsolvent effects[3] or the high effective ionic strength at the stern layer of a micelle would not be expected to alter significantly the reaction rate.

The data for the effect of detergents on the rate of S- to N-acyl transfer on mercaptoethylamines presented here demonstrates a strong rate inhibition by negative detergents, a negligible effect by nonionic detergents, and a small catalysis by positive detergents.

Experimental Section

CTAB was obtained from Merck, Darmstadt, Germany (pro Analysis grade Lot 252534), and was recrystallized three times from acetone–ethanol.

SDS was obtained from BDH, Poole, England (specially pure grade Lot 1262984), and was recrystallized from ethanol and shown to be free from sulfate, alcohols, or higher analogues by acid hydrolysis and vapor phase chromatography of the ether extracts.

S-Acetyl-β-mercaptoethylamine·HCl (hereafter referred as AMA) was synthesized by a published procedure;[12] mp 137–138 °C (lit. mp 137 °C[12]).

S-Octanoyl-β-mercaptoethylamine·HCl (OMA) was synthesized as described; mp 105–108 °C (lit. mp 111–113 °C[11]); S analysis; IR, UV, and NMR spectra are all in accord with structure.

All other reagents were analytical grade. Water which had been deionized and twice distilled in glass was used throughout.

Kinetics. The kinetics of the intramolecular conversion of S-acylmercaptoethylamines to the corresponding amides was followed spectrophotometrically at 25 °C (Masterline Forma Scientific bath) in the thermostated compartment of a Gilford recording spectrophotometer. The reaction was followed at 229 nm, and the measured extinction coefficient of the thioesters corresponded to those described.[8] The reaction cuvettes, containing all additions except the thioester, were checked for pH, after temperature equilibration, with a Metrohm pH meter equipped with a microcombination electrode. The pH rechecked after each kinetic run did not change. All reactions were started by adding 10 μL of a freshly prepared aqueous stock solution of the thioester (ca. 10^{-3} M). The stock solution was never used for more than 1 h. Reactions were followed for at least 4 half-lives. The first-order rate constants were calculated from log $(A_0 - A_t)$ vs. time plots.

NMR measurements were carried out in a Varian T-60 spectrometer.

Results

The cationic detergent hexadecyltrimethylammonium bromide (CTAB) catalyzed the S- to N-acyl transfer of S-octanoyl-β-mercaptoethylamine (Figure 1), the rate constant increasing sharply at CTAB concentrations greater than 3×10^{-4} M. The critical micelle concentration (cmc) of CTAB in water is 9×10^{-4} M.[3] It is known that both the addition of salts or amphiphilic electrolytes[1,3] can lower the cmc of this detergent. Taking 3×10^{-4} M as the effective cmc under our kinetic conditions, it is possible to calculate the maximum rate acceleration and the partition coefficient of the substrate between water and the micellar pseudophase.[13] According to this model, a unimolecular reaction can be treated using

$$k_\psi = \frac{k_m K(C_D - \text{cmc}) + k_o}{K(C_D - \text{cmc}) + 1} \quad (1)$$

where k_ψ is the observed first-order constant, C_D is the total detergent concentration, k_o is the observed first-order rate constant in the absence of detergent, K is the distribution coefficient of the reagent, and k_m is the rate constant in the micellar phase. k_m and K were iterated from an initial value of k_m taken as the observed first-order rate constant at the plateau (Figure 1). Only the data up to 5.5×10^{-3} M CTAB were used in this calculation. At pH 6.8 in 0.01 M NaH_2PO_4, k_o is 0.026 s^{-1}, the calculated k_m under the same conditions is 0.12 s^{-1}, so the rate acceleration by CTAB is 4.6-fold.

In order to discard the possibility of self-aggregation of the substrate that would modify the observed rate constant for the uncatalyzed reaction, the concentration of OMA was varied between 2.8×10^{-5} and 4.2×10^{-4} M. It was found that between these limits the first-order rate constant did not change. The values of k_ψ obtained at high detergent concentration deviate from the predicted values, indicating that the model described by eq 1 accounts only partially for all the data.

The inhibitory effect of sodium dodecyl sulfate (SDS) in this system is more pronounced than the (small) catalytic effect observed with CTAB (Figure 2).

Various models were considered in order to fit all the inhibition data. These models were based on assumptions of formation of aggregates containing substrate and SDS in definite

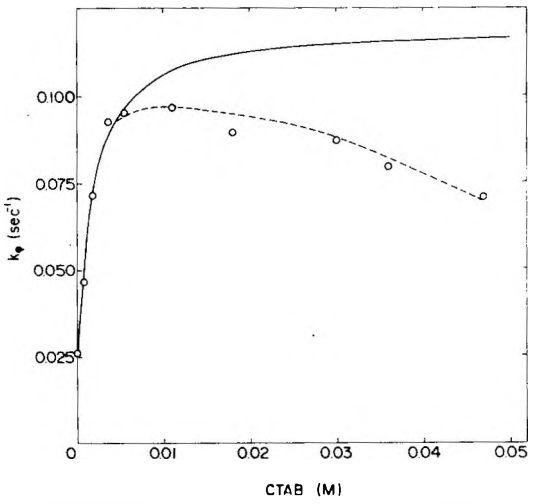


Figure 1. Catalysis of the S- to N-acyl transfer of S-octanoyl-β-mercaptoethylamine by CTAB. Solid line is calculated (see text).

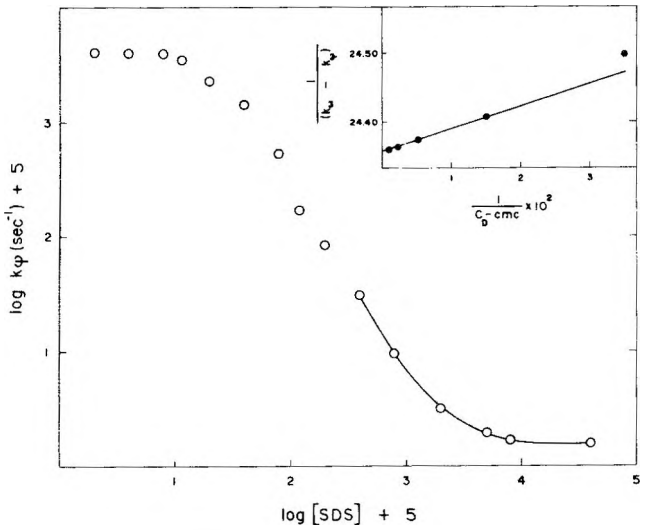


Figure 2. Effect of SDS on the S- to N-acyl transfer of S-octanoyl-β-mercaptoethylamine (OMA). Solid line is calculated, inset shows this same region of SDS concentration plotted according to eq 2 (see text). Initial concentration of OMA, 2×10^{-4} M.

proportion over the entire SDS concentration range used as shown in Scheme I. In this scheme, i represents the moles of OMA in the substrate–detergent aggregate, j the number of moles of detergent in the aggregate, K the equilibrium constant, and k_{ij} the rate constant for the S to N transfer in an aggregate with i moles of OMA and j moles of SDS. This type of model has been successfully employed in other aminolysis systems.[14] However, these models failed to give internally consistent results in this case. This failure is probably a reflection of multiple equilibrium between SDS and the substrate that results in an ensemble of mixed aggregates between OMA and SDS with varying i, j (Scheme I), and consequently, different k_{ij}. The i to j ratio would be expected to change with detergent concentrations. As the inhibition by SDS is readily observable at OMA/SDS ratios higher than 1 (Figure 2), the aggregates may even consist of $i > j$.

Scheme I

$$iS + jA \overset{K}{\rightleftharpoons} SiAj$$

$$k_o \downarrow \qquad \downarrow k_{ij}$$

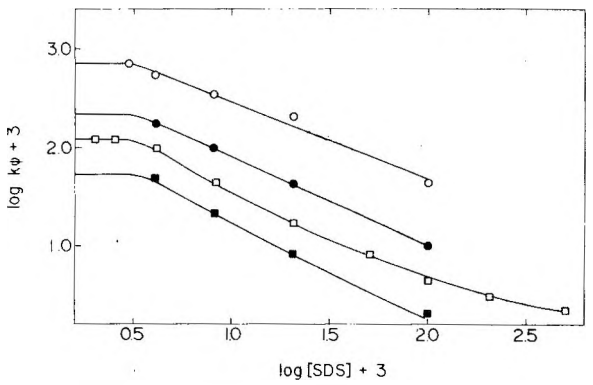


Figure 3. Effect of SDS on the S- to N-acyl transfer of S-acetyl-β-mercaptoethylamine. Solid lines were calculated according to eq 1; (■) pH 6.4, (□) pH 6.8, (●) pH 7.14, (○) pH 7.8. All buffers contained 0.02 M NaH_2PO_4 adjusted with NaOH to the desired pH.

Table I. Effect of Brij 35 on the Rate of S- to N-Acyl Transfer of S-Octanoyl-β-Mercaptoethylamine[a]

Brij 35, M × 10^4	$k_\psi \times 10^2$, s^{-1}
	4.4
2.7	4.3
5.5	4.4
11.0	3.7
22.0	4.0
55.0	2.5

[a] All reactions were carried out at 25 °C in 4.0×10^{-2} M Na phosphate buffer, pH 6.80; initial concentration of OMA was 2.54×10^{-4} M.

The experimental points obtained at SDS/OMA > 10, when the aggregate can be viewed as a typical SDS micelle, were fitted to the same distribution model[13] outlined above for the catalysis of the same reaction by CTAB (solid line in Figure 2) and is amplified in the inset using another form of eq 1:

$$\frac{1}{k_o - k_\psi} = \frac{1}{k_o - k_m} + \frac{1}{K(k_o - k_m)} \times \frac{1}{C_D - \text{cmc}} \qquad (2)$$

The iterative procedure gives $K = 8.2 \times 10^4$. Distribution coefficients of this order of magnitude had previously been observed in an intermolecular aminolysis system using a reactive micelle and oppositely charged ester as a substrate.[14] The k_m was calculated to be 1.5×10^{-5} s^{-1} and under those conditions cmc was taken as 1.2×10^{-3} M.

The rate of the S to N transfer is slightly inhibited by a nonionic detergent (Brij 35) (Table I).

In order to make an assessment of the relative importances of hydrophobic and electrostatic contributions to the effects of detergents described above, the S to N transfer reaction was studied using S-acetyl-β-mercaptoethylamine (AMA) as substrate. The rate of the S to N transfer reaction of AMA is unaffected by the addition of a positive detergent up to 100-fold the critical micelle concentration. This (lack of) effect is to be expected on the basis of previous data on aminolysis of charged esters[14] and indicates that AMA does not incorporate significantly in the CTAB micellar phase. SDS inhibits the rate of the S to N reaction of AMA (Figure 3). The inhibition results can be fitted to a simple distribution model using eq 1. The calculated parameters (k_m and K) were further analyzed varying the pH between 6.4 and 7.8 (Table II).

The maximum inhibition (k_o/k_m) by micellar SDS is consistently 100-fold at all the pHs studied. The rate increase with pH is consistent with the previously reported effect of pH in this reaction.[10] Both the effect of pH on k_m and on the distribution coefficient of the substrate (Figure 3 and Table II) indicate that the protonated form of II binds better to the

Table II. Effect of Sodium Dodecyl Sulfate on the Rate of *S*- to *N*-Acetyl Transfer in *S*-Acetyl-β-mercaptoethylamine[a]

pH	k_o, s^{-1}	k_m, s^{-1}	K
6.4	0.054	4.0×10^{-4}	322
6.8	0.122	1.52×10^{-3}	375
7.14	0.234	2.0×10^{-3}	279
7.8	0.722	7.0×10^{-3}	202

[a] All reactions were carried out at 25 °C in 2.0×10^{-2} M Na phosphate buffers. Initial substrate concentration was usually 2×10^{-4} M. See text for the description of the calculation of k_m (rate constant in the micellar phase) and K (distribution constant of substrate). k_o represents the rate constant in the absence of added detergent.

Table III. Line Broadening of the ^1H NMR Signal of the Bridge Methylene Hydrogens of $CH_3(CH_2)_6COS(CH_2)_2NH_3Cl$ (OMA) by Sodium Dodecyl Sulfate (SDS)[a]

OMA, M	SDS, M	Line width, Hz
0.025		1.6
0.025	0.125	2.6
0.025	0.188	2.0
0.025	0.250	2.0
0.025	0.375	2.0
0.025	0.500	2.0
0.050		1.7
0.050	0.220	5.6
0.050	0.325	3.6
0.050	0.375	3.6
0.050	0.500	4.0

[a] See Results and Experimental Section for details. Under the conditions used the uncertainty in the determination of the width at half-height is 0.1 Hz.

micelle, as expected for an association that is predominantly ionic.

As the effect of SDS on OMA can, as a limit, be ascribed to a simple effect on the acid dissociation constant of the amine (vide infra), we have carried out a limited nuclear magnetic resonance investigation of the OMA/SDS complexes in order to try to distinguish effects other than a pK shift of the terminal amine. A series of aqueous solutions of OMA containing various concentrations of SDS were prepared. It was calculated that under these conditions (pH 5.0 ± 0.2; measured at 1:100 dilution) due to both the pH decrease (see Table II) and the addition of SDS, NMR measurements could be carried out before any measurable change in the concentration of OMA could occur. The width at half-height of the signal from methylenic bridge group increases (Table III) and then decreases to a plateau value which is significantly higher than that of the width of the free compound. This variation in the width of the lines is consistent with our previous contention of the existence of a continuum of OMA/SDS aggregates with varying proportions. Detailed investigations of this complex were limited by the very low solubility of the complex(es) at these high OMA concentrations. Moreover, the $C_2(H_2)$ triplet of the octanoyl chain broadens considerably with the first SDS additions, making it impossible to resolve clearly. These results constitute an indication of decrease of conformational freedom of OMA upon incorporation to SDS aggregates.

Discussion

Micellar catalysis or inhibition often arises from concentration of the reagents in the micellar phase; this effect is, of course, absent in mono- and intramolecular reactions. If the uncatalyzed reaction is very sensitive to changes in the solvent or to the addition of electrolytes, rate modifications by micelles will reflect directly the incorporation of the substrate into a medium different from water. Thus, rate modifications by micelles are seldom interpretable in terms of intrinsic effects of the detergent aggregates on the reactivity of the substrate.

The most probable source of the inhibitory effect of SDS on the *S*- to *N*-acyl transfer of mercaptoethylamines would be a pK shift of the terminal ammonium ion caused by electrostatic interaction with the negative surface of the micelle. In the case of long-chain acyl substrates, a decrease in the flexibility of the substrate caused by both surface and hydrophobic contributions could lead to additional stabilization of the initial state, and thus increased inhibition, by the negatively charged micelle.

The simplest explanation for the rate decrease of the *S*- to *N*-acyl transfer of AMA is an increase in the pK of the ammonium ion. Indeed a 100-fold inhibition, that is observed for AMA, can be accounted for by an increase in pK of 2 pH units. pK displacements of this magnitude have been measured or inferred[1-3] in a number of micelle modified reactions. Were this effect to be the only inhibitory factor, the rate of reaction of the unprotonated form in the Stern layer would be unaffected. This would suggest little penetration of the amine into the micellar phase and is in accordance with the small degree of hydrophobic stabilization afforded by a single CH_3 group and the small distribution constant measured for AMA. As the pK of this ammonium ion has been reported as 9.1[8], the apparent pK on the SDS micelles would be of the order of 11.

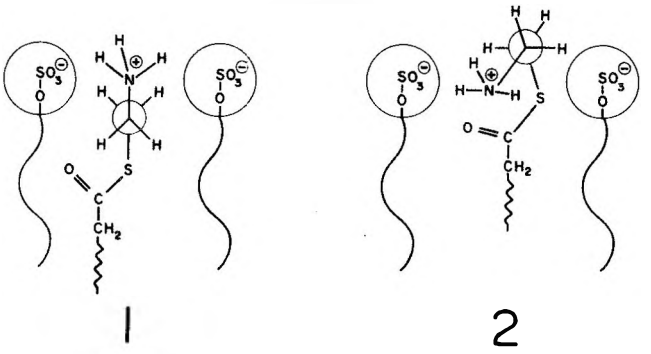
At high SDS/OMA ratios, where the inhibitory effect can be quantitatively analyzed, the micellar rate is slower than the water rate by a factor of 5×10^3. A pK shift is unlikely to be the sole cause of this inhibition. Although the effect of SDS on the pK of aliphatic amines has not been described, its effect on H_o for primary, secondary, and tertiary aromatic amines is, at the maximum, 1.25 units.[15] Moreover, the decrease in pK of dodecylammonium upon micellization (which can be visualized as the reverse of the effect of incorporation of an alkyl ammonium ion into a negative micelle) is not higher than 1.4 pH units.[16] This consideration and the effect of SDS on AMA allows one to set an upper limit of 2 pH units to the pK displacement produced by SDS on OMA. Thus, even taking into account the pK shift contribution, leading to a 100-fold inhibition, a rate decrease of, at least, 50-fold has to be explained.

This latter inhibition factor is most readily accounted for by assuming a decrease in the flexibility of substrate. Indeed the NMR data are unambiguous in the indication that the signal due to the methylene bridge protons is broadened by SDS. No signal splitting is observed under our conditions, strongly suggesting that the broadening is due not to a removal of the degeneracy, but rather to a decrease of the conformational freedom of this segment of the substrate.

Solutes have considerable mobility in the micellar phase,[3,17,18] and the motional freedom along the surfactant chain is only modestly restricted; however, the maximum motional restriction has been observed near the polar end of the detergent chain,[19] and the type of movement of the substrate can be restricted according to the relationship between the substrate and the micellar surface.[20] A good example of this is the observation that the addition of SDS causes an increase in the population of one of the isomers of *N*-octanoylsarcosinate,[21] demonstrating that favorable interactions between substrate and micelle can stabilize, significantly, one particular configuration of the substrate.

From the values of association constants of hydrophobic substrates with oppositely charged micelles,[14] it was expected that protonated OMA would interact favorably with SDS micelles, and this is reflected in the large value for the distri-

Scheme II



1 2

bution coefficient for this substrate. That this interaction has both electrostatic and hydrophobic components is implied by the 250-fold smaller distribution coefficient for AMA. The hydrophobic, or electrostatic interaction(s), will tend to stabilize the amine segment in the Stern layer; the hydrophobic contribution, on the other hand, will favor the insertion of the long acyl chain in the interior of the micelle. These interactions will favor an elongated configuration of the substrate (form 1, Scheme II). The molecular movement of OMA in SDS micelles will thus be nonisotropic, in the sense that the attainment of the bent conformation, necessary for attack leading to products, will be highly unfavorable (form 2, Scheme II) due, in part, to the exposure of the methylenic bridge to the solvent. Rotational anisotropy of a negatively charged spin probe (*N*-oxyl-4′,4′-dimethyloxazolidine derivative of 5-ketostearic acid) incorporated into a positively charged micelle has recently been described.[22] It has also been proposed, in a SDS inhibited system, that the ionic array of SDS with a positively charged substrate is tight in order to explain the observed stereoselectivity[23] of the reaction.

The rate of S to N transfer in OMA is enhanced about fivefold in the micellar phase of CTAB. The simplest explanation of this (small) effect would be a decrease in the pK of the terminal amine, thus increasing the concentration of the reactive (unprotonated) species. In a related system, it has been shown that micellization of dimethyl dodecyl ammonium chloride produces both an increase in the proton-exchange rate and a decrease in the pK of the ammonium ion of 1.4 pH units.[13] Taking this latter system as references, it would be expected that, in the absence of other effects, the rate acceleration caused by CTAB in the S to N transfer of OMA should be at least 30-fold. The rate acceleration obtained is significantly smaller, and the kinetic results can not be accommodated within the framework of a simple distribution model. This constitutes an indication of the occurrence of a mixed activation–inhibition effect by CTAB on this reaction.

Acknowledgments. This work was partially supported by Project Bioq/FAPESP. The authors thank Dr. F. Quina for his helpful comments and revision of the manuscript.

Registry No.—CTAB, 57-09-0; SDS, 151-21-3; AMA, 17612-91-8; OMA, 17612-92-9; Brij 35, 9002-02-0.

References and Notes

(1) C. A. Bunton, *Progr. Solid State Chem.*, **8**, 239 (1973).
(2) E. H. Cordes, Ed., "Reaction Kinetics in Micelles", Plenum Press, New York, N.Y., 1973.
(3) J. H. Fendler and E. J. Fendler, "Catalysis in Micellar and Macromolecular System", Academic Press, New York, N.Y., 1975.
(4) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw Hill, New York, N.Y., 1969.
(5) T. Wieland and H. Hornig, *Ann. Chem.*, **600**, 12 (1956).
(6) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *J. Am. Chem. Soc.*, **81**, 5089 (1959).
(7) R. B. Martin and A. Parcell, *J. Am. Chem. Soc.*, **83**, 4830 (1961).
(8) R. B. Martin, R. I. Hedrick, and A. Parcell, *J. Org. Chem.*, **29**, 3197 (1964).
(9) R. B. Martin and R. I. Hedrick, *J. Am. Chem. Soc.*, **84**, 106 (1962).
(10) R. E. Barnett and W. P. Jencks, *J. Am. Chem. Soc.*, **91**, 2358 (1969).
(11) W. O. Foye, R. N. Duvall, and J. Mickles, *J. Pharm. Sci.*, **51**, 168 (1962).
(12) T. Wieland and E. Bokelman, *Ann. Chem.*, **576**, 20 (1952).
(13) I. V. Berezin, K. Martinek, and A. K. Yatsimirski, *Russ. Chem. Rev.* (*Engl. Transl.*), **42**, 787 (1973).
(14) T. C. Bruice, J. Katzhendler, and L. R. Fedor, *J. Am. Chem. Soc.*, **90**, 1333 (1968).
(15) C. A. Bunton and L. Robinson, *J. Phys. Chem.*, **74**, 1062 (1970).
(16) F. M. Menger and J. L. Lynn, *J. Am. Chem. Soc.*, **97**, 948 (1975).
(17) S. Ohnishi, T. J. R. Cyr, and H. Fukushima, *Bull. Chem. Soc. Jpn.*, **43**, 673 (1970).
(18) T. Nakagawa and H. Jizomoto, *Kolloid Z. Z. Polym.*, **250**, 594 (1972).
(19) E. Williams, B. Sears, A. Allerhand, and E. H. Cordes, *J. Am. Chem. Soc.*, **95**, 4871 (1973).
(20) M. Shinitzky, A. C. Dianoux, C. Glitler, and G. Weber, *Biochemistry*, **10**, 2106 (1971).
(21) H. Takahashi, Y. Nakayama, H. Hori, K. Kihara, H. Okabayashi, and M. Okuyama, *J. Coll. Interface Sci.*, **54**, 102 (1976).
(22) J. R. Ernandes, S. Schreier, and H. Chaimovich, *Chem. Phys. Lipids*, **16**, 19 (1976).
(23) C. N. Sukenik, B. Weissman, and R. G. Bergman, *J. Am. Chem. Soc.*, **97**, 445 (1975).

Mechanism of the Meyer–Schuster Rearrangement

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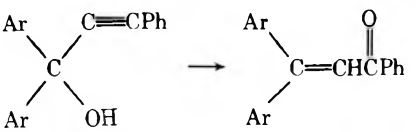
Received January 25, 1977.

The mechanism of the Meyer–Schuster rearrangement of tertiary arylpropargyl alcohols to α,β-unsaturated carbonyl compounds is discussed. The data, inverse solvent isotope effects, k_{H_2O}/k_{D_2O} = 0.36–0.48, ρ vs. σ^+ = −2.3 at the reaction site and −1.6 at the rearrangement terminus, $(k_H/k_d)_\alpha$ at the rearrangement terminus = 0.92, and relatively large negative $\Delta S^\ddagger$, all suggest an ion–dipole intermediate undergoing nucleophilic attack by H_2O as the rate-determining step. The rearrangement of eight triaryl- and diarylpropargyl alcohols is reported.

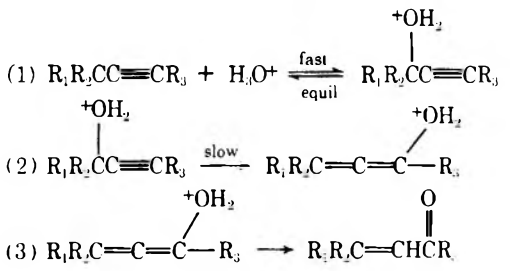
In 1922 Meyer and Schuster reported that triarylpropargyl alcohols, **1** and **2**, were converted in good yield to α,β-unsaturated ketones **3** and **4** by a variety of acidic catalysts such as CH_3COOH/H_2SO_4, HCl in ether, acetic anhydride, and acetyl chloride.[2] Several reviews concerned with the Meyer–Schuster and related Rupe rearrangements have appeared within the last 10 years.[3,4] Each suggests that alkynyl cations such as **5** are involved in the Meyer–Schuster rear-



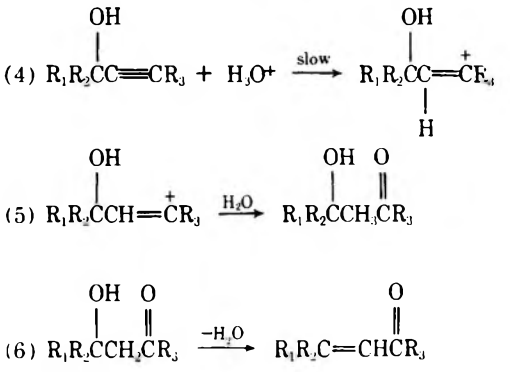
1 Ar = Ph **3**
2 Ar = *p*-ClC_6H_4 **4**

5

Scheme I. Acid-Catalyzed Preequilibrium



Scheme II. Acid-Catalyzed Hydration–Dehydration

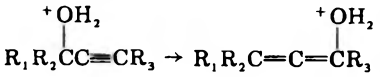


rangement, yet no firm evidence is available to support this contention. Indeed, the mechanistic evidence upon which pathways for the Meyer–Schuster rearrangement have been suggested has been acquired primarily from studies on propargyl alcohols undergoing the related Rupe rearrangement.[5-12] While we did not doubt the intermediacy of a cationic species, we did seek to establish the mechanism of this rearrangement in more detail than had previously been suggested. We therefore used the Schemes I and II as working hypotheses in our study. It should be noted that R_1, R_2, and R_3 must be chosen so that α hydrogens are not available for elimination from carbons adjacent to a cationic center. In our study, we chose R_1 and R_2 = aryl and R_3 = aryl or H in order to satisfy the earlier constraint as well as to avoid skeletal rearrangements known to occur when R_n = branched alkyl.[12]

Scheme I involves a rapid, preequilibrium step followed by slow rearrangement of the conjugate acid. Subsequent ketonization of the resulting allenol is considered rapid. Scheme II involves a rate-limiting proton transfer to carbon followed by rapid hydration of the resulting vinyl cation and subsequent rapid dehydration of the intermediate ketol. While Scheme II appeared unlikely on the basis of mechanistic evidence against its incursion in the Rupe rearrangement of 1-ethynylcyclohexanol to 1-acetylcyclohexene, we noted that the conditions required to effect Meyer–Schuster rearrangement of certain triarylpropargyl alcohols were not dissimilar to those under which arylacetylenes are hydrated to acetophenones via a mechanism involving a carbynium ion.[13]

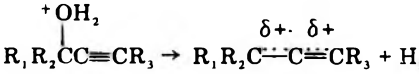
If Scheme I is examined it is apparent that step 2, i.e., the expected rate-limiting step, represents a multitude of kinetically indistinguishable mechanistic possibilities. Three of these are detailed below.

Intramolecular:



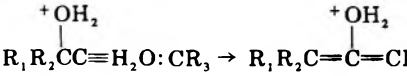
(a)

"Solvolytic":



(b)

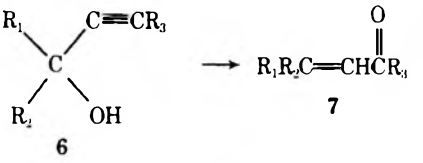
Intermolecular:



(c)

Equations a and b are the classical A-1 and A-2 versions of this rearrangement and imply *covalent* attachment of H_2O in the transition states. Equation b is meant to imply only *electrostatic* interactions, i.e., ion–dipole, of solvent and R^+.

The question of describing the mechanism involved here thus becomes one of deciding first whether proton transfer to the substrate is rate limiting (Scheme II) or not (Scheme I) and secondly, if Scheme I obtains, determining the site(s), i.e., number, and nature, electrostatic or covalent, of the interaction between substrate and associated water molecules. Our task then was to design mechanistic probes which would provide as much detail as possible regarding the rearrangement step. We elected to examine the kinetic behavior of tertiary ethynyl carbinols undergoing the Meyer–Schuster rearrangement exclusively and nearly quantitatively. Compounds **6a–h** were chosen for study.



6 **7**

a, $R_1 = R_2 = R_3 = C_6H_5$
b, $R_1 = R_2 = C_6H_5$; $R_3 = p\text{-}ClC_6H_4$
c, $R_1 = R_2 = C_6H_5$; $R_3 = p\text{-}CH_3C_6H_4$
d, $R_1 = R_2 = C_6H_5$; $R_3 = p\text{-}CH_3OC_6H_4$
e, $R_1 = R_3 = C_6H_5$; $R_2 = p\text{-}ClC_6H_4$
f, $R_1 = R_3 = C_6H_5$; $R_2 = p\text{-}CH_3OC_6H_4$
g, $R_1 = R_2 = C_6H_5$; $R_3 = H$
h, $R_1 = R_2 = C_6H_5$; $R_3 = D$

Results

Pseudo-first-order rates of rearrangement were measured spectrophotometrically at 3040 or 3100 Å in 40% dioxane:60% aqueous sulfuric acid. Excellent first-order plots were obtained to better than 90% rearrangement. Infinity absorbances indicated that the rearrangement **6** → **7** proceeded to greater than 97% completion in all cases based on molar absorptivities for **7** available in the literature.[14] Values of acidity function, H_0, are available for this medium in the literature.[15] Table I presents the computer-calculated rate data obtained in this study. Figures 1 and 2 display data selected to illustrate the substituent effects and solvent isotope effects observed here. Table II lists the acidity dependence information derived from Table I. Table III contains the secondary isotope-effect data calculated from the paired kinetic runs indicated in Table I, **6g/6h**. The activation parameters calculated from the data in Table I are $\Delta H^{\ddagger} = 20.9$ kcal mol^{-1} and $\Delta S^{\ddagger} = -7.5$ eu for **6a** and $\Delta H^{\ddagger} = 18.5$ kcal mol^{-1} and $\Delta S^{\ddagger} = -18.2$ eu for **6g** at 25 °C in 1.5 M H_2SO_4. Substituent effects vs. σ^+ are calculated to be $\rho = -2.3$ ($r = 0.984$) at the reaction center (C-1 in the alkynyl cation, **5**) and $\rho = -1.6$ ($r = 0.973$) at the propargyl position, i.e., C-3. The solvent isotope effects are calculated to be $k_{H_2O}/k_{D_2O} = 0.36$ for **6a** and 0.48 for **6g** in 1.5 M L_2SO_4 at 25 °C. The acidity required to effect measurable rates of rearrangement in these compounds precluded an evaluation of the incursion of specific or general acid catalysis.

Discussion

The inverse solvent isotope effects ($k_{H_2O}/k_{D_2O} < 1$) observed rule out any mechanism in which proton transfer is rate limiting. Consequently, the present discussion is confined to Scheme I.

H_0 are available for this medium in the literature.[15] Table I

Table I. Pseudo-First-Order Rate of Acid-Catalyzed Rearrangement 6 → 7 in 40:60 Dioxane/Aqueous H_2SO_4

Compd	T, °C	$M_{L_2SO_4}$[a]	H_0	10^4k_{obsd}, s^{-1}	Compd	T, °C	$M_{L_2SO_4}$[a]	H_0	10^4k_{obsd}, s^{-1}
6a	25.03 ± 0.03	0.74	0.85	0.0878	**6e**	25.03 ± 0.03	2.00	−0.02	0.417
		1.06	0.60	0.273			2.30	−0.21	0.881
		1.70	0.18	0.864			2.60	−0.41	1.77
		2.03	−0.03	2.13			2.74	−0.50	1.94
		2.30	−0.21	3.35			3.18	−0.79	5.43
		2.90	−0.63	15.6			3.51	−1.00	12.4
		0.84[b]	0.77[c]	0.432	**6f**	25.03 ± 0.03	0.34	1.18	1.45
		1.06[b]	0.60[c]	0.713			0.57	1.00	2.12
		1.25[b]	0.47[c]	1.04			0.75	0.84	3.70
		1.70[b]	0.18[c]	2.49			1.00	0.64	6.75
		1.95[b]	0.02[c]	3.87			1.35	0.41	16.3
		2.36[b]	−0.25[c]	9.36			1.70	0.18	34.6
	34.62 ± 0.02	0.63	0.93	0.310	**6g**	25.03 ± 0.03	1.15	0.53	0.0794
		0.67	0.90	0.325			1.30	0.43	0.111
		1.06	0.60	0.891			1.53	0.28	0.202
		1.23	0.49	1.23			1.63	0.22	0.235[d]
		1.54	0.28	2.26			1.84	0.08	0.334[d]
		1.84	0.08	4.12			2.12	−0.09	0.605[d]
	45.51 ± 0.04	0.43	1.16	0.590			2.38	−0.27	1.05[d]
		0.67	0.90	1.08	**6g**	25.03 ± 0.03	0.71[b]	0.91[c]	0.0592
		0.88	0.78	1.79			0.79[b]	0.80[c]	0.0772
		1.13	0.55	3.09			0.81[b]	0.78[c]	0.0889
		1.30	0.45	4.09			0.97[b]	0.65[c]	0.118
6b	24.98 ± 0.04	1.06	0.60	0.128			1.18[b]	0.53[c]	0.189
		1.13	0.55	0.190		35.00 ± 0.04	0.96	0.66	0.166
		1.46	0.33	0.321			1.13	0.55	0.237
		1.85	0.08	0.713			1.28	0.45	0.316
		2.21	−0.15	1.47			1.54	0.28	0.542
		2.60	−0.41	3.21			1.66	0.21	0.676
6c	25.03 ± 0.03	0.65	0.93	0.465			1.85	0.07	0.973
		0.66	0.92	0.495		44.10 ± 0.03	0.52	1.06	0.159
		1.02	0.63	1.13			0.58	0.99	0.205
		1.25	0.48	2.11			0.78	0.80	0.337
		1.46	0.33	3.28			1.00	0.63	0.537
		1.55	0.28	3.88			1.17	0.53	0.733
6d	25.03 ± 0.03	0.40	1.19	0.690			1.32	0.43	0.976
		0.58	0.99	1.20			1.54	0.29	1.53
		0.88	0.74	2.76	**6h**	25.03 ± 0.03	1.63	0.22[d]	0.262
		0.93	0.69	3.04			1.84	0.08[d]	0.355
		1.30	0.44	7.01			2.12	−0.09[d]	0.667
							2.38	−0.27[d]	1.14

[a] H_2SO_4 unless otherwise indicated. [b] $M_{D_2SO_4}$. [c] D_0, assuming $D_0 = H_0$ at constant M. [d] Paired runs, **6g/6h**, measured simultaneously in identical solutions.

Table II. Summary of Acidity Dependence Data for the Acid-Catalyzed Rearrangement 6 → 7, log $k_{obsd} = mH_0 + \log k_0$

Compd	Conditions	$-m$	Log k_0	r
6a	25 °C, 0.74–2.90 M H_2SO_4	1.483	−3.752	0.9981
	25 °C, 0.84–2.36 M D_2SO_4	1.301	−3.368	0.9998
	35 °C, 0.63–1.84 M H_2SO_4	1.335	−3.268	0.9995
	45 °C, 0.43–1.30 M H_2SO_4	1.200	−2.847	0.9968
6b	25 °C, 1.06–2.60 M H_2SO_4	1.338	−4.039	0.9977
6c	25 °C, 0.65–1.55 M H_2SO_4	1.415	−3.018	0.9987
6d	25 °C, 0.40–1.30 M H_2SO_4	1.348	−2.571	0.9993
6e	25 °C, 2.00–3.51 M H_2SO_4	1.461	−4.392	0.9976
6f	25 °C, 0.34–1.70 M H_2SO_4	1.413	−2.227	0.9975
6g	25 °C, 1.15–2.38 M H_2SO_4	1.388	−4.345	0.9984
	25 °C, 0.71–1.18 M D_2SO_4	1.303	−4.052	0.9936
	35 °C, 0.96–1.85 M H_2SO_4	1.314	−3.906	0.9995
	44 °C, 0.52–1.54 M H_2SO_4	1.251	−3.467	0.9994
6h	25 °C, 1.63–2.38 M H_2SO_4	1.341	−4.308	0.9963

Table III. Secondary Isotope Effect Data for Rearrangement 6g, h → 7g, h at 25 °C

$M_{H_2SO_4}$	H_0	k_H/k_D[a]	$\Delta\Delta F^{\ddagger}/D$
1.63	0.22	0.897	64
1.84	0.08	0.941	36
2.12	−0.09	0.907	58
2.38	−0.27	0.921	49

[a] Calculated from paired runs in Table I.

The Hammett plots above suggest an intermediate in which substantial charge is delocalized from the reaction center to the rearrangement terminus. Indeed, the magnitudes of ρ reported here for **6a–f** are similar to those observed in the solvolysis of triarylhaloallenes where ρ_X and $\rho_Y = -2.0$, thus implying a similar intermediate cationic species.[16] These compounds have been shown to solvolyze via a limiting mechanism in aqueous ethanol and aqueous acetone solutions. Indeed, these data do rule out any rearrangement mechanism which does not involve a cationic intermediate. The question remaining, however, is the degree and nature of involvement by H_2O in the transition state. Some information regarding

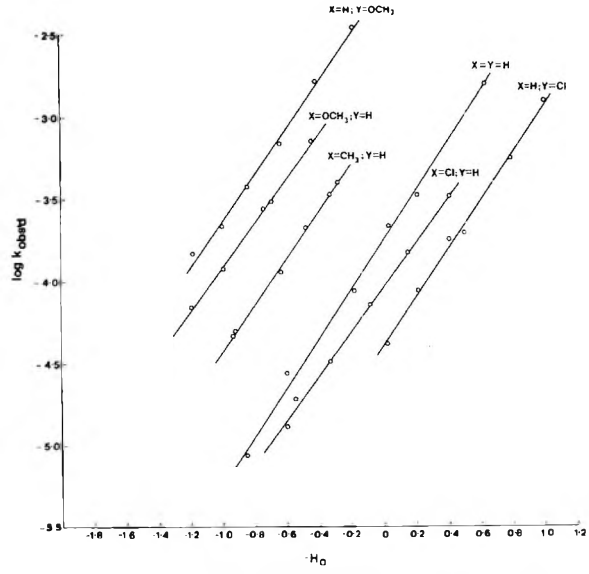


Figure 1. Substituent effects in Meyer–Schuster rearrangement of (*p*-YPh)C(OH)(Ph)C≡C(PhX-*p*).

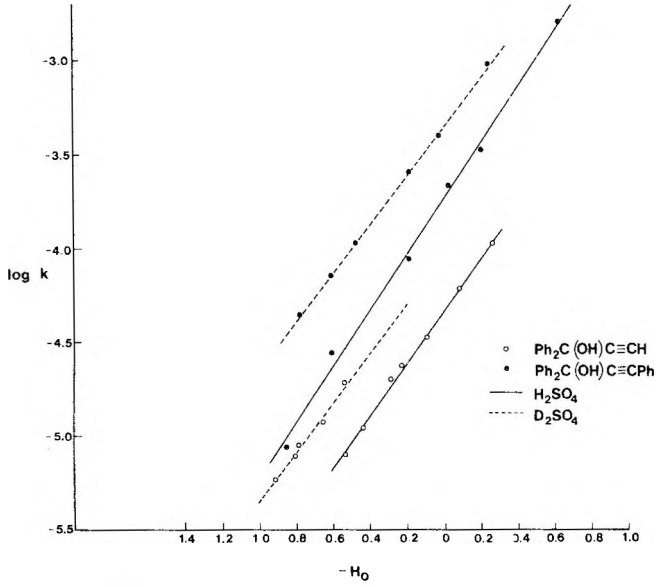


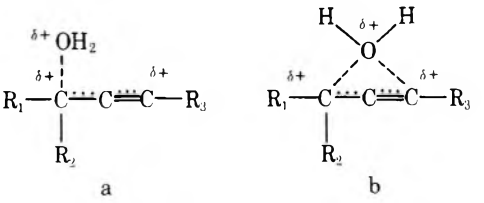
Figure 2. Solvent isotope effects in Meyer–Schuster rearrangement of $Ph_2C(OH)C{\equiv}CH$ and $Ph_2C(OH)C{\equiv}C{-}Ph$ at 25 °C in 40:60 dioxane:aqueous L_2SO_4.

this question can be obtained from a closer examination of the solvent isotope effects observed.

Bunton and Shiner suggested some time ago that a distinction could be made among appropriately chosen models for the transition states of acid-catalyzed reactions by assessing changes in hydrogen bonding strength and number upon formation of the transition-state model and using these changes to calculate the expected solvent isotope effect from a simple empirical expression.[17] While such treatments lead to ambiguous results in a few reported cases, an interesting and distinctive set of predictions is made for six reasonable models, a–f, of the transition state for the present reaction shown in Chart I. These results show that, in general, any covalent attachment of water in the transition state at C-1 or at C-3 leads to an increase in $\Sigma\nu_H - \Sigma\nu^{\ddagger}_H$, i.e., to an increase in k_{H_2O}/k_{D_2O}.[18] Thus, models a, b, and e, which allow covalent interaction by one or two H_2O molecules, exhibit calculated k_{H_2O}/k_{D_2O} ratios of greater magnitude than models c, d, and f which allow only electrostatic interactions of R^+ and H_2O.

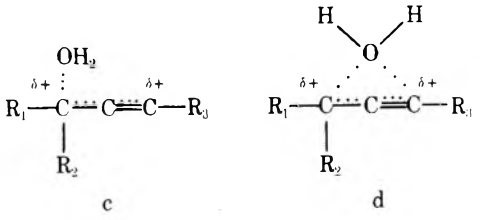
Chart I. Transition-State Models for Meyer–Schuster Rearrangement[a]

Unimolecular, covalent attachment of H_2O, calcd $k_{H_2O}/k_{D_2O} = 0.74$



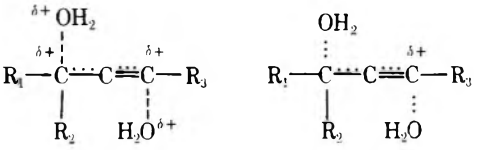
a b

Unimolecular ion–dipole interaction of R^+ and H_2O, calcd $k_{H_2O}/k_{D_2O} = 0.40$

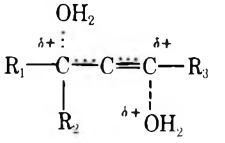


c d

Bimolecular



e, covalent calcd $k_{H_2O}/k_{D_2O} = 1.36$ f, ion–dipole calcd $k_{H_2O}/k_{D_2O} = 0.40$



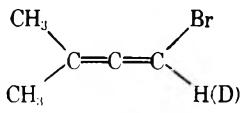
g, ion–dipole at reaction center partially covalent at rearrangement terminus, for calcd k_{H_2O}/k_{D_2O} see text

[a] (---) Covalent interaction; (···) electrostatic interaction.

Model g, which corresponds to nucleophilic attack, i.e., partial covalent attachment of H_2O at the rearrangement terminus, on a solvated ion, also predicts an isotope effect of large magnitude (vide infra). These calculations thus suggest that an ion–dipole pair is an intermediate in this rearrangement. That is to say, the covalent attachment suggested by transition-state models a, b, e, and to some extent g appears inconsistent with the low values of k_{H_2O}/k_{D_2O} observed here as well as with the magnitude of ρ reported above. Models c, d, and f all represent a solvated cation, and it is doubtful whether any chemical distinction should be made among them.[17]

The inverse α-secondary isotope effect, **6g/6h,** observed strongly supports the view that some rehybridization (sp → sp^2), i.e., covalent attachment at the rearrangement terminus, has occurred. The calculated maximum $(k_H/k_D)_\alpha$ for complete rehybridization sp → sp^2 is 0.78.[19-21] Thus, the present value $k_H/k_D = 0.92$ suggests substantially less (~34% of maximum) than complete rehybridization has taken place at the transition state. If one assumes that this represents an approximation of the degree of covalent attachment at the rearrangement terminus in **6g** and further assumes that the solvent isotope effect measured in **6a,** $k_{H_2O}/k_{D_2O} = 0.36$, is completely free of any covalent component, then an expected solvent isotope

effect of k_{H_2O}/k_{D_2O} = 0.46 for **6q** is calculated.[22] It is not unreasonable to expect the degree of covalent attachment of H_2O at the rearrangement terminus to increase with decreasing stability of the cation formed, as is likely to be the case between **6a** and **6g**. Indeed, the more negative entropy activation calculated for **6g**, −18.6 vs. −7.5 eu for **6a**, is also consistent with this view. Thus, the transition state for the Meyer–Schuster rearrangement of **6g** is apparently an event occurring between the formation of an electrostatically solvated cation and complete covalent attachment of H_2O at the rearrangement terminus. In solvolytic terminology this would be described as nucleophilic attack by solvent on an ion pair or in this case an ion–dipole pair. It is interesting to note that it has been shown recently that **8** undergoes solvolysis via nucleophilic attack of solvent on a tight ion pair of retained configuration and exhibits $(k_H/k_D)_\alpha$ ratios dependent upon solvent nucleophilicity being 1.20 in 60E and 1.28 in 97T.[20,23] Isotopic substitution in **9** as indicated results in no observable isotope effect.[24]



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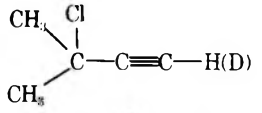

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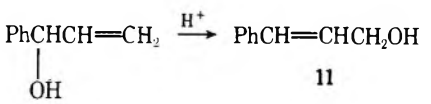
Finally, an alternative transition-state model involving a covalent or electrostatic interaction of one water molecule with two cationic centers similar to that suggested in the acid-catalyzed rearrangement of 1-phenyl-2-propen-1-ol (**10**) to 3-phenyl-2-propen-1-ol (**11**) appears unlikely in the present case owing to the linearity of the alkynyl cation, **5**, and the longer distance between cationic centers not present in the allylic cation intermediate involved in rearrangement of **10**.[25–28] Such a transition state is not ruled out by the present data. Our preference for the rate-limiting step, however, is a highly solvated delocalized cation undergoing nucleophilic attack by solvent or returning to starting alcohol by collapse to the conjugate acid. The reaction is thus controlled by formation of the thermodynamically favored allenol ⇌ α,β-unsaturated carbonyl tautomeric pair. This is further supported by noting that triarylchloroallenes yield only triarylpropargyl alcohols upon solvolysis. Unsaturated ketones are not observed under these conditions. Since the propargyl position is the exclusive site of nucleophilic attack by water on the R^+ generated solvolytically, the R^+ formed by loss of H_2O from the protonated alcohol must return faster than it forms the conjugate acid of the allenol, thus supporting the conclusion above that attack of H_2O at the rearrangement terminus is rate limiting in the present case.



10 **11**

Finally, the rapid exchange rates of carbonyl compounds with $H_2{}^{18}O$ preclude meaningful labeling studies regarding the inter- or intramolecularity of the rearrangement step. Exchange rates of unlabeled starting material and polarimetric rates on optically active starting materials are being undertaken, in an attempt to assess the freedom of the intermediate carbon ion. However, the resolution of aryl tertiary propargylic alcohols presents a demanding task. Rearrangement of aliphatic propargyl alcohols is also being studied.

Experimental Section

Materials. All melting points are uncorrected. IR spectra were obtained using a Perkin-Elmer Model 457 spectrophotometer. ^1H NMR spectra were obtained using a Hitachi Perkin-Elmer Model R-20B spectrometer, 60 MHz. Dioxane was ACS certified reagent grade and was used without further purification. Triarylpropargyl alcohols **6a–f** were prepared as described previously.[16] 1,1-Diphenyl-2-propyn-1-ol was prepared according to the method of Beumel and Harris.[29] This alcohol was deuterated by three exchanges in 0.20 M $NaOD/D_2O$ solution. No detectable ^1H NMR signal was observed at 100× amplitude. Deuterium oxide was obtained from Bio-Rad Laboratories, isotopic purity 99.88%. Deuteriosulfuric acid was obtained from Mallinckrodt Chemical Works, isotopic purity 99.5%.

Kinetic Measurements. All kinetic studies were performed on a Gilford Instruments Model 240 spectrophotometer. The cell compartment was thermostated using a PRT-regulated proportional temperature controller. Temperature measurement was accomplished with a Hewlett-Packard quartz thermometer.

A 1.25×10^{-4} M stock solution of the alcohol was prepared in dioxane. In a typical kinetic run, 10 mL of the stock solution was diluted with exactly 15.0 mL of aqueous sulfuric acid, resulting in a final concentration of approximately 5×10^{-5} M in propargyl alcohol. After mixing the solution thus obtained (10 s), a 1-cm quartz cell was rinsed twice, filled, and allowed to equilibrate in the cell compartment (10 min). The appearance of product absorbance at 3040 or 3100 Å was recorded vs. time against a blank identical with the sample except for the presence of substrate. Solvent deuterium isotope effects were measured identically except that a total volume of 10 mL was utilized.

A volumetrically measured and weighed portion of the kinetic solution was titrated against standard NaOH. The Hammett acidity function, H_0, was determined by reference to the scale of Torck, Hellin, and Coussemant for H_2SO_4 in 40:60 aqueous dioxane. Rate constants were calculated as described earlier.[19]

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—**6a**, 1522-13-0; **6b**, 35556-63-9; **6c**, 1522-14-1; **6d**, 35476-69-8; **6e**, 62698-34-4; **6f**, 62698-35-5; **6g**, 3923-52-2; **6h**, 62698-36-6.

References and Notes

(1) On leave 1976–77, Department of Chemistry, University of Aberdeen, Scotland, to whom the senior author is indebted for the use of facilities and gracious hospitality.
(2) K. H. Meyer and K. Schuster, *Chem. Ber.*, **55**, 819 (1922).
(3) S. Swaminathan and K. V. Narayan, *Chem. Rev.*, **71**, 429 (1971).
(4) S. A. Vartanyan and Sh. O. Banbanyan, *Russ. Chem. Rev.*, **36**, 670 (1967).
(5) H. Rupe and H. Werdenburg, *Helv. Chim. Acta*, **18**, 542 (1935), and 12 preceding papers in this series.
(6) C. D. Hurd and R. E. Christ, *J. Am. Chem. Soc.*, **59**, 118 (1937).
(7) J. D. Chanley, *J. Am. Chem. Soc.*, **70**, 244 (1948).
(8) W. S. Macgregor, *J. Am. Chem. Soc.*, **70**, 3953 (1948).
(9) Y. F. Hennion, R. B. Davis, and D. E. Maloney, *J. Am. Chem. Soc.*, **71**, 2813 (1949).
(10) I. Issei and O. Jokutero, *J. Pharm. Soc. Jpn.*, **79**, 866 (1960).
(11) R. Heilmann and R. Glenat, *Ann. Chim. (Paris)*, 175 (1963).
(12) M. Apparu and R. Glenat, *Bull. Chim. Soc. Fr.*, 1106, 113 (1968).
(13) D. S. Noyce and M. D. Schiavelli, *J. Am. Chem. Soc.*, **90**, 1020, 1023 (1968).
(14) G. Quinkert, M. Hintzmann, P. Michaelis, P. Jürges, H. Appelt, and V. Krüger, *Ann. Chim. (Paris)*, 38 (1971).
(15) B. Torck, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. Fr.*, 1657 (1962).
(16) M. D. Schiavelli, S. C. Hixon, H. W. Moran, and C. A. Boswell, *J. Am. Chem. Soc.*, **93**, 6989 (1971).
(17) C. A. Bunton and V. J. Shiner, Jr., *J. Am. Chem. Soc.*, **83**, 42, 3207, 3214 (1961).
(18) The values shown in Chart I arise from utilizing Bunton and Shiner's values of O–H stretching frequencies for hydrogen-bonded H_2O and H_3O^+, i.e., 3400 and 2900 cm^{-1}, respectively. The initial state here assumes a pK_a for the alcohol equal to that given for H_2O, i.e., 16. Covalently bound water molecules are assumed to be comparable to hydronium ion, while electrostatically bound water molecules are free to accept an additional hydrogen bond. Bunton and Shiner's notation has been retained; i.e., covalent interactions are indicated by dashed lines (- - -) and electrostatic interactions by dotted lines (· · ·).
(19) M. D. Schiavelli, T. C. Germroth, and J. W. Stubbs, *J. Org. Chem.*, **41**, 681 (1976).
(20) M. D. Schiavelli and D. Ellen Ellis, *J. Am. Chem. Soc.*, **95**, 7916 (1973).
(21) S. R. Hartshorn and V. J. Shiner Jr., *J. Am. Chem. Soc.*, **94**, 9002 (1972); and V. J. Shiner, Jr., private communication.
(22) The observed $RT \ln (k_H/k_D)_\alpha = -49$ cal is 0.34 times the calculated maximum $RT \ln (k_H/k_D)_\alpha = -146$ cal at 298 K. Thus, the expected $RT \ln (k_{H_2O}/k_{D_2O})_{6g}$ should equal $RT \ln (k_{H_2O}/k_{D_2O})_{6a} + 0.34[RT[\ln (k_{H_2O}/k_{D_2O})_{(covalent)}] - \ln (k_{H_2O}/k_{D_2O})_{6a}] = -605$ cal $+ 0.34[-173 - (-605)] = -460$ cal.

(23) M. D. Schiavelli et al., submitted for publication.
(24) V. J. Shiner, Jr., J. W. Wilson, G. Heinemann, and N. Soliday, *J. Am. Chem. Soc.*, **84**, 2408 (1962).
(25) H. L. Goering and R. E. Dilgren, *J. Am. Chem. Soc.*, **81**, 2556 (1959).
(26) H. L. Goering and R. E. Dilgren, *J. Am. Chem. Soc.*, **82**, 5744 (1960).
(27) H. Kwart and J. Herling, *J. Am. Chem. Soc.*, **85**, 226 (1963).
(28) See also Y. Pocker and M. J. Hill, *J. Am. Chem. Soc.*, **91**, 3243 (1969); M. Stiles and A. L. Longroy, *J. Org. Chem.*, **32**, 1095 (1967), for studies on related rearrangements.
(29) O. F. Beumel and R. F. Harris, *J. Org. Chem.*, **29**, 1872 (1964).

Thiyl Radical and Mercuric Ion Induced Cyclizations of Dimethyl Dipropargylmalonate and Dimethyl Propargyl-3-thiylallylmalonates

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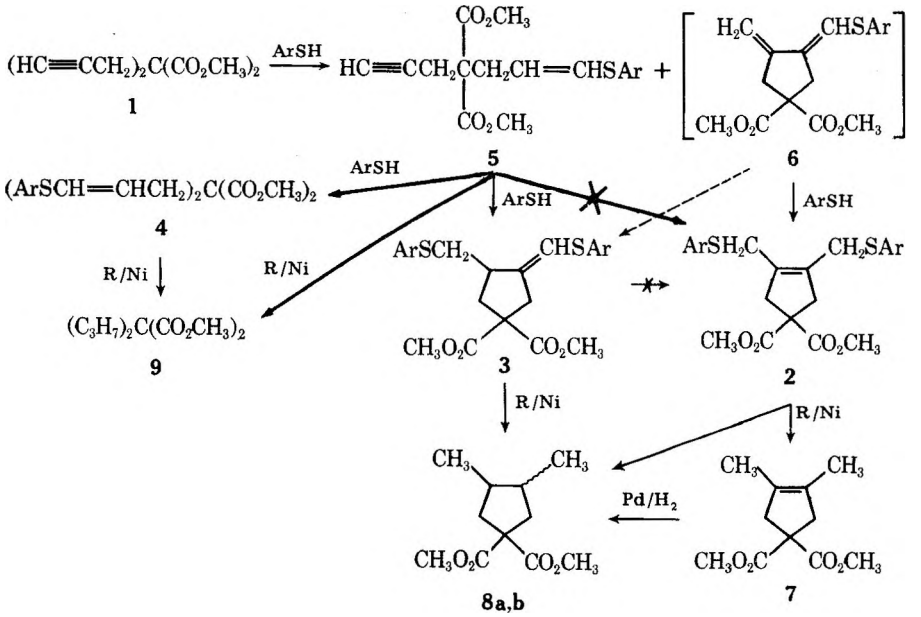
Received April 4, 1977

The first examples of radical-initiated cyclizations of a 1,6-diyne were found in the photochemical reactions of dimethyl dipropargylmalonate with thiophenols. The reactions are accompanied by formation of acyclic monothioenol ethers, which also undergo cyclization on reaction with thiophenols or with mercuric chloride. Cyclopentane products are formed in all of these reactions. Alternatively, the dipropargyl compound on direct reaction with aqueous mercuric chloride yields a diketone which can be cyclized to 5,5-dicarbomethoxy-3-methylcyclohex-2-enone.

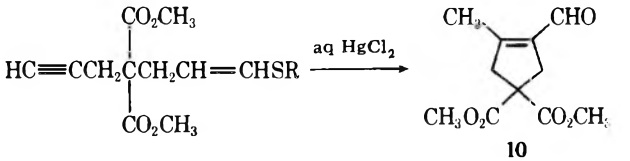
Geminal diallyl compounds undergo cyclization to cyclopentyl products in high yields on reaction with thiyl and other radicals.[1] However, 1,6-heptadiyne was reported to yield no radical induced cyclization but only an acyclic radical addition product.[2] While we also found that dimethyl dipropargylmalonate (1) gave only traces of cyclized material on photochemically initiated reaction with ethanethiol or butanethiol, a 2:1 mixture of the cyclized to uncyclized diadducts (**2, 3, 4**) and the uncyclized monoadduct **5** were formed in photochemical reactions with benzenethiol or *p*-toluenethiol.

A reaction of the monoadduct **5** with benzenethiol in the dark did not lead to any cyclization products, but on irradiation a mixture of the acyclic adduct **4** and the cyclization product **3** was formed. None of the encocyclic double bond isomer **2** could be detected in this reaction mixture, in contrast to the above thiol addition to the dipropargylmalonate, where as much endocyclic double bond isomer **2** as exocyclic double bond isomer **3** was obtained. Thus it was found that the cyclization product **2** does not arise from the acyclic adduct **5**, but that it is generated from the diacetylene **1** by direct cyclization to a presumed dimethylenecyclopentane intermediate **6**, which in turn can undergo 1,4 radical addition of benzenethiol to give **2** and probably 1,2 addition to give product **3**. The reactive intermediate **6** could not be isolated. While cyclizations of a cyanomalonyl radical with a terminal acetylenic group[3] and of a vinyl radical with a terminal vinyl group[4] have been shown to yield methylenecyclopentane products, the present result seems to be the first cyclization reaction of a vinyl radical with a terminal acetylene (i.e., the first example of a direct radical-initiated cyclization of a diacetylene).

Reductive desulfurization of the cyclization product mixture of **2** and **3** yielded the dimethylcyclopentene **7** and an epimeric mixture of the dimethylcyclopentanes **8a,b**. Hydrogenation of the olefin **7** also led to a cis/trans mixture of the dimethylcyclopentanes **8a,b**. Reductive desulfurization of the acyclic diadduct **4** and of the monoadduct **5** gave dimethyl di-*n*-propylmalonate (**9**). Since irradiation (a radical process) was required for the cyclization of the thioenol ether **5** with thiophenol, it was of interest to explore alternative ionic



cyclizations of this acetylenic thioenol ether. Its reaction with aqueous mercuric chloride gave the cyclopentenal **10** in 80% yield.



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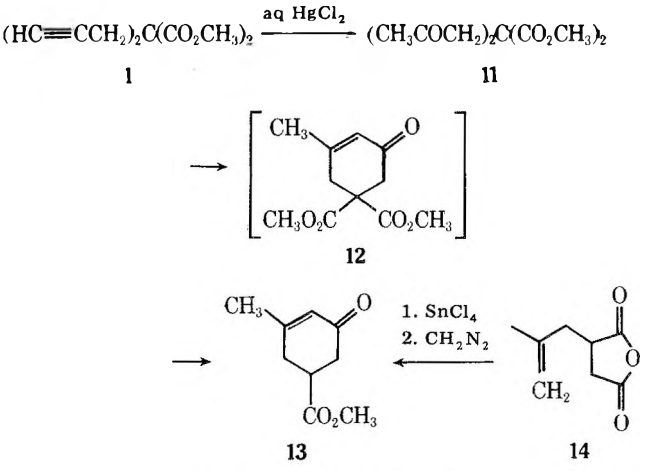
Under the same reaction conditions dimethyl dipropargylmalonate (**1**) was converted to the acyclic diketone **11**. The latter could be cyclized by sodium methoxide to the cyclohexenone **12**, which underwent monodecarbomethoxylation to the monoester **13**. The structures of these cyclohexenones are consistent with their spectroscopic data and could be confirmed by an alternative synthesis. Thus alkylation of maleic anhydride with isobutene and rearrangement of the olefinic anhydride **14** with stannic chloride followed by esterification also provided the enone ester **13**[5,6] obtained from the above reaction sequence.



1 **11** **12** **13** **14**

Experimental Section

Photochemical Reactions of Dimethyl Dipropargylmalonate (1) with Thiols. Dimethyl dipropargylmalonate (**1**) [bp 75–80 °C (0.01 mm), 87–88 °C, *m/e* 208], prepared by the procedure for the diethyl ester[7] in 82% yield, and 1 or 2 equiv of *p*-toluenethiol, or 2 equiv of thiophenol, or an excess of *n*-butanethiol or ethanethiol, were subjected to identical reaction conditions represented by the following procedure. Corresponding results are shown in Table I.

A solution of 0.80 g (3.8 mmol) of the dipropargyl compound **1**, 0.50 g (4.0 mmol) of p-toluenthiol, and 10 mg of diphenyl disulfide in 5 mL of dry benzene was sealed under a nitrogen atmosphere in a Pyrex tube and irradiated for 6 h with a 450-W high-pressure Hg lamp. Distillation of the reaction mixture gave 0.34 g of recovered dipropargyl compound **1**, 0.28 g of the acyclic monoadduct **5** [bp 120 °C (0.01 mm); IR ν_{max} 3300 cm^{-1}; NMR ($CDCl_3$) δ 7.2 (q, 4 H), 6.3 (m, 1 H), 5.6 (m, 1 H), 3.7 (s, 6 H), 2.8–3.1 (m, 4 H), 2.3 (s, 3 H), 2.05 (s, 1 H)], followed by a mixture of 0.40 g of the acyclic diadduct **4** and the cyclic diadducts **2** and **3** [bp 210–220 °C (0.01 mm); IR ν_{max} no acetylenic absorption at 3300 cm^{-1}; NMR ($CDCl_3$) δ 7.2 (m, 8 H), 5.2–6.2 (m, ≃2 H), 3.75 (s, 6 H), 2.7–3.2 (m, 6 H), 2.3 (s, 6 H).

An analogous diadduct mixture, bp 210–220 °C (0.02 mm), was obtained from reaction with 2 equiv of benzenethiol and separated by medium-pressure liquid chromatography on silica gel, eluting with chloroform at 80-lb pressure. Three fractions were collected. On reductive desulfurization (see below) the most rapidly eluted one (**4**) yielded dimethyl di-*n*-propylmalonate, while the other two gave only cyclopentyl products. The second eluate showed spectra corresponding to the thiomethylene structure **3**: *m/e* 428; NMR ($CDCl_3$) δ 7.2 (s, 10 H), 6.1 (s, 1 H), 3.7 (s, 6 H), 3.2 (s, 2 H), 3.1–2.6 (m, 5 H). The last fraction contained the cyclopentene **2**: *m/e* 428; NMR ($CDCl_3$) δ 7.2 (s, 10 H), 3.7 (s, 4 H), 3.1 (s, 4 H).

Comparison of the characteristic NMR signal at δ 6.1 for the exocyclic double bond of **3** with signals at δ 3.1–3.2 for **2** and **3** showed a 1:10 signal ratio in the initial mixture of diadducts, indicating approximately equal amounts of the isomers **2** and **3**.

Table I

Thiol	Registry no.	Wt % products: Recovered 1	Monoadducts 5	Diadducts 2, 3, 4
Thiophenol, 2 equiv	108-98-5	14	37	49
p-Toluenethiol, 1 equiv	106-45-6	33	27	40
p-Toluenethiol, 2 equiv		32	11	57
n-Butanethiol, excess	109-79-5	Trace	15	85
Ethanethiol, excess	75-08-1	46	31	23

Table II. Raney Nickel Reduction Products (%)

Mixture of thiol diadducts 2, 3, 4 from reaction of 1 with:	9	8a	8b
Thiophenol (2 equiv)	37	26	37
p-Toluenethiol (1 equiv)	49	28	23
p-toluenethiol (2 equiv)	49	28	23
n-Butanethiol (excess)	95	Trace	Trace
Ethanethiol (excess)	100		
From reaction of thiol monoadduct **5** with *p*-toluenethiol	22	50	28

Reaction of Dimethyl (3-*p*-toluenethiylallyl)propargylmalonate (5) with *p*-Toluenethiol. A solution of 100 mg (0.30 mmol) of the acyclic monoadduct **5**, 40 mg (0.32 mmol) of *p*-toluenethiol, and 10 mg of diphenyl disulfide in 5 mL of benzene was irradiated for 8 h as described above and distilled. The crude reaction product lacked the characteristic 1:1 pair of NMR singlets at δ 3.1 and 3.2 of the cyclopentene **2**, which was found in the reaction products of dimethyl dipropargylmalonate, but showed spectral characteristics of **3** and **4** at δ 6.1 and 2.6–3.1. Reductive desulfurization of the total reaction product gave dimethyl dipropylmalonate (**9**) and *trans*- and *cis*-1,1-dicarbomethoxydimethylcyclopentanes **8a,b** in ratios of 22:50:28, respectively. A corresponding reaction mixture stored without irradiation and diphenyl disulfide gave only dimethyl dirpopylmalonate (**9**) on subsequent reductive desulfurization.

Reductive Desulfurization of Reaction Products. The distilled thiol addition products (about 0.4 g) were heated at reflux in 10 mL of ethanol with about 3 g of W-6 Raney nickel for 10 h. Filtration and evaporation yielded desulfurized products sometimes showing allylic methyl singlets in NMR spectra due to the dimethylcyclopentene **7**. In those cases the reaction mixtures were hydrogenated further over 5% Pd/C catalyst in ethanol to the dimethylcyclopentane products **8a,b**. The mixtures of these products and dimethyl di-*n*-propylmalonate (**9**) were analyzed by GLC on a 6¼ ft column of 20% Carbowax on Firebrick at 145 °C. Under these conditions the reduction products had the following retention times: dimethyl di-*n*-propylmalonate (**9**), 8.2 min; 1,1-dicarbomethoxy-*trans*-3,4-dimethylcyclopentane[1] (**8a**), 10.4 min; 1,1-dicarbomethoxy-*cis*-3,4-dimethylcyclopentane[1] (**8b**) and 1,1-dicarbomethoxy-3,4-dimethylcyclopent-3-ene (**7**), 13 min. Hydrogenation of the cyclopentene **7** in the reaction mixture, by stirring under hydrogen over 5% Pd/C in ethanol, increased the amount of the *trans*-dimethylcyclopentane **8a** in accord with the hydrogenation of 1,2-dimethylcyclopentene, which gave a 4:1 *trans/cis*-1,2-dimethylcyclopentane ratio.[2] The composition of typical reduction product mixtures is shown in Table II. Products **8a,b** and **9** were identified by GLC enrichment with authentic samples[1] and matching of NMR spectra and mass fragmentation patterns.

4,4-Dicarbomethoxy-2-methylcyclopentenecarboxaldehyde (10). Irradiation of a solution of 1.8 g (8.6 mmol) of dimethyl dipropargylmalonate (**1**) 2.6 mL (35 mmol) of ethanethiol, and 12 mg of diphenyl disulfide in 3 mL of benzene for 6 h with a high-pressure 450-W Hg lamp and distillation of the mixture gave 1.1 g of recovered starting malonate (**1**), 0.75 g of monothiol adduct **5**, bp 120 °C (0.03 mm), and 0.55 g of diadduct **4**, bp 190 °C (0.01 mm). The lower boiling point product showed acetylenic absorption: IR ν_{max} 3300 cm^{-1}; NMR ($CDCl_3$) δ 6.2 (m, 1 H), 5.4 (m, 1 H), 3.75 (s, 6 H), 2.4–3.0 (m, 6 H), 2.1 (s, 1 H), 1.3 (t, 3 H); *m/e* 270. The higher boiling point product showed: no acetylenic IR absorption; NMR ($CDCl_3$) δ 6.0 (m, 2 H), 5.4 (m, 2 H), 3.7 (s, 6 H), 2.2–3.0 (m, 8 H), 1.2 (t, 6 H); *m/e* 332. On reductive desulfurization of either component only dimethyl di-*n*-propylmalonate (**9**) was obtained.

A solution of 0.20 g (0.74 mmol) of the lower boiling point fraction (5) and 0.65 g (2.4 mmol) of mercuric chloride in 7 mL of 4:1 acetonitrile/water was heated at reflux for 15 h, filtered, and distilled to 130 °C (0.05 mm) to give 0.14 g (80% yield) of the cyclopentyl aldehyde **10**: IR ν_{max} 1735, 1665 cm^{-1}; NMR ($CDCl_3$) δ 10.0 (d, 1 H), 3.8 (s, 6 H), 3.3 (s, 4 H), 2.2 (s, 3 H); *m/e* 226. The product showed a single peak in GLC on a 10-ft methylsilicone column at 200 °C. DNP derivative mp 201–202 °C.

Anal. Calcd for $C_{17}H_{18}N_4O_8$: C, 50.24; H, 4.47; N, 13.79. Found: C, 49.03; H, 4.40; N, 13.93.

4,4-Dicarbomethoxy-2,6-heptanedione (11). A solution of 4.0 g (19 mmol) of dimethyl dipropargylmalonate (1) in 60 mL of acetonitrile and 15 mL of water and 15.6 g (58 mmol) of mercuric chloride was heated at reflux for 12 h. Concentration under vacuum, extraction of the aqueous mixture with ether, washing of the extract with aqueous sodium sulfide, concentration, and distillation gave 4.2 g (90% yield) of the diketone **11**: bp 130 °C (0.5 mm); mp 54–55 °C; IR ν_{max} 1740, 1720 cm^{-1}; NMR ($CDCl_3$) δ 3.8 (s, 6 H), 3.3 (s, 4 H), 2.2 (s, 3 H); *m/e* 244.

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.10; H, 6.56. Found: C, 54.31; H, 6.69.

5-Carbomethoxy-3-methyl-2-cyclohexenone (13). A. A solution of 2.6 g (11 mmol) of 4,4-dicarbomethoxy-2,6-heptanedione (11) and 0.58 g (11 mmol) of sodium methoxide in 50 mL of methanol was heated at reflux for 15 h. The reaction mixture was acidified with dilute aqueous HCl, concentrated, and partitioned between water and dichloromethane. Distillation of the organic extract at 110 °C (0.05 mm) gave 1.5 g (85% yield) of a single product: IR ν_{max} 1730, 1665, 1620 cm^{-1}; UV λ_{max} 245 nm; NMR ($CDCl_3$) δ 5.9 (s, 1 H), 3.7 (s, 3 H), 3.4–3.7 (m, 5 H), 2.0 (s, 3 H); *m/e* 168; and one peak in GLC at 16.5 min on a 10-ft methylsilicone column at 200 °. DNP derivative mp 126–127 °C (reported[5,6] 149–150 °C).

Anal. Calcd for $C_{15}H_{16}N_4O_6$: C, 51.87; H, 4.32; N, 16.14. Found: C, 51.79; H, 4.55; N, 16.04.

B. A solution of 3.0 g of methallylsuccinic anhydride (**14**) and 5.0 g of stannic chloride in 25 mL of dichloromethane was stirred at 0 °C for 1 h and at 20 °C for 20 h. Addition of water and dilute aqueous HCl, extraction with dichloromethane, and concentration gave a crude product which was dissolved in aqueous HCl, extraction with dichloromethane, and concentration gave a crude product which was dissolved in aqueous sodium bicarbonate, washed with ether, and recovered by acidification and extraction with dichloromethane, yielding 2.8 of gummy product. Recrystallization from ether–ligroin gave 1.4 g of the acid corresponding to ester **13** with mp 88–90 °C (reported[5,6] mp 92–94 °C). A solution of this compound in ether on reaction with diazomethane gave the ester **13**, identical in all spectroscopic properties with the product obtained above. The mixture melting point of corresponding DNP derivatives was not depressed.

Acknowledgment. This work was supported by the Cancer Institute of the National Institutes of Health, Research Grant PHS CA R01-12010.

Registry No.—**1**, 63104-44-9; **2**(Ar = *p*-tolyl), 63104-45-0; **2** (Ar = Ph), 63133-61-9; **3** (Ar = *p*-tolyl), 63104-46-1; **3** (Ar = Ph), 63104-47-2; **4** (Ar = *p*-tolyl), 63104-48-3; **5** (Ar = *p*-tolyl), 63104-49-4; **5** (Ar = Ph), 63104-50-7; **10**, 63104-51-8; **10** DNP, 63104-42-7; **11**, 63104-52-9; **13**, 63104-53-0; **13** DNP, 63104-43-8; **14**, 18908-20-8; mercuric chloride, 7487-94-7.

References and Notes

(1) M. E. Kuehne and R. B. Damon, *J. Org. Chem.*, **42**, 1825 (1977), and references cited therein.
(2) N. D. Brace, *J. Org. Chem.*, **32**, 2711 (1967).
(3) M. Julia and C. James, *C. R. Acad. Sci.*, **255**, 959 (1962).
(4) G. F. Hennion and R. H. Ode, *J. Org. Chem.*, **31**, 1975 (1966).
(5) D. D. Phillips and A. W. Johnson, *J. Am. Chem. Soc.*, **77**, 5977 (1955).
(6) A. W. Johnson, *J. Org. Chem.*, **21**, 587 (1956).
(7) G. Eglinton and A. R. Galbraith, *J. Chem. Soc.*, 889 (1959).

1,9,10-Anthyridines

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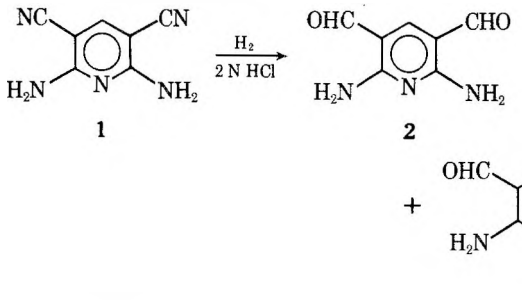
Received April 12, 1977

The Friedländer condensation of 2,6-diaminopyridine-3,5-dicarboxaldehyde and ketones was investigated as a possible synthetic route to substituted and fused 1,9,10-anthyridines. Condensation of this bis-o-amino aldehyde with acenaphthenone gave the fused, fully aromatic diacenaphtho[1,2-*b*:1′,2′-*i*]1,9,10-anthyridine in 65% yield. Condensations with deoxybenzoin, α-tetralone, and acetophenone, on the other hand, resulted in the formation of the 5,10-dihydro-1,9,10-anthyridine moiety, rather than the expected fully aromatic 1,9,10-anthyridine nucleus. It was demonstrated that base-catalyzed hydride transfer from the solvent on the anthyridine initially formed in the reaction medium resulted in the overall reduction of this heterocyclic system. Oxidation of the dihydroanthyridines with nitrobenzene or nitric acid gave the fully aromatic anthyridines in moderate yield. Prolonged oxidation of 2,8-diphenyl-5,10-dihydro-1,9,10-anthyridine with hot nitric acid gave mainly 2,8-diphenyl-5(10*H*)-1,9,10-anthyridone. Friedländer condensation of 2-amino-5,6-diphenylpyridine-3-carboxaldehyde and deoxybenzoin gave 2,3,6,7-tetraphenyl-1,8-naphthyridine in excellent yield.

The linear fusion of benzene rings leads to the well documented "acene" homologous series.[1] Very little information on the analogous series, containing the pyridine ring as building unit, is available. Contrary to the linear carbocyclic series, introduction of heteroatoms in such polycondensed systems gives rise to an increasing number of isomeric ring structures. The fusion of pyridine rings through their 2,3 bonds is of special interest because such condensed systems have been proposed for the structural unit of pyrolyzed poly(acrylonitrile).[2] In earlier work we have described a new and facile approach to the 1,8-naphthyridine heterocyclic system.[3] We now wish to report a new synthetic method for its next higher homolog, containing three linearly annelated pyridine rings: 1,9,10-anthyridine. Very few compounds containing this fundamental heterocyclic system have been reported.[4] The parent compound was only recently synthesized in a six-step sequence starting from 2,6-diaminopyridine.[5] Our familiarity with the synthetic opportunities present in the *o*-amino aldehyde functional group prompted us to approach the anthyridine skeleton via Friedländer condensation of appropriate *o*-amino aldehydes with ketones.

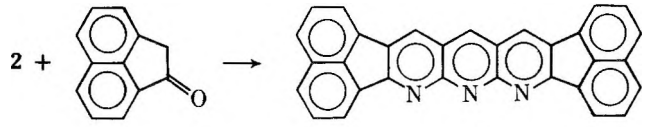
This synthetic strategy required either 2,6-diaminopyridine-3,5-dicarboxaldehyde **2** or 2-amino-1,8-naphthyridine-3-carboxaldehyde. Hydrogenolysis of *o*-aminonitriles seemed a most promising synthetic method for the elaboration of the *o*-amino aldehyde functional group. Hydrogenation of the readily available[6] 2,6-diamino-3,5-dicyanopyridine **1** suspended in 2 N HCl produced the desired bis-*o*-amino aldehyde

2 in moderate yield together with 2,6-diamino-3-methylpyridine-5-carboxaldhyde **3**. The latter apparently is the result of further reduction of **2**.



The poor solubility of 1 in 2 N HCl and the excellent solubility of **2** in the reaction medium prevented us from altering the course of the hydrogenation by limiting the hydrogen supply. It was found, however, that treatment of 1 in 2 N HCl with a small amount of copper eliminated this undesirable side reaction, resulting in the formation of **2** in 70% yield. The exact role of copper in this treatment is not well understood. It seems clear, however, that the presence of copper salts deactivate the hydrogenation catalyst. The hydrogenolysis of 2-amino-3-cyano-1,8-naphthyridine[7] under similar conditions did not result in the formation of the corresponding *o*-amino aldehyde. Examination of the reaction products indicated the absence of the fully aromatic 1,8-naphthyridine system and therefore this approach to the 1,9,10-anthyridine skeleton was not further investigated.

Base-catalyzed condensation of **2** with acenaphthenone in 1-propanol gave the fully condensed polycyclic diacenaphtho[1,2-*b*:1′,2′-*i*]1,9,10-anthyridine **4**, orange needles, mp >500 °C, in 65% yield. This fused system represents the first example of the incorporation of the anthyridine system into a polycyclic framework. The lower homolog of **4**, diacenaphtho[1,2-*b*: 1′,2′-*g*] 1,8-naphthyridine, was recently synthesized in this laboratory.[3]



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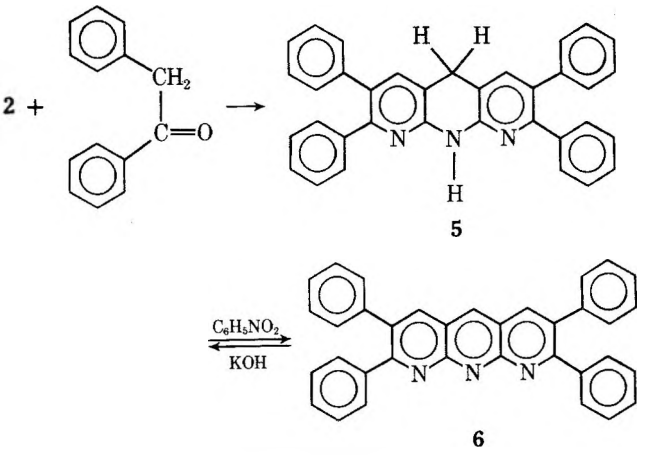
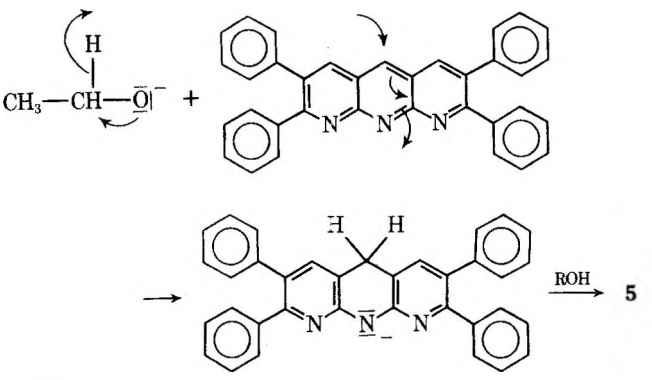
Condensation of **2** and deoxybenzoin, on the other hand, did not result in the formation of the fully aromatic anthyridine ring system, as evidenced by strong, sharp absorptions at 3410 and 1250 cm^{-1} in the infrared spectrum of the reaction product. This was confirmed by its mass spectrum which showed peaks at *m/e* 485 (15%), 486 (15%), 487 (100%) and 488 (40%). The presence of the NH functional group, the observed molecular ion and its principal fragmentation (loss of hydrogen) seemed to suggest a dihydroanthyridine structure for the reaction product **5** (see further). Analysis is in agreement with this formulation. NMR data could not be obtained due to the very poor solubility of **5**. Numerous attempts to alter the outcome of this condensation reaction by changing the solvent, the base employed, and its concentration (KOH in methanol, sodium ethoxide in ethanol) invariably resulted in the same reaction product. Therefore we focused our attention on the transformation of **5** into the desired fully aromatic anthyridine structure. It was found that brief treatment of **5** with boiling nitrobenzene resulted in the formation of 2,3,7,8-tetraphenyl-1,9,10-anthyridine **6** in 45% yield (based on 2), obtained as bright yellow needles (benzene).

Spectroscopic and analytical data are in agreement with the proposed structure. Comparison of the infrared spectra of **5** and **6** indicated the absence of absorptions at 3410 and 1250 cm^{-1}, characteristic of **5**, in the fully aromatic structure **6**.



Oxidation of **5** with nitric acid (30%) was equally successful and resulted in the formation of **6** in 80% yield. Reaction with chromic anhydride in acetic acid was ineffective, due to poor solubility of **5** in the reaction medium.

The formation of fully aromatic heterocyclic systems in condensation reactions of aromatic *o*-amino aldehydes and ketones is well documented and constitutes the basis for the synthetic utility of the Friedländer condensation.[9] The unusual formation of a reduced heterocyclic system (**5**) in such condensation reaction seemed to suggest that **5**, obtained from **2** and deoxybenzoin, could have resulted from further reaction of the fully aromatic tetraphenylanthyridine **6** initially formed in the basic reaction medium. Indeed, refluxing a solution of **6** in 1-propanol containing KOH gave a precipitate (90%), identical in all respects with **5**, obtained directly from **2** and deoxybenzoin. However, direct attack of the hydroxyl group cannot account for the formation of the reduced anthyridine moiety in **5**. Furthermore, it was found that reaction of **6** with potassium hydroxide in a 3:1 molar ratio resulted in the formation of **5** in nearly 90% yield. Addition of sodium ethoxide to **6** in ethanol resulted in the formation of **5**, identical with the product obtained from KOH. It is clear therefore that neither the base nor the solvent is incorporated into the formation of **5** from **6**. Apparently hydride transfer from the solvent takes place resulting in the reduction of the heterocyclic system. Hydride attack on the central ring will result in the formation of a stabilized amide anion, which is then protonated by the solvent, with regeneration of an alkoxide ion. The complete reduction of **6** is ensured by the very poor solubility of **5** since this will shift possible equilibria to the right. This base-catalyzed reduction of the anthyridine moiety proved to be a fast reaction. Addition of methanolic KOH to a 10^{-4} M solution of **6** in boiling 1-propanol resulted in the formation of a precipitate (**5**) within minutes after the addition. It is not surprising therefore that during the base-catalyzed condensation of **2** and deoxybenzoin no anthyridine could be isolated in the reaction mixture.

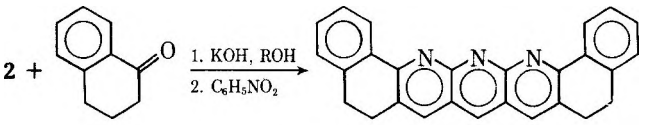


Reduction of **6** with a typical hydride donor such as sodium borohydride gave **5**, identical with the product obtained from

6 and potassium hydroxide, confirming the reduction of the anthyridine ring system in the presence of alcoholic potassium hydroxide. A similar base-catalyzed reduction of an electron deficient system was observed in the formation of 3,3′-dimethoxyazoxybenzene from *m*-nitroanisole in ethanol containing sodium ethoxide.[10] Although the position of hydride attack on the anthyridine ring system could not be ascertained due to the insolubility of 5 in NMR solvents, it seems reasonable that such attack would occur on the central pyridine ring. Such enhanced reactivity of the central ring is well documented for linearly fused carbocyclic ring systems.[1]

Although it is conceivable that 5 could arise from initial hydride attack on the pyridine ring of 2, this was not observed; 2 is stable in base under the reaction conditions employed for the synthesis of 6. Finally, it should be noted that 6 as well as 5 are stable in boiling 2 N HCl.

Condensation of 2 with α-tetralone followed by oxidation of the insoluble intermediate dihydro compound gave the fused anthyridine, 5,6,10,11-tetrahydrodinaphtho[1,2-*b*:2′,1′-*i*]1,9,10-anthyridine, 7, in 50% overall yield.



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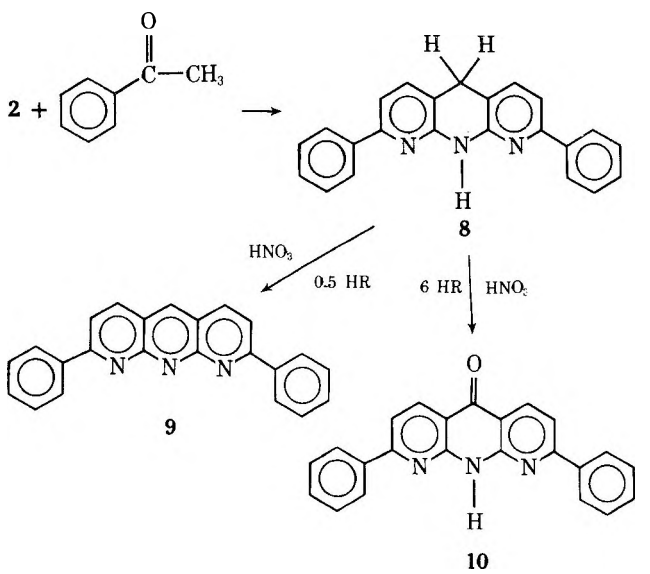
Friedländer condensation of 2 and acetophenone proceeded faster than the condensation with deoxybenzoin. Once again the major product was the dihydroanthyridine 8, as evidenced by its analysis, infrared, and mass spectrum. However, careful analysis of the reaction mixture revealed the presence of a small amount (~5%) of the fully aromatic 2,8-diphenyl-1,9,10-anthyridine 9. The dihydroanthyridine 8, obtained from benzene as a colorless compound, turned bright yellow on standing. Its mass spectrum revealed the appearance of a very intense peak at *m/e* 349, indicative of the presence of the anthyridone moiety (see below). Brief treatment of 8 with hot nitric acid (30%) gave the fully aromatic anthyridine 9 in 65% yield, together with a small amount of 2,8-diphenyl-5(10H)-1,9,10-anthyridone 10. Longer reaction times resulted in an increase of the anthyridone 10 at the expense of 9. Oxidation of 8 could also be carried out with boiling nitrobenzene as described earlier for the synthesis of tetraphenylanthyridine. No anthyridone 10 was detected under these reaction conditions.

As mentioned earlier, nitric acid oxidation of 5 gave only the fully aromatic tetraphenylanthyridine 6. The heterogeneous nature of this reaction effectively prevents overoxidation of 6 into the corresponding anthyridone. The conversion of 8 into 9 and 10, on the other hand, is a homogeneous process.



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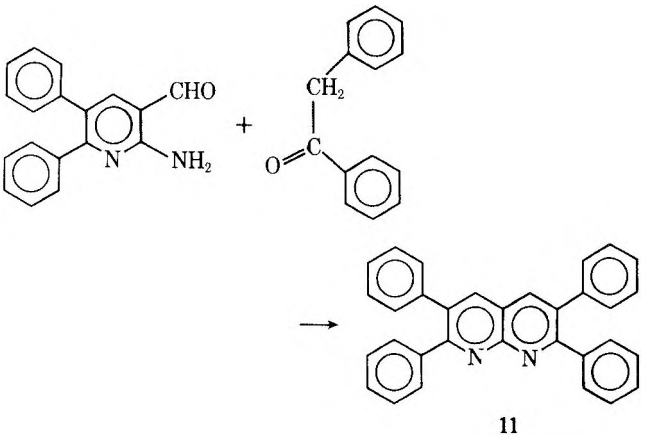
10

It is noteworthy that condensations of 2 with the reported ketones in the presence of small amounts of base typically employed in Friedländer reactions (~10 mol %) were not successful; the starting bis-o-amino aldehyde was recovered in nearly quantitative yield. The successful, *direct* synthesis of the fully aromatic, fused anthyridine 4 is possible due to its insolubility in the reaction medium, which greatly retards hydride transfer.

Finally, it should be noted that the formation of dihydro derivatives is not observed in the Friedländer condensations of *o*-amino aldehydes leading to the lower homologous 1,8-naphthyridine system, as exemplified by the high yield synthesis of 2,3,6,7-tetraphenyl-1,8-naphthyridine 11 from 2-amino-5,6-diphenylpyridine-3-carboxaldehyde[8] and deoxybenzoin.



11

Experimental Section

General. NMR spectra were recorded with a Varian A-60 and/or Varian XL-100 with FT spectrometer using TMS as an internal standard. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU6E instrument; infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer and UV spectra on a Cary-15 instrument. All melting points are uncorrected. Microanalyses were done by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Instranal Laboratory, Inc., Rensselaer, N.Y.

2,6-Diaminopyridine-3,5-dicarboxaldehyde 2. A suspension of 4.0 g (0.025 mol) of finely divided 2,6-diamino-3,5-dicyanopyridine[6] 1 in 800 mL of 2 N HCl was stirred with 0.4 g of thin copper wire for 3 h. The copper was removed and the resulting suspension was hydrogenated at 40 °C over Pd/C (5%). The latter was introduced in three successive additions (0.35 g each). Each portion was allowed to react until no more hydrogen was absorbed. Vigorous stirring or shaking was essential for a successful hydrogenolysis. After the theoretical amount of hydrogen was absorbed, the catalyst was filtered and the resulting solution was neutralized (NH_4OH) to yield a thick, white precipitate (3.5 g, 70%). Recrystallizations from dimethylformamide and water gave fibrous needles, mp 295 °C (dec). IR (Nujol): 3400, 3300, 3175, 2740, 1675, 1640, 1610, 1525, 1280, 1180, 1155, 1035, 925, 805, 775, and 735 cm^{-1}; NMR δ (DMSO-d_6) 9.61 (s, 2, CHO), 8.28 (s, 1, H-4), 8.06 (broad, 4, NH_2); mass spectrum M^+ at *m/e* 165.

Anal. Calcd for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.44. Found C, 50.79; H, 4.09; N, 25.37.

2,6-Diamino-3-methylpyridine-5-carboxaldehyde 3. The hydrogenation of 1 without prior treatment with copper gave a mixture of 2 and 3 in a 1:2 ratio (as evidenced by the NMR spectrum). Extraction of the crude reaction product with ethanol, followed by concentration of the resulting solution, gave 3 in 40% yield; mp 207 °C (from EtOH); IR (Nujol) 3400, 3080, 2700, 1665, 1590, 1515, 1280, 1220, 1135, 1040, 920, 850, 770, 735, and 725 cm^{-1}; NMR δ (DMSO-d_6) 9.36 (s, 1, CHO), 7.33 (s, 1, H-4), 7.25 (broad, 2, 6-NH_2), 6.63 (broad, 2, 2-NH_2), 2.00 (s, 3, CH_3); mass spectrum M^+ at *m/e* 151.

Anal. Calcd for $C_7H_9N_3O$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.49; H, 5.89; N, 27.72.

Diacenaphtho[1,2-*b*:1′,2′-*i*]1,9,10-anthyridine 4. To a refluxing

solution of 0.6 g (0.0036 mol) of **2** and 1.6 g (0.01 mol) of acenaphthenone in 50 mL of 1-propanol were added 10 drops of methanolic KOH (20%). Reflux was continued for 24 h. The precipitate was washed with chloroform to yield 1.0 g (65%) of **4**, recrystallized from acetic acid as yellow-orange needles, mp > 500 °C; IR (Nujol) 1635, 1585, 1540, 1430, 1325, 1205, 1190, 1085, 1025, 915, 825, 805, 780, 770, and 735 cm^{-1}; UV ($CHCl_3$) 344 (ε 87 000), 362 (117 400), 405 (22 600), 414 (21 900) and 430 (23 200) nm.

Anal. Calcd for $C_{31}H_{15}N_3$: C, 86.70; H, 3.52; N, 9.78. Found: C, 86.46; H, 3.68; N, 9.62.

2,3,7,8-Tetraphenyl-5,10-dihydro-1,9,10-anthyridine 5. (a) From Deoxybenzoin. To a refluxing solution of 0.99 g (0.006 mol) of **2** and 2.45 g (0.012 mol) of deoxybenzoin in 150 mL of 1-propanol was added 1 mL of methanolic KOH (25%). The mixture was refluxed for 3 days to yield 1.8 g of an orange-colored precipitate **5** (65%), recrystallized from a large volume of *o*-dichlorobenzene, mp > 300 °C (dec). IR (Nujol) 3410, 1590, 1580, 1495, 1435, 1400, 1360, 1300, 1290, 1250, 1190, 1170, 1150, 1070, 1020, 955, 940, 910, 895, 815, 790, 775, 755, 750, 745, 715, 705, and 690 cm^{-1}. Mass spectrum M^+ at *m/e* 487 (100%).

Anal. Calcd for $C_{35}H_{25}N_3$: C, 86.21; H, 5.17; N, 8.62. Found: C, 86.27; H, 4.97; N, 8.72.

(b) From KOH and 6. To a refluxing suspension of 0.5 g of **6** in 100 mL of 1-propanol was added 0.13 mL of methanolic KOH (10%). Reflux was continued for 8 h to yield 0.35 g of **5**, identical in all respects with product obtained above.

2,3,7,8-Tetraphenyl-1,9,10-anthyridine 6. (a) Nitrobenzene. A mixture of 1.6 g of **5** and 30 mL of nitrobenzene was heated until a clear solution resulted. The solution was then refluxed for 30 min. The cooled solution was filtered and set aside for 2 h and filtered again, if necessary. The product was precipitated with petroleum ether and recrystallized from benzene to yield 1.15 g (77%) of **6**, bright yellow crystals, mp 322–323 °C. An analytical sample was prepared by column chromatography (alumina and $CHCl_3$). IR (Nujol) 1605, 1590, 1570, 1510, 1400, 1310, 1300, 1190, 1175, 1145, 1070, 1050, 1015, 995, 950, 930, 915, 810, 780, 765, 750, 730, 715, 700, and 690 cm^{-1}; NMR δ (DMSO-d_6) 9.43 (s, 1, H-5), 8.76 (s, 2, H-4 and H-6), 7.41 (s, 20, phenyl protons). Mass spectrum M^+ at *m/e* 485.

Anal. Calcd for $C_{35}H_{23}N_3$: C, 86.57; H, 4.77; N, 8.65. Found: C, 86.61; H, 4.79; N, 8.60.

(b) Nitric Acid. A suspension of 0.5 g of **5** in 60 mL of nitric acid (30%) was stirred at room temperature for 5 h. The mixture was then heated at 80 °C for 30 min, cooled, and filtered. The precipitate was washed with dilute ammonium hydroxide to yield 0.42 g of **6**, identical with product obtained from nitrobenzene.

5,6,10,11-Tetrahydrodinaphtho[1,2-*b*:2′,1′-*i*]1,9,10-anthyridine 7. To a refluxing solution of 0.5 g (0.003 mol) of **2** and 1.0 g (0.007 mol) of α-tetralone in 75 mL of 1 propanol was added 0.6 mL of methanolic KOH (25%). The mixture was refluxed for 40 h, and the precipitate was collected and washed with acetone to yield 0.82 g (69%) of a product similar to that observed from **2** and deoxybenzoin (IR absorptions at 3400 and 1250 cm^{-1}). The product was refluxed in 10 mL of nitrobenzene for 40 min and was precipitated with petroleum ether. Recrystallization from chloroform gave 0.5 g (70%) of **7**, mp 303 °C. An analytical sample was obtained by column chromatography (alumina, chloroform). IR (Nujol) 1630, 1590, 1520, 1490, 1425, 1390, 1300, 1275, 1250, 1220, 1165, 1140, 1100, 1020, 970, 940, 915, 870, 810, 800, 785, 740, 730, and 690 cm^{-1}.

Anal. Calcd for $C_{27}H_{19}N_3$: C, 84.13; H, 4.97; N, 10.90. Found: C, 84.16; H, 4.98; N, 10.86.

2,8-Diphenyl-5,10-dihydro-1,9,10-anthyridine 8. To a refluxing solution of 0.5 g (0.003 mol) of **2** and 0.84 g (0.007 mol) of acetophenone in 75 mL of 1-propanol was added 1 mL of methanolic KOH (20%). The mixture was refluxed for 3 h. The precipitate was collected and recrystallized immediately from a large volume of boiling benzene (600 mL) to yield 0.450 g (45%) of **8**, white product, mp >270 °C (decomposition). IR (Nujol) 3350, 1590, 1570, 1425, 1260, 835, 810, 760, 750, and 690 cm^{-1}. Mass spectrum M^+ at *m/e* 335.

Anal. Calcd for $C_{23}H_{17}N_3$: C, 82.36; H, 5.11; N, 12.53. Found: C, 82.39; H, 5.01; N, 12.60.

The filtrate was concentrated on the rotary evaporator to approximately 50 mL and set aside to crystallize. The precipitate was filtered and was recrystallized from benzene to give 0.04 g of **9**, identified by its infrared spectrum (see below).

2,8-Diphenyl-1,9,10-anthyridine 9. A mixture of 0.4 g of **8** in 80 mL of nitric acid (30%) was stirred at room temperature for 20 min. The mixture was heated slowly to 80 °C and was kept at this temperature for 30 min. The resulting solution was cooled rapidly, and the crystalline material was filtered and washed extensively with dilute NH_4OH and water. Recrystallization from ethanol yielded 0.25 g (60%) of **9**, pale yellow needles, mp 300–302 °C. IR (Nujol) 1620, 1590, 1575, 1520, 1430, 1315, 1300, 1275, 1230, 1155, 940, 830, 820, 790, 770, 760, 745, and 700 cm^{-1}; NMR δ ($CDCl_3$) 8.75 (s, 1, H-5), 8.48 (m, 4, ortho protons on phenyl rings), 8.40 (d, 2, H-4 and H-6, J_{H3-H4} = 8 Hz), 8.04 (d, 2, H-3 and H-7), 7.61 (m, 6, remaining phenyl protons). Mass spectrum M^+ at *m/e* 333.

Anal. Calcd for $C_{23}H_{15}N_3$: C, 82.86; H, 4.54; N, 12.60. Found: C, 82.94; H, 4.50; N, 12.55.

2,8-Diphenyl-5(10*H*)-1,9,10-anthyridone 10. A mixture of 0.4 g of **8** in 80 mL of nitric acid (30%) was heated at 80 °C for 6 h. The solution was cooled; the crystalline material was filtered, and was washed with dilute NH_4OH and water. Chromatography (alumina, $CHCl_3$) followed by recrystallization from ethanol gave 0.225 g of **10**, mp 279–280 °C. An analytical sample was prepared by sublimation at 165 °C and 1 mmHg. IR (Nujol) 3155, 1610, 1585, 1420, 1265, 1235, 810, 790, 760, and 695 cm^{-1}; NMR δ ($CDCl_3$) 9.36 (broad singlet, 1, H-10), 8.79 (d, 2, H-4 and H-6, J_{H3-H4} = 8 Hz), 8.17 (m, 4, ortho protons on phenyl rings), 7.76 (d, 2, H-3 and H-7), 7.56 (m, 6, remaining phenyl protons). Mass spectrum M^+ at *m/e* 349.

Anal. Calcd for $C_{23}H_{15}N_3O$: C, 79.07; H, 4.33; N, 12.03. Found: C, 79.11; H, 4.35; N, 11.97.

2,3,6,7-Tetraphenyl-1,8-naphthyridine 11. To a refluxing solution of 0.55 g (0.002 mol) of 2-amino-5,6-diphenylpyridine-3-carboxaldehyde[8] and 0.395 g (0.002 mol) of deoxybenzoin in 5 mL of ethanol were added two drops of methanolic KOH (20%). Reflux was continued for 36 h to yield 0.79 g (90%) of **11**, recrystallized from chloroform, mp 301–302 °C; IR (Nujol) 1590, 1570, 1515, 1390, 1250, 1170, 1070, 1045, 1010, 945, 930, 910, 810, 770, 735, 710, 700, and 685 cm^{-1}; NMR δ ($CDCl_3$) 8.20 (s, 2, H-4 and H-5), 7.58 (m, 4, ortho protons on phenyl rings 2 and 7), 7.31 (s, 16, remaining phenyl protons). Mass spectrum M^+ at *m/e* 434.

Anal. Calcd for $C_{32}H_{22}N_2$: C, 88.45; H, 5.10; N, 6.44. Found: C, 88.32; H, 5.05; N, 6.36.

Acknowledgment. This work was supported in part by the U.S. Army Research Office, Durham, N.C. We wish to thank David R. Rogemoser for his expert assistance.

Registry No.—**1**, 63196-29-2; **2**, 36986-81-9; **3**, 63196-30-5; **4**, 63196-31-6; **5**, 63196-32-7; **6**, 63196-33-8; **7**, 63196-34-9; **8**, 63196-35-0; **9**, 63196-36-1; **10**, 63196-37-2; **11**, 63196-38-3; acenaphthenone, 2235-15-6; deoxybenzoin, 451-40-1; α-tetralone, 529-34-0; acetophenone, 98-86-2; 2-amino-5,6-diphenylpyridine-3-carboxaldehyde, 54595-59-4.

References and Notes

(1) E. Clar, "Polycyclic Hydrocarbons", Vol. I, Academic Press, New York, N.Y., 1964.
(2) C. G. Overberger and J. A. Moore, *Adv. Polym. Sci.*, **7**, 125–127 (1970), and references cited therein.
(3) P. Caluwe and T. G. Majewicz, *J. Org. Chem.*, **40**, 2566 (1975).
(4) S. Carboni, A. Da Settimo, D. Bertini, P. L. Ferracini, O. Livi, and I. Tonetti, *J. Heterocycl. Chem.*, **9**, 801 (1972), and references cited therein.
(5) S. Carboni, A. Da Settimo, and I. Tonetti, *J. Heterocycl. Chem.*, **7**, 875 (1970).
(6) E. L. Little, Jr., W. J. Middleton, D. D. Coffman, V. A. Engelhardt, and G. N. Sausen, *J. Am. Chem. Soc.*, **80**, 2836 (1958).
(7) E. M. Hawes and D. G. Wibberley, *J. Chem. Soc., C*, 1564 (1967).
(8) G. Evens and P. Caluwe, *J. Org. Chem.*, **40**, 1438 (1975).
(9) L. A. Paquette, "Principles of Modern Heterocyclic Chemistry", W. A. Benjamin, New York, N.Y., 1968, p 277.
(10) Th. Rotarski, *Ber.*, **41**, 865 (1908).

Reactions of Phenoxides with Nitro- and Halo-Substituted Phthalimides

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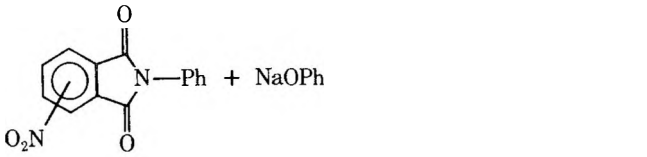
Received November 29, 1976

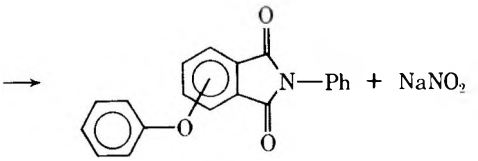
Phenoxides reacted with nitro- or halo-substituted phthalimide derivatives (1) to give high yields of ether imides (2). The order of leaving group reactivity in these systems was $NO_2 > F > Cl$. 3-Substituted isomers were more reactive toward displacement than the 4-substituted isomers and electron-withdrawing groups on the imide nitrogen slightly increased the rate of displacement. The phenoxy-substituted phthalimides 2 were labile to displacement by other phenoxide nucleophiles. Nitrite ion, a product of the nitro displacement, also reacted with the starting nitrophthalimides, especially at elevated temperatures.

The aromatic nucleophilic displacement of activated nitro groups has been known for many years,[1] but has only recently become a valuable synthetic tool. This reaction has permitted synthesis of many previously inaccessible compounds. Gorvin[2] and Radlmann[3] have demonstrated the displacement of nitro groups activated by ketone groups. Caswell and co-workers[4] have reported displacement by methoxide anion on 3-nitro-*N*-substituted phthalimide derivatives, although yields were low. Aromatic nitro groups are displaced intramolecularly by nitrogen, oxygen, sulfur, and carbon nucleophiles.[5] Beck[6] has displaced nitro groups activated by nitriles, esters, and aldehyde groups. Cyano-activated nitrobenzenes have been converted to phenols.[7] Very recently Kornblum[8] has reported the displacement reactions of nitrobenzenes substituted by a variety of electron-withdrawing groups.

We wish to present our results on the reaction of phenoxide nucleophiles with nitro- and halo-substituted phthalimide derivatives. Wirth and Heath[9] in these laboratories demonstrated that in dipolar aprotic solvents phenoxides react with both 3- and 4-nitro-*N*-phenylphthalimide (**1e** and **1h**) to give the corresponding phenyl ethers **2a** and **2f** in excellent yield.



1e, h

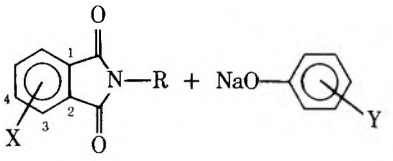


2a, f

The potential synthetic utility of this reaction has been explored to learn the following: (1) the effectiveness of the phthalimide ring to activate nitro or halo displacement; (2) the ease of halo vs. nitro displacement in this system; (3) the relative reactivity of different phenolate nucleophiles; (4) the susceptibility of the product ether to further reaction; and (5) the stability of the starting imide and product to the sodium nitrite produced by displacement of the nitro group.

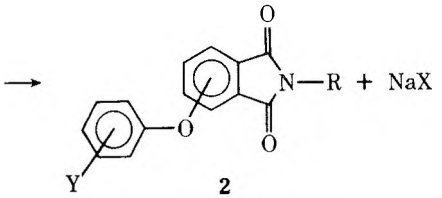
Results and Discussion

The model reaction is shown below. We examined various compounds of formula 1 to obtain information concerning the effect of group R and the orientation of group X. The starting phthalimides were synthesized from the substituted phthalic anhydride and appropriate amine by refluxing in acetic acid.



1

R = alkyl, aryl
X = nitro, halo



2

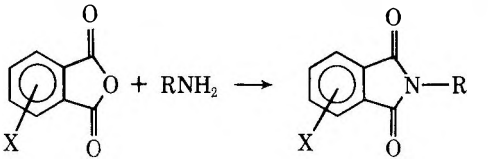
These are described in Table I; ^{13}C NMR data for all starting materials and products are given in the supplementary material. In addition, 4-nitrophthalonitrile (**3**) and diisobutyl 4-nitrophthalate (**4**) were synthesized for comparison. Each was then converted to the corresponding phenyl ether with sodium phenoxide. The products (**2a–g**) are summarized in Table II.

In general, the reactions between sodium phenoxide and the substituted phthalimides 1 proceed quantitatively[10] in DMF or Me_2SO at 25–60 °C. Reaction times varied from <5 min to several hours. The 3- and 4-chloro-*N*-phenylphthalimides (**1a** and **1j**) gave the ethers **2a** and **2f** as the major products (85 and 87% yield, respectively), accompanied by at least two unknown side products, which may arise from attack of phenoxide at the imide carbonyls. Attempts to identify these products are currently under way.

The relative reactivities of the halo–nitro pairs toward sodium phenoxide were determined by competitive experiments in dimethyl sulfoxide. These results are presented in Table III.

Several conclusions can be drawn concerning sodium phenoxide displacement on *these systems*. As Miller pointed out,[11] the order of group mobility in activated aromatic S_N2 reactions depends markedly on the nucleophilic reagent used. When the nucleophilic (or bond-forming) atom belongs to the first horizontal row of the periodic table, the normal mobility order is F > Cl. The nitro group may be either a better or a worse leaving group than the fluorine atom, depending upon the system employed.[12] In the phthalimides, the nitro group is displaced by phenoxide about six to nine times faster than fluorine, depending upon the isomer (3 or 4) and the N substituent. The fluoro derivative reacted approximately four times faster than the chloro derivative in the 4-halo-*N*-methylphthalimide system. Although substitution at nitrogen has little effect on the rate of 3-nitro displacement (there is only a factor of 4 between **1f** and **1g**), the more electron

Table I. Starting Imides Synthesized from Phthalic Anhydride Derivatives[a]

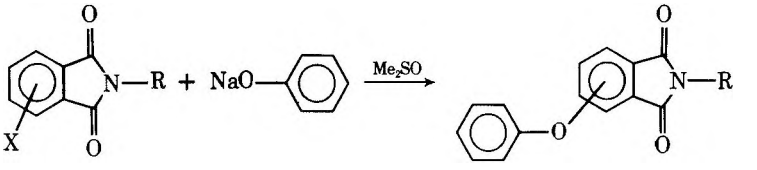


1

Registry no.	Compd	X	R	Mp,[b] °C	Mp, lit	m/e[c]
42899-83-2	**1a**	3-Cl	C_6H_5	191–192.5	189–190[e]	257 (100)[d]
42899-84-3	**1b**	3-F	C_6H_5	148–150	151–152[f]	241 (100)
63197-15-9	**1c**	3-NO_2	4-$CH_3OC_6H_4$	193.5–195[a]		298 (100)
53555-10-5	**1d**	3-NO_2	4-$CH_3C_6H_4$	151–152.5	154[g]	282 (100)
19065-85-1	**1e**	3-NO_2	C_6H_5	137–138	138[g]	268 (100)
53555-03-6	**1f**	3-NO_2	4-ClC_6H_4	193.5–195.5[a]		302 (70)[d]
2593-81-9	**1g**	3-NO_2	CH_3	111–112	112–113[h]	206 (30)
40392-27-6	**1h**	4-NO_2	C_6H_5	192.5–194	194[g]	268 (100)
63197-16-0	**1i**	4-F	C_6H_5	183–184[a]		241 (100)
26491-49-6	**1j**	4-Cl	C_6H_5	189.5–191[a]		257 (100)[d]
41663-84-7	**1k**	4-NO_2	CH_3	175–177	175–176[h]	206 (100)
63196-44-1	**1l**	4-F	CH_3	99–100	99–100[i]	179 (100)
63197-17-1	**1m**	4-Cl	CH_3	134–135.5	135[h]	366 (100)

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the table. [b] All samples were recrystallized from ethanol. [c] Value for molecular ion and its relative intensity. [d] One chlorine isotope cluster was observed. [e] G. J. Marriot and R. Robinson, *J. Chem. Soc.*, 134 (1939). [f] R. G. Fowler, L. R. Caswell, and L. I. Sue, *J. Heterocycl. Chem.*, **10**, 407 (1973). [g] M. T. Bogert and L. Boroschek, *J. Am. Chem. Soc.*, **23**, 740 (1901). [h] R. Dabard and J. Tirouflet, *Bull. Soc. Chim. Fr.*, 565 (1957). See also W. Flitsch, *Chem. Ber.*, **94**, 2494 (1961). [i] See ref 19.

Table II. Phenoxy-Substituted Phthalimides[a]



2

Registry no.	Compd	R	Group displaced (X)	Mp,[b] °C	m/e[c]
63197-18-2	**2a**	C_6H_5	3-NO_2, 3-Cl, 3-F	135–137	315 (91)
63197-19-3	**2b**	4-$CH_3OC_6H_4$	3-NO_2	178.5–179.5	345 (100)
63197-20-6	**2c**	4-$CH_3C_6H_4$	3-NO_2	174–176	329 (100)
63197-21-7	**2d**	4-ClC_6H_4	3-NO_2	172–174	349 (100)[d]
63197-22-8	**2e**	CH_3	3-NO_2	145–147.5	253 (100)
63197-23-9	**2f**	C_6H_5	4-NO_2, 4-Cl, 4-F	165–166	315 (100)
63197-24-0	**2g**	CH_3	4-NO_2, 4-Cl, 4-F	118–119.5	253 (100)

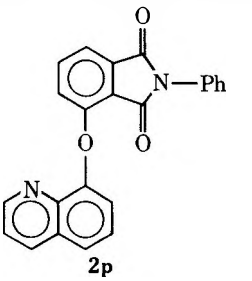
[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all the compounds listed in the table. [b] All samples were recrystallized from ethanol. [c] Value for molecular ion and its relative intensity. [d] One chlorine isotope cluster was observed.

withdrawing the group attached to the phthalimide nitrogen, the faster is the rate of nitro displacement. Compare **1c** (4′-methoxy) and **1f** (4′-chloro), where the ratio is only 2.[13]

3-Nitrophthalimides react three to five times faster than the 4-nitro isomers; for example, compare **1e** and **1h**, **1g** and **1k**. These small rate differences may reflect the inductive effect of the ortho carbonyl in the 3 isomer, as well as relief of the steric interaction between the 3-nitro group and the ortho carbonyl.[14] The rate ratio drops to 3.2 for the fluoro-substituted *N*-phenyl derivatives, possibly because of a decrease in this steric interaction in the 3 isomer. These rate differences are valid only for this particular solvent (Me_2SO) or possibly the family of dipolar aprotic solvents. In a less polar solvents such as THF, the rate ratio between the 3- and 4-nitro isomers in both the *N*-phenyl and *N*-methyl system was >100. All of these compounds were completely soluble in THF and solubility differences cannot be affecting the relative rates. Thus the dipolar aprotic solvent levels the rate differences between the 3 and 4 isomers found in THF.[15]

Ester carbonyls do not activate nitro-group displacement nearly as well as do the imide carbonyls (**4** vs. **1h**). Cyano groups are much more potent than carbonyls (**1h** vs. **3**). This is also reflected in the ease with which high molecular weight polymer is formed in the reaction of 2,4-or 2,6-dinitrobenzonitrile with bisphenols.[16]

Reactions with Other Phenoxide Derivatives. Various substituted phenoxides reacted cleanly with **1e** to give the ether imides in Table IV. Even 8-hydroxyquinoline gave **2p**



2p

Table III. Relative Reactivity of 1 toward Sodium Phenoxide in Dimethyl Sulfoxide at 25 °C[a]

Compd	X	R	Relative rate (1m ≡ 1)
1m	4-Cl	CH_3	1
1j	4-Cl	C_6H_5	*b*
1a	3-Cl	C_6H_5	*b*
1l	4-F	CH_3	4
1i	4-F	C_6H_5	20
1k	4-NO_2	CH_3	37
1b	3-F	C_6H_5	65
1h	4-NO_2	C_6H_5	130
1g	3-NO_2	CH_3	170
1c	3-NO_2	4-$CH_3OC_6H_4$	340
1d	3-NO_2	4-$CH_3C_6H_4$	430
1e	3-NO_2	C_6H_5	520
1f	3-NO_2	4-ClC_6H_4	670

[a] In this series diisobutyl 4-nitrophthalate (4) has a relative rate of <0.5 and 4-nitrophthalonitrile (3) has a relative rate of ~7500. [b] An accurate value could not be obtained for this compound because of side reactions. However, we believe its order in the series is correct.

in 82% yield. This reaction thus offers the opportunity to assemble a wide variety of functionalized systems which contain an ether linkage. The ^{13}C NMR chemical shifts for these compounds are tabulated (see supplementary material).

Relative reactivities of substituted phenoxides were determined in competitive experiments in anhydrous dimethylformamide at room temperature (Table V). Electron-releasing substituents increase the rates, but sodium *p*-nitrophenoxide was unreactive. Sodium thiophenoxide reacted over 100 times faster than sodium phenoxide.[17]

Ether Exchange Reactions. An activated ether group may also be displaced.[18] We found the ether imides (**2**) to be susceptible to exchange with other phenoxides to give an equilibrium mixture of ether imides. The position of the equilibrium was related to the nucleophilicities of the phenoxides involved. The enhanced reactivity of sulfur was demonstrated by the fact that the equilibrium lay almost completely toward the 3-(4-methylthiophenoxy)-*N*-phenylphthalimide (**6**). 3-Phenoxyphthalimides react more rapidly than the 4 isomers. Reactions involving the 3 isomers were essentially complete within 1 h at 120 °C in anhydrous dimethylformamide. The rate of phenoxy displacement is slower than chloro displacement. Results of these exchange studies are presented in Table VI.

Reaction with Sodium Nitrite. The reaction of a sodium phenoxide derivative with a nitro-substituted imide produces an equivalent amount of sodium nitrite in addition to an ether imide. The stability of the imide ring in the presence of sodium nitrite was uncertain, so the reactions between the nitro imide or ether imide and sodium nitrite were studied. At 60 °C, 3-nitro-*N*-phenylphthalimide was stable to anhydrous sodium nitrite in dimethylformamide for 2–3 h, although the color changed from light yellow to dark red. A precipitate formed after this time. At 135 °C, darkening and precipitation occurred much faster. The precipitate, identified as disodium 3-nitrophthalate, probably arose from a ring-opening reaction of the nitroimide. The product 3-phenoxy-*N*-phenylphthalimide is stable to sodium nitrite in DMF at 60 °C for 48 h. This imide should be much more stable to ring-opening reactions because of the electron-donating group in the 3 position rather than the electron-withdrawing nitro group. An electron-withdrawing group should activate one imide carbonyl for attack by a nucleophile. We conclude that these displacements by phenoxide should be conducted at as low a temperature and as briefly as possible to minimize the side reactions with nitrite ion.[19]

In summary, the reaction of phenoxides with halo or nitro *N*-substituted phthalimides is an excellent synthetic route to a wide variety of phenoxyphthalimides. In many cases, reaction in dipolar aprotic solvents at room temperature gave quantitative yields of products in <5 min. In Me_2SO or DMF, the relative reactivity of the leaving group was $NO_2 > F > Cl$ and the 3-substituted isomers were more reactive than the corresponding 4 isomers. Substitution of electron-withdrawing groups on the imide nitrogen increased the rate of reaction slightly, as did the use of electron-rich phenoxide derivatives. The phenoxy group of the product was also susceptible to displacement by other phenoxides. At 120 °C ether exchange occurred readily to give equilibrium mixtures of phenoxyphthalimides. Since the nitrite produced in the displacement reaction was also reactive at elevated temperatures, particularly toward the starting nitro imide derivatives, nitro displacements should be performed under mild conditions.

Further studies of the displacement of nitro and halo groups in derivatives of phthalic acid will be presented in subsequent papers.

Table IV. Properties of Phenoxyphthalimides[a] from 1e

Registry no.	Compd	Y	% yield[b]	Mp,[c] °C	*m/e*[d]
63197-25-1	**2h**	*p*-NO_2	72[g]	212–215 (chlorobenzene)	360 (25)
63197-26-2	**2i**	*p*-Cl	98	169–170.5	349 (100)[e]
63181-79-3	**2j**	*p*-CH_3	97	162–163	329 (100)
63197-27-3	**2k**	*p*-OCH_3	94	155.5–157	345 (100)
63197-28-4	**2l**	*m*-CN	98	167.5–168.5	340 (100)
63197-29-5	**2m**	*p*-C(=O)CH_3	94	157.0–158.5	357 (13)
63197-30-8	**2n**	*m*-CO_2H	95	221.5–222.5	359 (100)
63197-31-9	**2o**	*m*-NH_2	85	*f*	330 (100)

[a] Satisfactory analytical data (± 0.4% for C, H, N) or an exact mass determination (for **2m** and **2o**) were reported for all new compounds listed in the table. [b] Phenoxide salts for **2h–2k** were prepared from NaOMe; phenoxide salts for **2l–2o** were prepared from NaOH. See Experimental Section for details. [c] All samples were recrystallized from ethanol unless indicated. [d] Value for molecular ion and its relative intensity. [e] One chlorine isotope cluster was observed. [f] A sharp melting point could not be obtained for this compound. [g] Two unidentified side products were also formed in this reaction.

Table V. Reactivity of 4-Y-C_6H_4ZNa with 3-Nitro-*N*-phenylphthalimide (1e) in Dimethylformamide at Room Temperature

Registry no.	Y	Z	Relative rate (NaOPh ≡ 1)
824-78-2	NO_2	O	<0.01
1193-00-6	Cl	O	0.4
139-02-6	H	O	1
1121-70-6	CH_3	O	3.5
1122-95-8	OCH_3	O	7.7
10486-08-5	CH_3	S	>350[a]

[a] Under these conditions (DMF, 25 °C, 0.5 h) no ether exchange took place even between 3-phenoxy-*N*-phenylphthalimide (**2a**) and sodium *p*-methylthiophenoxide.

Table VI. Ether Exchange Reactions

$$\mathbf{2a} + 4\text{-}XC_6H_4ONa \overset{DMF}{\rightleftarrows} \mathbf{2h\text{-}k} + C_6H_5ONa$$

X	Starting material	Temp, °C	Time, h	% **2a**	% **2h–k**
CH_3	**2a**	60	26	44	56
			165	32	68
	2a	120	1	30	70
	2j	60	17	21	79
			140	36	64
	2j	120	1	35	65
OCH_3	**2a**	120	1	23	77
			3	21	79
			16	19	81
	2k	120	1	24	76
			3	21	79
			16	20	80
Cl	**2a**	120	1	85	15
			2.5	84	16
			16	95	5
	2i	120	1	92	8
			2.5	90	10
			16	96	4
NO_2	**2a**	120	1	100	0
			2	100	0
	2h	120	1	100[a]	0

$$\mathbf{2j} + 4\text{-}CH_3C_6H_4SNa \overset{DMF}{\rightleftarrows} \mathbf{6} + 4\text{-}CH_3C_6H_4ONa$$

Starting material	Temp, °C	Time, h	% **2j**	% **6**
2j	120	1	3	97
		2	3	97
6	120	1	4	96
		2	4	96
		16	4	96

$$\mathbf{2f} + 4\text{-}CH_3\text{-}C_6H_4ONa \overset{DMF}{\rightleftarrows} \mathbf{2q} + C_6H_5ONa$$

Starting material	Temp, °C	Time, h	% **2f**	% **2q**
2q	60	17	7	93
		43	13	87
		67	17	83
		140	26	74
2f	120	1	63	37
		2.25	39	61
		3.75	37	63
		20.5	39	61
2q	120	1	30	70
		2	32	68
		16	34	66

[a] Other side products formed, no **2h** is present.

Experimental Section

Infrared spectra were taken on a Perkin-Elmer 457 grating infrared spectrophotometer in chloroform solution or as a KBr pellet. Mass spectra were determined on a CEC 21-104 analytical mass spectrometer at 70 eV. Vapor-phase chromatography (VPC) was carried out on a Hewlett Packard 5750 research chromatograph using a 6 ft 10% UCW-98 on 80/100 Chromosorb W column with temperature programming from 200 to 300 °C at 10°/min. Melting points were determined on a Thomas-Hoover instrument and are uncorrected. C, H, N analyses were determined on a Perkin-Elmer 240 C, H, N analyzer.

Anhydrous DMF and Me_2SO were purchased from Burdick and Jackson Laboratories. Toluene and glacial acetic acid were reagent-grade chemicals and were used as purchased. The aniline was distilled before use. The phenol derivatives were used as purchased.

Preparation of Nitro- and Halophthalic Anhydrides. 3- and 4-Nitrophthalic Anhydride. Pure samples of these compounds were prepared by distillation of the reaction mixture obtained from the nitration of phthalic anhydride. We wish to thank N. C. Cook and J. M. Gasaway for a generous supply of these materials.

3-Chlorophthalic anhydride was prepared from 3-nitrophthalic anhydride and chlorine as described by Newman and Scheurer.[20]

4-Chlorophthalic anhydride was prepared from 4-nitrophthalic anhydride and chlorine by the preceding method.

3-Fluorophthalic anhydride was prepared by a toluene/acetic anhydride ring closing of the corresponding diacid, which was purchased from Columbia Chemical Co.

4-Fluorophthalic anhydride was prepared from potassium fluoride and 4-nitrophthalic anhydride.[21] We thank R. L. Markezich for a generous supply of this material.

4-Nitrophthalonitrile (3) was prepared (mp 140.5–142 °C) using the procedure of Drew and Kelly.[22]

4-Nitrodiisobutyl phthalate (4) was synthesized from 4-nitrophthalic anhydride and isobutyl alcohol in refluxing xylene with a trace of *p*-toluenesulfonic acid. The distilled yield was 82%.[23]

Preparation of Nitro- or Halo-Substituted Phthalimide Derivatives 1a–m. Compounds **1a–m**, prepared by refluxing the appropriate phthalic anhydride derivative and desired amine in glacial acetic acid under nitrogen, are described in Table I. The ^{13}C NMR data for these compounds are contained in Table VII (see supplementary material). All compounds had ^1H and infrared spectra consistent with their assigned structures. Detailed experimental conditions are given below for the synthesis of two of these compounds.

3-Chloro-*N*-phenylphthalimide (1a). A mixture of 20.0 g (0.109 mol) of 3-chlorophthalic anhydride and 250 mL of glacial acetic acid was stirred under a nitrogen atmosphere at room temperature. To this stirred mixture was added 10.38 g (0.112 mol) of aniline, and the resulting mixture was slowly heated to reflux. Initially a thick white precipitate formed, but upon heating a homogeneous solution was obtained. The solution was heated at reflux for 3 h and then cooled to room temperature. The white crystals were collected and dried; 26.4 g (94% yield). Recrystallization from absolute ethanol gave mp 191–192.5 °C.

4-Chloro-*N*-methylphthalimide (1m). Methylamine, 0.56 g (0.018 mol), was added to a mixture of 3.00 g (0.016 mol) of 4-chlorophthalic anhydride and 5.0 mL of glacial acetic acid at 0 °C. The mixture was heated at reflux for 2–3 h under nitrogen, then cooled to room temperature and filtered to give 2.85 g (89%), mp 134–135.5 °C (ethanol).

Preparation of Phenoxides. The various sodium phenoxides were prepared from sodium hydroxide or freshly prepared sodium methoxide in methanol and the phenol. The resulting salts were thoroughly dried, stored, and handled under dry nitrogen.

Sodium *p*-Methylphenoxide. Sodium Methoxide Method. Sodium metal, 10.65 g (0.463 mol), was dissolved in 600 mL of anhydrous methanol under nitrogen in an ice bath. Then 50.11 g (0.463 mol) of *p*-methylphenol was added and the clear solution was stirred for 1 h at room temperature. The methanol was removed under reduced pressure. The resulting white powder was dried (0.2 Torr/80 °C) to give 54.1 g (98%).

Sodium *m*-Cyanophenoxide. Sodium Hydroxide Method. A mixture of 1.19 g (0.010 mol) of *m*-hydroxybenzonitrile, 0.80 g of 50% aqueous sodium hydroxide, 23 mL of Me_2SO, and 23 mL of toluene was heated at reflux under nitrogen until no visible traces of water could be seen in the Dean–Stark trap. This trap was then replaced with a recirculating trap (essentially a Dean–Stark trap in which the collected distillate is returned to the pot through a tube in the bottom of the trap) packed with calcium hydride, and the condensed distillate was passed through this trap until no bubbling took place in it. The

toluene was distilled from the system. The mixture was cooled to room temperature and the 3-nitro-*N*-phenylphthalimide was added under nitrogen.

Preparation of Phenoxyphthalimide Derivatives (2a–g). Each of the phthalimide derivatives **1a–m** was stirred with sodium phenoxide in anhydrous dimethyl sulfoxide under nitrogen. All reactions were followed by removing aliquots at timed intervals, adding these aliquots to a methylene chloride/water mixture, and subjecting the methylene chloride solution to VPC analysis. All the reactions were run for 2 h at room temperature except **1a, 1i, 1j, 1k,** and **1m,** which were run at 50 °C. A detailed experimental procedure is given below.

3-Phenoxy-*N*-(4-chlorophenyl)phthalimide (2i). A mixture of 0.9893 g (8.5 mmol) of sodium phenoxide, 2.5810 g (8.5 mmol) of 3-nitro-*N*-(4-chlorophenyl)phthalimide, and 26 mL of anhydrous Me_2SO was stirred under nitrogen at room temperature. After 1 h, an aliquot was added to a methylene chloride/1.2 N hydrochloric acid mixture. This mixture was shaken and the methylene chloride layer was dried and subjected to VPC analysis. The remainder of the reaction mixture was added to 300 mL of 1.2 N hydrochloric acid solution. The white precipitate was collected, washed, and dried; 2.72 g (90%). Recrystallization from absolute ethanol gave the analytical sample, mp 172–174 °C (Table II).

Reaction of 1e with 8-Hydroxyquinoline: Formation of 2p. 8-Hydroxyquinoline, 1.45 g (0.01 mol), was converted to its salt by the sodium hydroxide method. The toluene was distilled from the system and 2.68 g (0.01 mol) of **1e** was added at 60 °C. The mixture was stirred at 60 °C for 6 h and then cooled and added to ice water. The precipitate was collected and dried; 3.01 g (82% yield), mp 195.5–196.5 °C (ethanol). See supplementary material for ^{13}C NMR assignments.

Anal. Calcd for $C_{23}H_{14}N_2O_3$: C, 75.4; H, 3.9; N, 7.6; mol wt 366.1003. Found: C, 74.8; H, 4.0; N, 7.7; mol wt 366.1004 (mass spectrum).

4-(4-Methylphenoxy)-*N*-phenylphthalimide (2q). A mixture of 14.58 g (0.112 mol) of sodium 4-methylphenoxide, 30.0428 g (0.112 mol) of 4-nitro-*N*-phenylphthalimide, and 200 mL of Me_2SO was stirred at 60 °C under a nitrogen atmosphere for 3 h. The mixture was cooled and added to a 1.2 N hydrochloric acid solution. The precipitate was collected and dried to give 34.8 g (94%): mp 177–178 °C (ethanol); ^1H NMR (Me_2SO-d_6) δ 2.35 (methyl, s, 3), 6.9–8.0 (aryl, m, 12); IR (KBr) C=O 1712 (s), 1770 cm^{-1} (m). See supplementary material for ^{13}C NMR assignments.

Anal. Calcd for $C_{21}H_{15}NO_3$: C, 76.6; H, 4.6; N, 4.3; mol wt 329. Found: C, 76.8; H, 4.5; N, 4.2; mol wt 329 (mass spectrum).

4-Phenoxyphthalonitrile. This compound can be prepared from the reaction of sodium phenoxide with 4-nitrophthalonitrile (**3**) in Me_2SO as described in ref 24. We thank D. R. Heath for a sample of this material.

Diisobutyl 4-Phenoxyphthalate (5). A mixture of 5.0 g (0.015 mol) of diisobutyl 4-nitrophthalate (**4**), 1.80 g (0.015 mol) of sodium phenoxide, and 50 mL of DMF was heated at 100 °C for 1 h under nitrogen. The reaction mixture was cooled to room temperature and added to 200 mL of 1.2 N hydrochloric acid. The resulting mixture was extracted well with ether, and the ether extracts were washed with water and a saturated salt solution to give 5.5 g of a light yellow oil. This material was distilled through a short-path distillation column to give 5.1 g (89%) of diisobutyl 4-phenoxyphthalate, bp 198–201 °C (0.53 Torr). See supplementary material for ^{13}C NMR assignments.

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.1; H, 7.0.

3-(4-Methylthiophenoxy)-*N*-phenylphthalimide (6). A mixture of 1.46 g (0.010 mol) of the sodium salt of *p*-methylthiophenol, 2.51 g (0.010 mol) of 3-chloro-*N*-phenylphthalimide (**1a**), and 25 mL of anhydrous dimethylformamide was stirred at 60 °C under a nitrogen atmosphere. After 2 h, the mixture was cooled to room temperature and poured into 500 mL of 1.2 N hydrochloric acid solution. The precipitate was collected and dried to give 3.35 g (97%), mp 203.5–205 °C (ethyl acetate), of desired product (**6**).

Anal. Calcd for $C_{21}H_{15}NO_2S$: C, 73.02; H, 4.38; N, 4.06; S, 9.28; mol wt 345. Found: C, 73.3; H, 4.6; N, 3.8; S, 9.5; mol wt 345 (mass spectrum).

Competition Experiments: Reactivity toward Sodium Phenoxide (Table III). Anhydrous sodium phenoxide was accurately weighed into a flask under nitrogen. Equimolar amounts of the two compounds being studied and an internal standard (*o*-terphenyl) were then dissolved in enough Me_2SO to make a 10% solution. An aliquot was added to a mixture of 1.2 N hydrochloric acid and chloroform. The chloroform layer was dried, and this solution analyzed to determine the composition of the starting mixture. The Me_2SO solution was then added to the sodium phenoxide and this mixture was stirred under nitrogen at room temperature. After 1 h, an aliquot was analyzed (VPC) as described above. Using the equation presented by Huisgen,[25] the relative rates of reactivity were calculated:

$$\frac{K_A}{K_B} = \frac{\log A_0 - \log (A_0 - x)}{\log B_0 - \log (B_0 - x)}$$

A_0 = initial concentration of A, B_0 = initial concentration of B, $(A_0 - x)$ = amount of A unreacted, and $(B_0 - x)$ = amount of B unreacted.

Competition Experiments: Reactivities of the Nucleophiles (Table V). Two different nucleophiles (10 mmol each) were dissolved in 25 mL of anhydrous dimethylformamide, followed by 2.68 g (10 mmol) of 3-nitro-*N*-phenylphthalimide. The mixture was stirred for 0.5 h at room temperature under nitrogen, and an aliquot of the homogeneous solution was added to 1.2 N hydrochloric acid and extracted well with chloroform. If the reaction mixture was not homogeneous, the entire reaction mixture was so treated. The chloroform solution was dried and subjected to VPC analysis, which was calibrated with standards. Each competition was run in duplicate and the average values were used to calculate the relative reaction rates.

Ether Exchange Reactions (Table VI). All reactions were run in anhydrous dimethylformamide under a nitrogen atmosphere.

Typically, a mixture of 1.0 g (3.0 mmol) of 3-(4-methylphenoxy)-*N*-phenylphthalimide (**2j**) and 0.35 g (3.0 mmol) of sodium phenoxide was stirred with 10 mL of anhydrous DMF under a nitrogen atmosphere. The mixture was placed in a bath at 60 °C and aliquots were added to a mixture of 1.2 N hydrochloric acid and chloroform, as before, and analyzed. Ratios for the two imides were calculated from the corrected peak areas.

The final reaction mixture was poured into 1.2 N hydrochloric acid/ice to give 0.92 g of material. ^{13}C analysis indicated only two compounds were present and proton NMR analysis showed the ratio of **2a/2j** to be 33/67.

Reaction of Sodium Nitrite with 3-Nitro-*N*-phenylphthalimide (1e). A mixture of 0.24 g (3.5 mmol) of anhydrous sodium nitrite, 1.0 g (3.7 mmol) of **1e,** and 10 mL of anhydrous DMF was stirred under nitrogen at 60 °C. Within 15 min, the solution became dark red in color, but no precipitate formed during 3 h. The reaction mixture was cooled to room temperature and poured into a 1.2 N hydrochloric acid/ice mixture. The resulting precipitate was collected and dried to give 0.98 g of yellow powder, identical with the starting material by VPC, IR, and ^1H and ^{13}C NMR.

After 48 h at 60 °C, the reaction mixture was very dark in color and a white precipitate (0.17 g) had formed. This solid was dissolved in water, acidified, and extracted with ether to give 3-nitrophthalic acid. An NMR of the initial white precipitate in D_2O was identical with the NMR of the disodium salt of 3-nitrophthalic acid.

The initial filtrate was poured into a 1.2 N hydrochloric acid/ice mixture; the resulting precipitate (0.65 g) was starting material (IR), but VPC analysis showed the presence of two minor impurities which were not identified.

A mixture of 2.68 g (10 mmol) of imide (**1e**), 0.75 g (10.8 mmol) of anhydrous sodium nitrite, and 50 mL of anhydrous DMF stirred under nitrogen at 135 °C almost immediately turned very red. After 5 min, the solution was dark red-black in color and precipitate formed. After 4 h, at 135 °C, the solution was cooled and filtered to give 1.0 g (39%) of disodium 3-nitrophthalate. The filtrate was poured into a 1.2 N hydrochloric acid/ice mixture and extracted with chloroform. The chloroform extracts gave 1.5 g of a red oil containing many unidentified components.

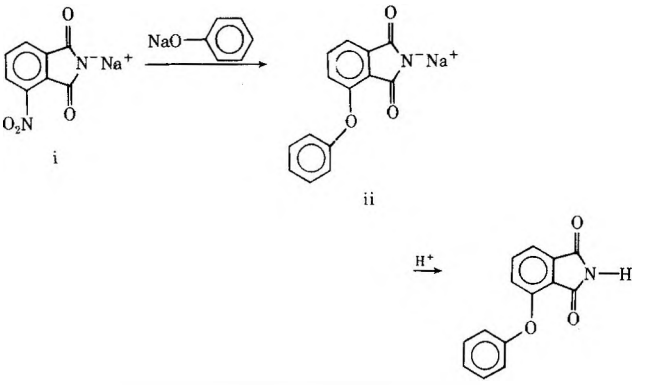
Reaction of Sodium Nitrite with 3-Phenoxy-*N*-phenylphthalimide (2a). A mixture of 1.0 g (3.1 mmol) of **2a,** 0.21 g (3.0 mmol) of anhydrous sodium nitrite, and 10 mL of anhydrous dimethylformamide was stirred under nitrogen at 60 °C for 48 h. The solution slowly turned light yellow, but no detectable precipitate was formed. The cooled mixtures was added to a 1.2 N hydrochloric acid/ice mixture to give 0.95 g of **2a.** No new products were found.

Acknowledgments. We would like to thank H. M. Relles, T. Takekoshi, and J. S. Manello for many helpful discussions concerning this work. In addition, we would like to thank H. M. Relles, J. D. Cargioli, E. A. Williams, and G. C. Levy for their help in obtaining and interpreting the ^{13}C spectra, which have been of great value to us in much of this study.

Registry No.—**2p,** 63197-32-0; **2q,** 63196-28-1; **3,** 31643-49-9; **4,** 53577-26-7; **5,** 63197-33-1; **6,** 58045-38-8; 3-chlorophthalic anhydride, 117-21-5; 3-fluorophthalic anhydride, 652-39-1; 3-nitrophthalic anhydride, 641-70-3; 4-nitrophthalic anhydride, 5466-84-2; 4-fluoro-

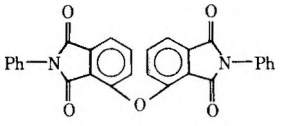
phthalic anhydride, 319-03-9; 4-chlorophthalic anhydride, 118-45-6; aniline, 62-53-3; 4-methoxyaniline, 104-94-9; 4-methylaniline, 106-49-0; 4-chloroaniline, 106-47-8; methylamine, 74-89-5; 8-hydroxyquinoline, 148-24-3; sodium, 1440-23-5; *p*-methylphenol, 106-44-5; *N*-phenylphthalimide, 520-03-6.

Supplementary Material Available. Tabulated ^{13}C NMR chemical shifts for all phthalimides contained in Tables I, II, and IV (Table VII) as well as **2p, 2q,** and **5** (7 pages). Ordering information is given on any current masthead page.



References and Notes

(1) W. Reinders and W. E. Ringer, *Recl. Trav. Chim. Pays-Bas*, **18**, 326 (1899); J. F. Bennett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951).
(2) J. H. Gorvin, *Chem. Ind. (London)*, **36**, 1525 (1967).
(3) E. Radlmann, W. Schmidt, and G. E.Nischk, *Makromol. Chem.*, **130**, 45 (1969).
(4) L. Caswell and T. Kao, *J. Heterocycl. Chem.*, **3**, 333 (1966); see also R. Fowler, L. Caswell, and L. Sue, *ibid.*, **10**, 407 (1973), for the reaction of methoxide with *N*-substituted 3-halophthalimides.
(5) For an example, see T. W. M. Spence and G. Tennant, *J. Chem. Soc., Perkin Trans. 1*, 835 (1972).
(6) J. R. Beck, *J. Org. Chem.*, **37**, 3224 (1972); **38**, 4086 (1973); J. R. Beck, R. L. Sobcyak, R. G. Suhr, and J. A. Yahner, *ibid.*, **39**, 1839 (1974); J. R. Beck and J. A. Yahner, *ibid.*, **39**, 3440 (1974).
(7) R. D. Knudsen and H. R. Snyder, *J. Org. Chem.*, **39**, 3343 (1974).
(8) N. Kornblum et al., *J. Org. Chem.*, **41**, 1560 (1976).
(9) See, for example, J. G. Wirth and D. R. Heath, U.S. Patent 3 838 097 (1974).
(10) Yields of >95% can be obtained by pouring the reaction mixture into water and recovering the product by filtration. No attempt was made to maximize the yields of these crude products, which were clean by VPC analysis.
(11) J. Miller, "Aromatic Nucleophilic Substitution", Elsevier, New York, N.Y., 1968, p 137.
(12) J. Miller, ref 11, p 165.
(13) Placement of a negative charge on nitrogen causes the reaction to be very sluggish. Displacement of the nitro group from the phthalimide salt (i) by phenoxide to give ii requires heating at 120 °C for 16 h in DMF. Reaction with the corresponding 4 isomer is incomplete after 48 h at 120 °C.
(14) Support for the contention of steric interaction between the 3 substituent and the ortho carbonyl group is found in the ^{13}C NMR spectrum of 3-nitro-*N*-phenylphthalimide (**1e**) (see Table VII). Both carbonyl B and C-2 of this molecule are shifted upfield relative to the calculated values, which suggests steric compression between the nitro and carbonyl group. For a discussion of steric compression shifts, see G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, p 24.
(15) Perhaps Me_2SO also levels the rate differences between the different leaving groups. Many examples are known. See, for example, ref 11, Chapter 8.
(16) D. R. Heath and J. G. Wirth, U.S. Patent 3 730 946 (1973).
(17) A detailed study of the reaction of thiophenoxide nucleophiles with these systems will appear in a subsequent publication in this journal.
(18) W. T. Reichle, *J. Org. Chem.*, **37**, 4254 (1972), see also A. B. Newton and J. B. Rose, *Polymer*, **13**, 465 (1972).
(19) One of the more likely products produced is the bisether iii. For a detailed study of this type of reaction, see R. L. Markezich and O. S. Zamek, *J. Org. Chem.*, companion paper, this issue.



iii

(20) M. S. Newman and P. G. Scheurer, *J. Am. Chem. Soc.*, **78**, 5004 (1956).
(21) R. L. Markezich, unpublished results. See also N. Ishikawa, T. Tanabe, and D. Hayashi, *Bull. Chem. Soc. Jpn.*, **48**, 359 (1975).
(22) D. K. Drew and D. B. Kelly, *J. Chem. Soc.*, 630 (1941).
(23) F. J. Williams, H. M. Relles, J. S. Manello, and P. E. Donahue, *J. Org. Chem.*, companion paper, this issue.
(24) D. R. Heath and J. G. Wirth, U.S. Patent 3 787 475 (1974).
(25) U. Burgerand and R. Huisgen, *Tetrahedron Lett.*, **35**, 3057 (1970).

Reactions of Phenoxides with Nitro-Substituted Phthalate Esters

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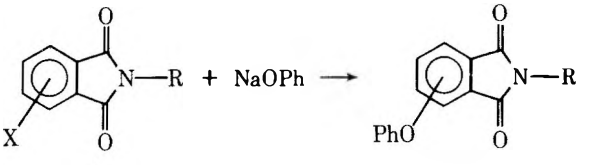
Aromatic nucleophilic nitro displacement by phenoxides on nitro-substituted phthalate esters is discussed. The differences in behavior between the 3-nitro (**5a–d**) and 4-nitro (**4a–d**) isomers were investigated. The 4 isomers gave excellent yields of the phenoxy substituted derivatives **6**. Side reactions were prominent for the 3-nitro isomers in degrees depending on the alkyl groups of the ester function. The majority of the side products can be explained by nucleophilic attack on the alkyl group of the ester, resulting in cleavage of the alkyl–oxygen bond. A rationale for the relative displacement rates of these two isomers is presented.

The reaction of phenoxides with nitro- or halo-substituted phthalimides (**1**) is an excellent synthetic route to ether imide derivatives (**2**).[1] We wish to report the results of studies on the reactions of phenoxides with nitrosubstituted phthalate esters.[2] Examples of aromatic displacement reactions using an ester activating group were reported as early as 1890,[3] but this group was used only in conjunction with other activating groups. The displacement of nitro groups activated by only one ester group was subsequently observed in dipolar aprotic solvents.[4,5] No attack of the nucleophile at either the carbonyl or alkyl group of the ester was observed in any of these systems.

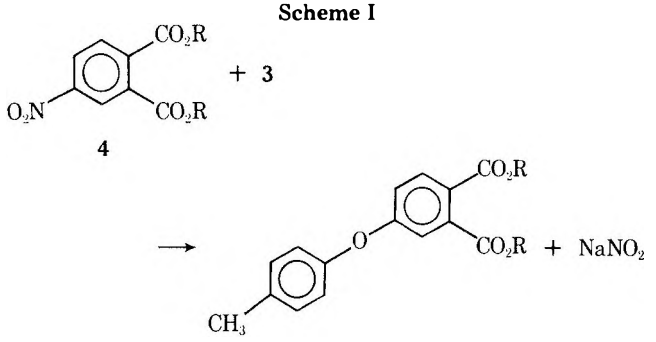


1 **2**

Results and Discussion

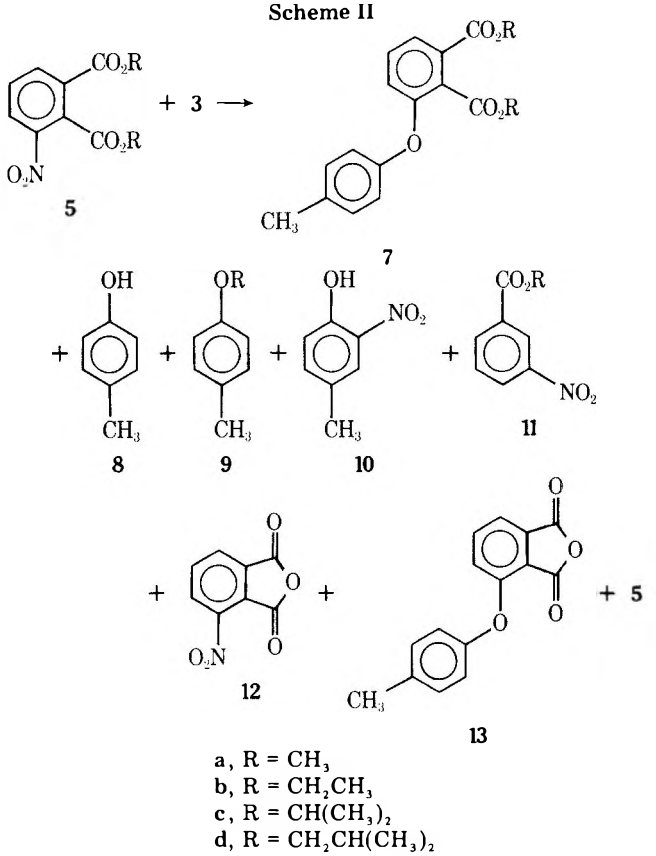
Reactions with Sodium 4-Methylphenoxide. The reaction of sodium 4-methylphenoxide (**3**) with eight dialkyl nitrophthalates (**4a–d** and **5a–d**) was examined to determine

Scheme I



a, R = CH_3
b, R = CH_2CH_3
c, R = $CH(CH_3)_2$
d, R = $CH_2CH(CH_3)_2$

Scheme II

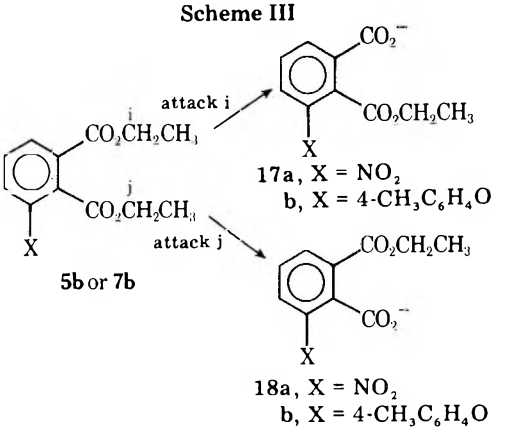


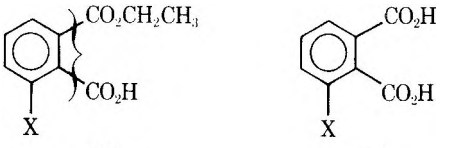
a, R = CH_3
b, R = CH_2CH_3
c, R = $CH(CH_3)_2$
d, R = $CH_2CH(CH_3)_2$

the effect of the alkyl group on the course of the reaction and to judge the importance of the location of the nitro group. The reaction of **3** with the 4-nitro derivatives (**4a–d**) in DMF at 100 °C for 1 h gave excellent yields of the ether derivatives **6a–d** (Scheme I). There was no trace of 4-methylphenyl alkyl ether (**9**) (the product of phenoxide attack at the alkyl group) in any of these systems. The reactions were complete in 1 h; thereafter **6** was slowly destroyed with time by reaction with the sodium nitrite formed as a by-product of the displacement. Attempts to generate the nucleophile in situ by using a carbonate base and 4-methylphenol (**8**) were less successful due to hydrolysis of the ester groups of **4**. These results are summarized in Table I.

The reaction of **3** with the 3-nitro isomers (**5**) proved to be more complex (Scheme II). Several side reactions occurred in addition to nitro displacement. For example, the reaction of **3** with **5b** gave the eight products indicated as well as three unidentified minor products. It is unknown if **12** was formed during the reaction or if compounds such as **14b** or **15** (X = NO_2) were formed and then underwent ring closure during VPC analysis to give **12**. It is likely that **13** originated from **14b**

Scheme III





14b **15**

or **15** (X = 4-$CH_3C_6H_4O$) and was not actually formed during the reaction (see Experimental Section). Subsequent analysis of the reaction mixture by GC/mass spectroscopy indicated the presence of diethyl 3-ethoxyphthalate (**16**) as a minor component.

The majority of these products can be explained as arising from the attack of a nucleophile upon the alkyl group of the esters. Such an attack (Scheme III) in the case of **3** leads to the ether **9** and either **17** or **18**. As has been shown for the corresponding phenyl esters,[6] either **17a** or **18a** can thermally decarboxylate during the reaction to give only the meta derivative corresponding to **11b**. Protonation of either **17a** or **18a** upon workup gives the acid esters **14b** (X = NO_2). The thermal treatment of these materials during VPC analysis can result in the formation of 3-nitrophthalic anhydride (**12**) by loss of ethanol. Attack of **3** at an ester group of **7b** can also generate the ether **9b** as well as the acid ester salts **17b** and **18b**. These salts apparently did not thermally decarboxylate under the reaction conditions but, instead, were protonated on workup and ring closed during VPC analysis to give the observed anhydride **13**. Considering the differences in the carbanionic stabilizing influences of $-NO_2$ vs. 4-$CH_3C_6H_4$, it is not surprising that **17a** and/or **18a** underwent decarboxylation while **17b** and/or **18b** did not.

Formation of **17** and **18** can also result from attack by the nitrite anion generated by nitro displacement at either the alkyl group (which would also produce ethyl nitrite) or at the carbonyl group to give ethoxide. Either of these processes could ultimately give ethoxide and **17** or **18**. Ring closure of **17** or **18** would also generate ethoxide. Formation of **16** results from reaction of this ethoxide with **5b**.

Finally, **10** was probably produced during the workup of the reaction mixture and not during the reaction itself. If the reaction mixture was worked up under neutral rather than acidic conditions, no **10** was found and the amount of **8** recovered was increased. Undoubtedly, nitrous acid produced from the sodium nitrite formed in the nitro displacement reaction reacted with **8** during acidic workup to produce a species (probably the corresponding nitroso compound) which ultimately led to **10**. This hypothesis is supported by appropriate control experiments (see Experimental Section).

The product distributions for the reaction of **3** with **5a–d** are contained in Table II. These results indicate that the alkyl

Table I. Displacement Yields for 4-Nitro Isomers (4)

Registry no.	Compd	Alkyl group	Nucleophile	Conditions	% Yield of 6 (VPC)
610-22-0	**4a**	CH_3–	**3**	1 h (100 °C), DMF	98
				2 h (100 °C), DMF	90
				5 h (100 °C), DMF	86
2050-19-3	**4b**	C_2H_5–	**3**	1 h (100 °C), DMF	93
				2 h (100 °C), DMF	93
				3 h (100 °C), DMF	87
	4b	C_2H_5–	4-$CH_3C_6H_4OH/K_2CO_3$	1.5 h (100 °C), DMF	15
				16 h (100 °C) + 6.5 h (135 °C), DMF	48
				16 h (100 °C) + 24 h (135 °C), DMF	41
	4b	C_2H_5–	4-$CH_3C_6H_4OH/Na_2CO_3$	5.5 h (150 °C), DMF	37
				16 h (150 °C), DMF	46
13325-36-5	**4c**	$-CH(CH_3)_2$	**3**	1 h (100 °C), DMF	95–99
53577-26-7	**4d**	$-CH_2CH(CH_3)_2$	**3**	1 h (125 °C), DMF	95–99

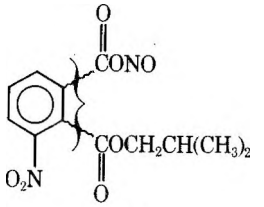
Table II. Reactions of Dialkyl 3-Nitrophthalates (5) with 3 in DMF at 150 °C for 3 h. VPC % Yields

R	Registry no.	8	10	9	11	12	5	13	7
CH_3	13365-26-9	5	1	61	11	17	4	7	12
CH_3CH_2	62351-79-5	4	15	24	9	7	10	5	39
$(CH_3)_2CH$	63181-75-9	6	14	5	2		10	1	53
$(CH_3)_2CHCH_2$	63181-76-0		22	≤1			8		74

group greatly influenced the course of the reaction. Changing the alkyl group from methyl to ethyl to isopropyl to isobutyl changed the yield of the ethers (**9a–d**) formed by attack at the alkyl group from 61 to 24 to 5 to ≤ 1. Concurrently, the amount of the other side products resulting from this alkyl (or carbonyl) group attack also decreased in this series. For example, the nitro ester (11) formed by decarboxylation decreased steadily from R = methyl (11%) to R = isobutyl (0%). Simultaneously, as the percent of alkyl (or carbonyl) attack decreased, the yield of the nitro displacement product (**7a–d**) increased steadily from 12 to 74%. The yield of **7d** in the isobutyl system could not be increased further. Apparently the sodium nitrite produced attacked the remaining **5d** and deactivated it for further displacement. This suggestion is supported (Table II) by the fact that approximately 22% of unreacted 4-methylphenol is isolated (in the form of 2-nitro-4-methylphenol) following workup at the end of the reaction.

The ease of the apparent attack of the phenoxide nucleophile at the alkyl group of the ester is surprising in the light of what has been reported in the literature. Until Bunnett's[7] disclosure of the formation of dimethyl ether from the reaction of sodium methoxide with methyl benzoate, the bimolecular cleavage of the alkyl oxygen bond in the hydrolysis of carboxylic esters was almost unknown.[8] Recently, there have been other reports[9] of this type of reaction, although few examples have been reported in which alkyl ethers of phenols were formed. It appears, however, that in these 3-nitro-substituted phthalate esters, S_N2 attack of the phenoxide nucleophile at the alkyl group is prominent and takes place not only with the methyl esters, but also with the ethyl esters and even to a small degree with the isopropyl systems.[10]

It is noteworthy that no other products were detected by VPC analysis in the diisobutyl 3-nitrophthalate system. It is likely that, at least in the very hindered isobutyl system, nitrite attacks a carbonyl group, rather than the alkyl group, to give **19**. Thereafter, the conversion of **19** to the sodium salt of **14d** by reaction with another nucleophile (nitrite, isobutoxide, or phenoxide) should be facile. Once these conversions have occurred, decomposition of this salt by intramolecular E2 elimination to give isobutylene and monosodium 3-nitrophthalate is feasible. If this occurred, the product would not be observed by VPC analysis.



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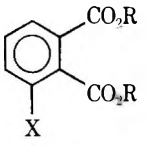
Relative Rates of Nitro Displacement in 4 and 5. A competition reaction containing equivalent amounts of **4d, 5d,** and **3** produced **6d** as the only product. It can be estimated that the 4 isomer **4d** reacted at least two orders of magnitude *faster* than the 3-nitro isomer **5d.** This is in marked contrast to the relative rates of displacement in the phthalimide series where the 4-nitro isomers displaced several times *slower* than the corresponding 3-nitro isomers.[1]

In the case of **4d** vs. **5d,** the reason for the large rate difference is probably steric in origin. In the Meisenheimer intermediate from **6d** (**20**), little steric inhibition of resonace should be encountered (especially in the conformer drawn) and stabilization of the negative charge by the para ester carbonyl should be substantial. On the other hand, there is no Meisenheimer complex conformer derived from **5d** capable of resonance stabilization of the negative charge, which would be as free of steric interactions as **20.** In **21** or **22** resonance stabilization of the negative charge by the ortho ester carbonyl would simultaneously require severe steric compressive interactions to be generated, thus making **21** or **22** much higher in energy than **20.** Assuming similar ground-state energies for **4d** and **5d,** this energy difference for the intermediates would account for the rate difference.

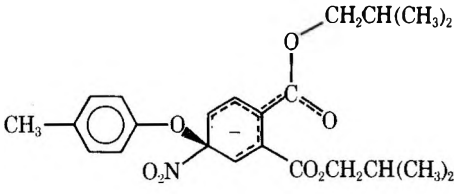
Spectral data are in agreement in this argument. The 2-carbobutoxy group in **5d** resides mainly in its least sterically hindered conformation, in which the carbonyl carbon and both oxygens are in a plane perpendicular to the plane of the ring. The carbonyl stretching region in the infrared spectrum of **5b** shows two strong bands at 1735 and 1745 cm^{-1}. The former is in agreement with an aryl-conjugated ester carbonyl (1-carboalkoxy),[11] while the latter is what would be expected for an unconjugated, saturated ester carbonyl.[11] This is consistent with a 2-carboalkoxy group having no appreciable overlap with the aromatic ring. On the other hand, **4b** showed only a single

Table III. Reaction of Sodium Nitrite with I at 150 °C in DMF



I

Registry no.	R	X	Equiv of $NaNO_2$	% starting material remaining				
				0.5 h	1.0 h	3.0 h	5.0 h	10.0 h
131-11-3	CH_3–	H	2	83	55	13	5	
84-66-2	CH_3CH_2–	H	2	100	96	88	79	59
84-69-5	$(CH_3)_2CHCH_2$–	H	2	91	86	86	84	82
	CH_3–	NO_2	2	13	4	0		
	CH_3CH_2–	NO_2	2	88	68	23	9	
	CH_3–	H	1	73	60	55	55	



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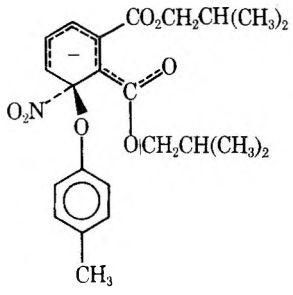

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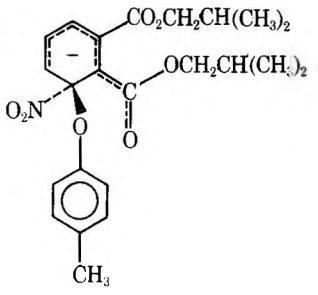

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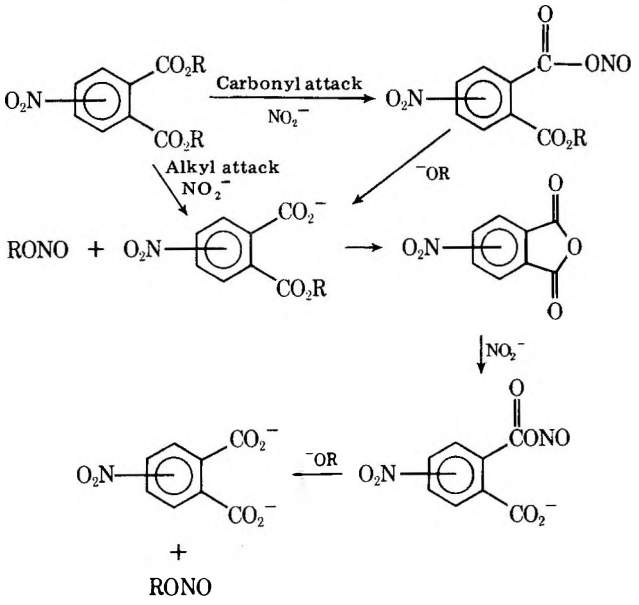
carbonyl band at 1735 cm^{-1} typical of normal aryl-conjugated ester carbonyls.

The Reaction of Sodium Nitrite with Phthalate Esters. Reactions were carried out in DMF at 150 °C using 1 or 2 equiv of anhydrous sodium nitrite and the following esters: dimethyl phthlate, diethyl phthalate, diisobutyl phthalate, dimethyl 3-nitrophthalate, and diethyl 3-nitrophthalate. The amount of unreacted ester was monitored as a function of time (Table III).

Several interesting results were obtained: (1) the more hindered the ester group, the slower the rate of destruction (isobutyl < ethyl < methyl); (2) substitution of a nitro group on the phthalate ring increased the rate of destruction; (3) 2 equiv of sodium nitrite were necessary for complete destruction of the esters. In all of these reactions a precipitate was formed at a rate corresponding to the rate of ester destruction.

At the present time, it is not possible to distinguish nitrite attack at the carbonyl from nitrite attack at the alkyl group, although in either case 2 equiv of nitrite are necessary. A change in alkyl groups from methyl to isobutyl should hinder attack at both the carbonyl group and the alkyl group. Substitution of a nitro group on the phthalate ring should facilitate nucleophilic attack on the carbonyl group, but it should also increase the efficiency of the phthalate salt as a leaving group if attack does take place at the alkyl group. Since 2 equiv of sodium nitrite are necessary for total ester destruction and the resulting product has no alkyl groups present, the two mechanisms for phthalate ester destruction by sodium nitrite given in Scheme IV are plausible.

Scheme IV



In summary, the reaction of phenoxides with nitrophthalate esters was found to be greatly dependent upon the structure of the ester derivative. Side reactions were prominent for the 3-nitro isomers in degrees depending on the alkyl groups of the ester function (Me > Et > isopropyl > isobutyl). The majority of the side products can be explained by nucleophilic attack on the alkyl group of the ester, resulting in cleavage of the alkyl oxygen bond. The corresponding 4-nitro esters gave essentially quantitative yields of the phenoxy-substituted products and were at least two orders of magnitude more reactive than the 3-nitro derivatives.

Further studies of the displacement of nitro and halo groups in derivatives of phthalic acid will be presented in subsequent papers.

Experimental Section

Infrared spectra were taken on a Perkin-Elmer 457 grating infrared spectrophotometer in chloroform solution or as a KBr pellet. Mass spectra were determined on a CEC 21-104 analytical mass spectrometer at 70 eV. Vapor-phase chromatography (VPC) was carried out on a Hewlett Packard 5750 research chromatograph using a 6 ft 10% UCW-98 on 80/100 Chromosorb W column with temperature programming and a thermal conductivity detector. Melting points were determined on a Thomas-Hoover instrument and are uncorrected. C, H, N analyses were determined on a Perkin-Elmer 240 C, H, N analyzer.

Anhydrous DMF and Me_2SO were purchased from Burdick and Jackson Laboratories. 4-Methyl-2-nitrophenol (**10**) and methyl 4-methylphenyl ether (**9a**) were obtained from the Aldrich Chemical

Co. The sodium salt of 4-methylphenol was prepared by reaction with anhydrous sodium methoxide as has been described previously.[1] For displacement reactions, temperatures listed are oil bath temperatures. In general, the actual solution temperatures were 2–5 °C cooler.

VPC yields were determined by using an internal standard (*m*-terphenyl, biphenyl, or *o*-terphenyl) in the reaction mixture. Aliquots were removed at timed intervals and added to a 1.2 N hydrochloric acid solution. This mixture was extracted with ether and the ether extracts were dried over anhydrous magnesium sulfate and then subjected to VPC analysis. Peak areas were calculated by weighing photocopies of each peak and were corrected for detector response differences.

Preparation of Nitro Esters 4 and 5. These esters were prepared by refluxing a mixture of 3- or 4-nitrophthalic anhydride, a catalytic amount of *p*-toluensulfonic acid, and equal volumes of the appropriate alcohol and xylene (ca. 25% concentration). The reaction mixtures were worked up with an ether extraction (bicarbonate wash) to give the crude nitro ester. ^{1}H NMR spectra and elemental analyses follow (^{13}C NMR assignments are contained in the Supplementary Material, Table VI). The aromatic multiplets in the ^{1}H NMR of **4a–d** were superimposable on one another and distinctly different from those of **5a–d.**

4a: mp 66–67 °C (lit. 65 °C);[12] ^{1}H NMR ($CDCl_3$) δ 1.40 (methyl, s, 6), 7.7–8.6 (aromatic, m, 3).

4b: mp 33–35 °C (lit. 33–34 °C);[13] ^{1}H NMR ($CDCl_3$) δ 1.40 (methyl, t, J = 7 Hz, 6), 4.44 (methylene, q, J = 7 Hz, 4) 7.7–8.6 (aromatic, m, 3).

4c: mp 41–42 °C [lit. bp 172 °C (3 Torr)];[14] ^{1}H NMR ($CDCl_3$) δ 1.40 (methyl, d, J = 6 Hz, 12), 5.32 (methine, septet, J = 6 Hz, 2), 7.7–8.6 (aromatic, m, 3).

4d: ^{1}H NMR ($CDCl_3$) δ 1.04 (methyl, d, $J \simeq$ 7 Hz, 12), 1.6–2.4 (methine, m, 2), 4.14 (methylene, d, $J \simeq$ 6 Hz, 4), 7.7–8.6 (aromatic, m, 3). Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33; mol wt 323. Found: C, 59.7; H, 6.6; N, 4.3; mol wt 323 (mass spectrum).

5a: mp 69–70 °C (lit. 67–69 °C);[12] ^{1}H NMR ($CDCl_3$) δ 4.00 (methyl, s, 3), 4.07 (methyl, s, 3), 7.7–8.6 (aromatic, m, 3).

5b: mp 44–45 °C (lit. 46 °C);[13] ^{1}H NMR ($CDCl_3$) δ 1.40 (methyls, triplet, $J \simeq$ 7 Hz, 6), 4.40 and 4.50 (methylenes, quartets, $J \simeq$ 7 Hz, 4), 7.5–8.5 (aromatic, m, 3).

5c: mp 41–42 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 and 1.43 (methyls, doublets, J = 6 Hz, 12), 5.25 and 5.35 (methines, septets, J = 6 Hz, 2), 7.5–8.5 (aromatic, m, 3). Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74; mol wt 295. Found: C, 57.0; H, 6.0; N, 4.7; mol wt 295 (mass spectrum).

5d: bp 165–166 °C (0.25 Torr); ^{1}H NMR ($CDCl_3$) δ 1.00 (methyl, d, $J \simeq$ 7 Hz, 12), 1.6–2.4 (methine, m, 2), 4.08 and 4.15 (methylenes, each d, $J \simeq$ 7 Hz, 4), 7.40–8.35 (aromatic, m, 3). Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33; mol wt 323. Found: C, 59.8; H, 6.6; N, 4.0; mol wt 323 (mass spectrum).

Reaction of 3 with 4-Nitro Esters 4a–d to give 6a–d. An equimolar mixture of **3** and the desired nitro ester was stirred with DMF (10% solution) under nitrogen for 1 h at 150 °C. The cooled reaction mixture was added to 1.2 N hydrochloric acid and extracted with ether. The ether extracts were washed with 1.2 N HCl, water, 5% sodium carbonate, water, and a saturated salt solution. The ether solution was dried and concentrated to give the crude product, **6,** in 90–95% yield. This material was purified by distillation for **6b–d.** ^{1}H and ^{13}C NMR data for these compounds are in the supplementary material (Tables IV and V).

6a: oil. Anal. Calcd for $C_{17}H_{16}O_5$: C, 68.0; H, 5.4; Found: C, 67.8; H, 5.5.

6b: bp 163–165 °C (0.05 Torr); n^{24}D 1.5482. Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14; mol wt 328. Found: C, 69.7; H, 5.9; mol wt 328 (mass spectrum).

6c: bp 175–177 °C (0.05 Torr); n^{24}D 1.5330. Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79; mol wt 356. Found: C, 71.7; H, 7.0; mol wt 356 (mass spectrum).

6d: bp 194–199 °C (0.20 Torr); n^{24}D 1.5292. Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34; mol wt 384. Found: C, 71.5; H, 7.5; mol wt 384 (mass spectrum).

Reaction of 4b with 4-Methylphenol and Potassium Carbonate. A mixture of 2.67 g (0.01 mol) of **4b,** 1.08 g (0.01 mol) of **8,** 1.38 g (0.01 mol) of anhydrous potassium carbonate, 1.41 g of *m*-terphenyl, and 26 mL of anhydrous DMF was stirred at 100 °C under nitrogen for 16 h and then at 135 °C for additional 24 h. Aliquots were removed at timed intervals and worked up as described above. Analysis indicated the presence of **4b, 6b,** and a peak with the same retention time as 4-nitrophthalic anhydride. There was no peak present with the retention time of the ether **9b** (see Table I).

Reaction of Diethyl 3-Nitrophthalate (5b) with 3. Identification of Products. A mixture of 4.84 g (0.037 mol) of **3,** 9.94 g (0.037 mol) of **5b,** and 100 mL of anhydrous DMF was stirred at 150 °C for 3 h under nitrogen. The mixture was cooled to room temperature and poured into a large excess of 1.2 N HCl. This solution was thoroughly extracted with ether; the ether extracts were washed with water and a saturated sodium chloride solution, and were dried over anhydrous magnesium sulfate. The dried ether extracts were concentrated to give a brown oil. Analysis of this oil by VPC showed the presence of 11 peaks. Coinjection of authentic samples allowed for the tentative assignment of structure to compounds **8, 9b, 10, 11b, 12, 5b, 13,** and **7b** (in order of retention time). The crude reaction mixture was dissolved in ether and washed with a 5% sodium bicarbonate solution, which removed compounds **12** and **13** (thought to have arisen from carboxylic acid derivatives). The ether solution was reconcentrated and the residue was fractionally distilled through a short-path distillation head. The following fractions were collected: (1) 48–60 °C (0.01 mm); (2) 50–126 °C (0.01 mm); (3) 126–163 °C (0.05 mm); (4) 164–165 °C (0.05 mm); (5) 165 °C (0.05 mm).

Fraction 1 contained compounds **8** and **9b.** Washing an ethereal solution of this mixture with a 10% sodium hydroxide solution removed compound **8.** A ^{1}H NMR of this mixture showed two singlets of almost equal height at 1.6 and 1.65 ppm for the methyl groups of **8** and **9b.** Fraction 2 contained mostly compound **11b** as well as some **8.** Infrared and ^{1}H NMR analysis of this fraction were very similar to the spectra of an authentic sample of **11b** (see below). Fraction 3 was very minor. Fraction 4 contained a trace of compound **5b** ($-NO_2$ band at 1530 cm^{-1} in infrared) and compound **7b.** Fraction 5 contained only compound **7b** as evidenced by its ^{13}C and ^{1}H NMR. The infrared showed a strong carbonyl band at 1720 cm^{-1} and the complete absence of a band at 1530 cm^{-1} for the $-NO_2$ group.

A sample of the original brown oil was analyzed by GC/mass spectroscopy on a Varian MAT-111 equipped with a 10 ft by 2 mm column packed with 3% OV-17 on 100/120 Gas Chrom Q. The compounds were identified in order of elution. The *m/e* values for the parent and base ions as well as for other key ions are as follows: compound, *m/e* (% of base): **9b,** 136 (58), 108 (100), 107 (88); **8,** 108 (85), 107 (100); **11b,** 167 (30), 150 (100); **16,** 266 (4), 221 (40), 193 (29), 44 (100); **5b,** 222 (12), 194 (100); **13,** 254 (100), 181 (63); **7b,** 328 (43), 237 (100), 165 (55).

Reaction of Dimethyl 3-Nitrophthalate (5a) with 3. The reaction of **5a** with **3** was run as described for **5b** to given an oil. Analysis by VPC showed the presence of seven peaks (**7a** and **13** were one peak) and by co-enrichment with authentic samples the structures for the compounds **8, 10, 9a, 11a, 12, 5a, 13,** and **7a** were assigned. The following compounds were identified in order of elution by GC/mass spectroscopy. The *m/e* values for the parent and base ions as well as for other key ions are as follows: compound, *m/e* (% of base): **8,** 108 (42), 107 (65), 28 (100); **9,** 122 (100), 121 (53), 107 (36), 77 (39); **11a,** 181 (17), 150 (100), 104 (3); dimethyl 3-methoxyphthalate (**16a**), 224 (7), 193 (100); **5a,** 208 (100); 104 (35); one peak **13,** 254 (20), 237 (100), 209 (31); **7a,** 300 (51).

Reaction of Diisopropyl 3-Nitrophthalate (5c) with 3. The reaction of **5c** with **3** was run as described for **5b** to give an oil. The structures of the products in this oil were identified by co-enrichment with authentic samples. In addition, the structures of **9c** [*m/e* 150, 108 (− propylene)], **5c,** and **7c** were verified by GC/mass spectroscopic analysis of the reaction mixture.

Reaction of Diisobutyl 3-Nitrophthalate (5d) with 3. A mixture of 3.17 g (0.0244 mol, *0.0043 mol excess*) of **3,** 6.50 g (0.0201 mol) of **5d,** and 40 mL of DMF was stirred under nitrogen at 150 °C for 3 h. The reaction mixture was worked up as described for **5b** to give 7.86 g of oily residue. A 0.50-g sample of this residue was analyzed by ^{13}C NMR spectroscopy (Me_2SO-d_6) and found to contain **7d** (approximately 70 mol %), 2-nitro-4-methylphenol (**10**) (approximately 25 mol %), and **5d** and/or acid esters corresponding to **5d** (**14d,** approximately 5 mol%).

The remainder (7.36 g) of the crude product was redissolved in 650 mL of ether and extracted with 5% NaOH (which removed most of the color from the organic layer), water, and saturated NaCl, and then dried ($MgSO_4$). Solvent evaporation now gave 5.41 g of an orange oil which by VPC and ^{13}C NMR (Me_2SO-d_6) was virtually pure **7d.**

The remaining 4.91 g of crude product was distilled under vacuum. Fraction 1: bp 182–186 °C (0.20 mm); 0.77 g; VPC and ^{13}C NMR (Me_2SO-d_6) analysis indicated this was approximately 90% **7d** and approximately 10% **5d.** Fraction 2: bp 187–190 °C (0.20 mm); 3.72 g; VPC indicated this was >99% **7d;** the mass spectrum showed a molecular ion at 384 (calcd 384). The overall yield of **7d** (fraction 2 + 90% of fraction 1 + 2 × 0.50 g ^{13}C NMR samples) was approximately 70%. This latter fraction also gave correct elemental analyses.

Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.5; H, 7.4.

Identification of Isobutyl 4-Methylphenyl Ether (9d). A mixture of 0.47 g of **3**, 1.17 g of **5d**, and 12.0 mL of anhydrous DMF was stirred at 150 °C for 3.5 h under a nitrogen atmosphere. The mixture was cooled to room temperature and added to neutral water in an attempt to prevent the formation of **10**. The mixture was extracted thoroughly with methylene chloride and the methylene chloride extracts were washed extremely thoroughly with a 5% sodium hydroxide solution. The methylene chloride phase was dried and subjected to GC/mass spectroscopic analysis, which showed the presence of the ether **9d** [*m/e* 164, 108 (− isobutylene)]. This spectrum was identical with the spectrum of a sample of **9d** which was prepared from the reaction of **3** with isobutyl bromide. The structure of the sample from bromo displacement was also verified by its ^{1}H NMR ($CHCl_3$): δ 1.0 (ether aliphatic methyls, doublet, $J \simeq 6$ Hz, 6); 1.6–2.3 (ether methine, m, 1); 2.25 (aromatic methyl, s, 3); 3.63 (ether methylene, d, $J \simeq 6$ Hz, 2); 6.90 (aromatic, center of A_2B_2, 4).

Determination of the Extractability by Sodium Bicarbonate of 12 and 13 from Diethyl Ether. A mixture of 0.0953 g of **12**, 0.1255 g of **13**, 0.0380 g of biphenyl, and 15 mL of anhydrous diethyl ether was subjected to VPC analysis. The ethereal solution was washed with 2 × 15 mL of 5% aqueous sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The ethereal solution was again subjected to VPC analysis, which showed none of **12**, but did show the presence of ca. 65% of the initial amount of **13**. This extractive procedure was repeated using the corresponding phthalic acid derivatives. After washing with 5% sodium bicarbonate, there was no trace of either of the diacids in the ether. Since extraction of the crude reaction product from **5b** + **3** with bicarbonate removed all traces of **13**, it is likely that **13** is arising from ring closure during VPC analysis of **14b** or **15** (X = 4-$CH_3C_6H_4O$).

Determination of the Importance of pH on the Formation of 2-Nitro-4-methylphenol (10) During Work-up of Mixtures Containing 4-Methylphenol (8) and Sodium Nitrite. A mixture of 2.30 g of **3**, 2.44 g of sodium nitrite, 4.92 g of diisobutyl phthalate, and 49 mL of anhydrous DMF was stirred under nitrogen at 140 °C. After 5 h, the mixture was cooled to room temperature and divided into three equal portions, which were worked up as follows: (1) The mixture was added to 150 mL of neutral water and the aqueous mixture was extracted thoroughly with ether. The ether extracts were washed with 1.2 N HCl and a saturated NaCl solution. After being dried over anhydrous $MgSO_4$, the ethereal solution was concentrated and the residue was analyzed by ^{13}C NMR, which showed only **8** and the starting diester. (2) The mixture was added to 150 mL of a 1% acetic acid solution. This solution was worked up as described above. Analysis by ^{13}C NMR showed 83% of **8** and 17% of **10**. (3) The mixture was added initially to 1.2 N HCl and worked up as described above. Analysis by ^{13}C NMR showed 3% of **8** and 97% of **10**.

Reactions of Dialkyl Esters with Sodium Nitrite. Dimethyl Phthalate and Sodium Nitrite. A mixture of 2.5210 g of dimethyl phthalate, 1.7916 g of sodium nitrite (2 equiv), and 2.0019 g of biphenyl (internal standard) was stirred in 25 mL of DMF in a 150 °C oil bath under nitrogen. Aliquots were removed at timed intervals and worked up by adding them to a 1.2 N HCl solution and extracting the mixture with methylene chloride. The resulting organic solution was subjected to VPC analysis. The results are tabulated in Table III.

The reaction was repeated except that no internal standard was used. The reaction mixture was heated for 5 h at 150 °C, cooled to room temperature, and filtered. The precipitate was washed with fresh DMF and thoroughly dried to give >80% (some DMF present) of disodium phthalate; no methyl ester protons were detected by ^{1}H NMR.

Competition Reaction between Diisobutyl 3- and 4-Nitrophthalate. A mixture of 1.8423 g of **4d** (0.0057 mol), 1.8423 g of **5d** (0.0057 mol), and 0.6555 g of o-terphenyl was stirred at room temperature with 24 mL of anhydrous DMF under nitrogen. A small aliquot was removed at zero time and added to 1.2 N HCl and extracted with methylene chloride. VPC analysis of this material showed that the two starting esters did not separate. To this mixture was added 0.7407 g (0.0057 mol) of sodium *p*-methylphenoxide (**3**) and the stirred homogeneous mixture was placed in a 100 °C oil bath. Aliquots were removed at 1 and 2 h and worked up as described above. VPC analysis of each point showed that only **6d** was formed. The mixtures were subsequently enriched with **7d** and reexamined by VPC to ensure that none of it was present.

Based on the result, it can be estimated that under these reaction conditions, the difference in rate between these two isomers toward reaction with **3** is *at least* two orders of magnitude. The calculation employed follows (where A = **4d** and B = **5d**):

$$\frac{k_A}{k_B} = \frac{\log A_0 - \log (A_0 - x)}{\log B_0 - \log (B_0 - x)}$$

where A_0 = initial concentration of A (4 isomer) = 1, B_0 = initial concentration of B (3 isomer) = 1, $(A_0 - x)$ = amount of A (4 isomer) unreacted = 1% = 0.01, and $(B_0 - x)$ = amount of B (3 isomer) unreacted = 99% = 0.99.

$$\frac{k_A}{k_B} = \frac{0 - \log(0.01)}{0 - \log(0.99)} = \frac{-(-2.00)}{-(-0.004)} = \frac{2.00}{0.004} = 500$$

Preparation of Authentic Samples. 3-(4-Methylphenoxy)-phthalic Anhydride (13). A sample of 3-(4-methylphenoxy)-*N*-phenylphthalimide was prepared from 3-nitro-*N*-phenylphthalimide and **3**.[1] A mixture of 200 mL of ethylene glycol, 40 mL of 25% aqueous NaOH, and 19.74 g of 3-(4-methylphenoxy)*N*-phenylphthalimide was heated at reflux (135 °C in solution) for 18 h and then added to 2000 mL of 1 N HCl with stirring and cooling. The precipitated solid was filtered, washed with 0.1 N HCl, then with water, and dried in vacuo at 60 °C. The yield of 3-(4-methylphenoxy)phthalic acid was 15.61 g (96%): ^{1}H NMR (Me_2SO-d_6) δ 2.30 (methyl, s, 3), 6.7–7.7 (aryl, m, 7), 9.2 (–COOH, br s, 2); IR (KBr) C=O 1688, (s) 1708 (s), OH 2900 cm^- (br); ^{13}C NMR will appear in a subsequent publication.[6] A mixture of 54.4 g of this diacid, 300 mL of acetic acid, and 40.8 g of acetic anhydride was heated at reflux for 2 h and then all solvent was removed in vacuo. The residue, after being recrystallized from cyclohexane, gave 39.6 g (78%) of **13**: mp 117–118 °C; ^{1}H NMR ($CDCl_3$) δ 2.33 (methyl, s, 3), 6.7–7.7 (aryl, m, 7); IR (KBr) C=O 1782 (vs), 1840 cm^{-1} (s); ^{13}C NMR was in accord with the assigned structure;[6] UV (Et_2O) λ_{max} 229 (ε 20 800), 333 mμ (ε 5200), $\lambda_{shoulder}$ 324 mμ (ε 4900).

Anal. Calcd for $C_{15}H_{10}O_4$: C, 70.9; H, 3.9; mol wt 254. Found: C, 70.8; H, 4.1; mol wt 254 (mass spectrum).

Dimethyl 3-(4-Methylphenoxy)phthalate (7a). A mixture of 1.00 g of 3-(4-methylphenoxy)phthalic acid, 1.02 g of potassium carbonate, 0.93 g of dimethyl sulfate, 1 mL of 10% methanolic potassium hydroxide, and 20 mL of acetone was heated at reflux under a nitrogen atmosphere for 6 h. The mixture was cooled to 25 °C and the salts were removed by filtration. These salts were washed thoroughly with acetone and the combined acetone filtrates were added to water and extracted well with chloroform. The chloroform extracts were washed with 5% sodium bicarbonate and water and dried over anhydrous magnesium carbonate. The solution was concentrated to give 0.75 g (68% yield) of **7a** as an oil. The structure of the compound was established by its ^{1}H and ^{13}C NMR spectra: ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3), 3.83 (s, 6), 7.25 (m, 7); see supplementary material (Table V) for ^{13}C NMR data.

Anal. Calcd for $C_{17}H_{16}O_5$: C, 68.0; H, 5.4; mol wt 300. Found: C, 68.3; H, 5.5; mol wt 300 (mass spectrum).

Diethyl 3-(4-Methylphenoxy)phthalate (7b). A solution containing 11.0 g (0.043 mol) of 3-(4-methylphenoxy)phthalic anhydride (**13**), 20 mL (15.8 g, 0.34 mole) of ethanol, and 1.0 g of *p*-toluenesulfonic acid hydrate in 180 mL of xylene was treated as has been described for the esterification of the nitro anhydrides. In this manner, the product **7b** was obtained as an oil, 13.98 g (99%); ^{1}H NMR ($CDCl_3$) δ 1.26 and 1.33 (ester methyls, both triplets, $J \simeq 7$ Hz, 6), 2.30 (aromatic methyl, s, 3), 4.33 (ester methylenes, q, $J \simeq 7$ Hz, 4), 6.70–7.80 (aromatic, m, 7); see supplementary material (Table V) for ^{13}C NMR data.

Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14; mol wt 328. Found: C, 69.5; H, 6.4; mol wt 328 (mass spectrum).

The following ester was prepared by a method analogous to the preparation of **7b** above.

Diisopropyl 3-(4-Methylphenoxy)phthalate (7c). ^{1}H NMR ($CDCl_3$) δ 1.31 and 1.37 (ester methyls, doublets $J \simeq 6$ Hz, 12), 2.30 (aromatic methyl, s, 3), 5.23 and 5.28 (ester methines, septets, $J \simeq$ Hz, 2), 6.74–7.80 (aromatic, m, 7); ^{13}C NMR, see supplementary material (Table V).

Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79; mol wt 356. Found: C, 70.5; H, 7.0; mol wt 356 (mass spectrum).

Preparation of Alkyl m-Nitrobenzoates (11). A mixture of *m*-nitrobenzoyl chloride, the anhydrous alcohol of choice, and dried pyridine was stirred under nitrogen for 16 h. The cooled mixture was added to 1.2 N hydrochloric acid and the solid was collected and dried. The ^{13}C NMR data for the compound are in the supplementary material.

11a: 86% yield; mp 78–80 °C (lit. 78 °C);[13] ^{1}H NMR ($CDCl_3$) δ 4.05 (methyl, s, 3); by using *o*-nitrobenzoyl chloride, a sample of methyl *o*-nitrobenzoate was prepared and shown to separate from the meta isomer by VPC analysis.

11b: 66% yield, mp 40–41 °C (lit. 41 °C);[13] IR ($CHCl_3$) carbonyl at 1715, nitro bands 1525 and 1350 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (methyl, t, 3), 4.22 (methylene, q, 2).

11c: 60% yield, oil; ^{1}H NMR ($CDCl_3$) δ 1.40 (methyl, d, 6), 5.25

(methine, septet, 1), 7.60 (aromatics, t, 1), 8.33 (aromatic, m, 2), 8.75 (aromatic, m, 1).

Preparation of Alkyl 4-Methylphenyl Ethers (9). A mixture of the appropriate alkyl iodide, **3**, and THF was refluxed under nitrogen fro 16 h. The mixture was then cooled, filtered, and added to water. The aqueous solution was extracted with ether and the ether extracts were washed and dried to give the crude product. ^{13}C NMR data for the compounds are in the Supplementary Material.

9b: 81% yield; bp 140 °C (15 Torr); ^1H NMR ($CDCl_3$) δ 1.35 (t, 3), 2.13 (s, 3), 3.95 (q, 2), and an A_2B_2 aryl region centered at 6.90 (m, 4).

9c: 76% yield; ^1H NMR ($CDCl_3$) δ 1.30 (d, 6), 2.25 (s, 3), 4.45 (septet, 1), 6.90 (center of A_2B_2 aromatic, 4).

Acknowledgments. We would like to thank Dr. E. A. Williams and J. D. Cargioli for their assistance in obtaining and interpreting the ^{13}C spectra, which have been of great value to us in much of this study.

Registry No.—**3**, 1121-70-6; **6a**, 63181-68-0; **6b**, 63181-69-1; **6c**, 63181-70-4; **6d**, 63181-71-5; **7a**, 63181-72-6; **7b**, 63215-75-8; **7c**, 63181-73-7; **7d**, 63181-74-8; 8, 106-44-5; **9b**, 622-60-6; **9c**, 22921-10-4; **9d**, 33426-69-6; **10**, 119-33-5; **11a**, 618-95-1; **11b**, 618-98-4; **11c**, 6268-23-1; **13**, 63181-77-1; **14d**, 63181-78-2; **16a**, 32136-52-0; sodium nitrite, 7632-00-0; 3-nitrophthalic anhydride, 641-70-3; 4-nitrophthalic anhydride, 5466-84-2; 3-(4-methylphenoxy)-*N*-phenylphthalimide, 63181-79-3; 3-(4-methylphenoxy)phthalic acid, 63181-80-6.

Supplementary Material Available: A discussion of the ^1H and ^{13}C NMR data as well as the ^{13}C NMR assignments for **4**–**11** and **14d** (Tables IV–VI) (9 pages). Ordering information is given on any current masthead page.

References and Notes

(1) F. J. Williams and P. E. Donahue, *J. Org. Chem.*, this issue, companion paper.
(2) Related preliminary work was carried out in our laboratories: see D. R. Heath and J. G. Wirth, U.S. Patent 3 787 475 (1974).
(3) See J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273, 312 (1951), and references cited therein.
(4) D. R. Heath and J. G. Wirth, U.S. Patent 3 763 210 (1973).
(5) J. R. Beck, *J. Org. Chem.*, **38**, 4086 (1973); N. Kornblum et al., *ibid.*, **41**, 1560 (1976).
(6) F. J. Williams, H. M. Relies, P. E. Donahue, and J. S. Manello; *J. Org. Chem.*, this issue, companion paper.
(7) J. F. Bunnett, M. M. Robinson, and F. C. Pennington, *J. Am. Chem. Soc.*, **72**, 2378 (1950).
(8) For a discussion of the $B_{AL}2$ mechanism for ester hydrolysis, see E. S. Gould, "Mechanism and Structure in Organic Chemistry", Holt, Rinehart, and Winston, New York, N.Y., 1959, p 342.
(9) See, for example, R. A. Sneen and A. M. Rosenberg, *J. Org. Chem.*, **26**, 2099 (1961); E. W. Wadsworth and T. I. Crowell, *Tetrahedron Lett.*, **13**, 1085 (1970); E. W. Thomas and T. I. Crowell, *J. Org. Chem.*, **37**, 744 (1972); E. E. Smissman, M. D. Corbeth, S. El-Antably, and K. C. Kroboth, *ibid.*, **37**, 3944 (1972), and references contained therein. For a discussion of the reaction of sodium phenoxide with methyl trichloroacetate to give anisole, see A. C. Pierce and M. M. Joullie, *ibid.*, **27**, 3968 (1962).
(10) We have found that ether formation also takes place in the reaction of sodium phenoxide with diethyl phthalate and ethyl *m*-nitrobenzoate. These and other studies of this type of reaction will be presented in a separate communication.
(11) L. J. Bellamy, "The Infrared Spectra of Complex Molecules", Wiley, London, 1962, p 179.
(12) D. Twiss and R. V. Heinzelmann, *J. Org. Chem.*, **15**, 496 (1950).
(13) "Dictionary of Organic Compounds", 4th ed, Oxford University Press, New York, N.Y., 1965.
(14) E. V. Kuynetsov and A. P. Bogdanov, *T. Kazan. Khim-Tekhnol. Inst.*, **No. 26**, 78 (1959).
(15) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, New York, N.Y., 1959, p 85.
(16) (a) G. L. Nelson, G. C. Levy, and J. D. Cargioli, *J. Am. Chem. Soc.*, **94**, 3089 (1972); (b) K. N. Scott, *ibid.*, **94**, 8564 (1972).

A Direct Synthesis of Phenoxy-Substituted Phthalic Anhydrides by Aromatic Nucleophilic Displacement

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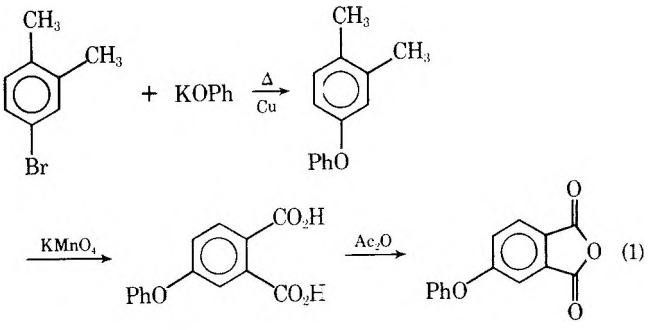
Received November 29, 1976

Phenoxides react with nitro-, fluoro-, or chloro-substituted phthalic anhydrides to give phenoxy-substituted phthalic anhydrides. The success of the reaction was dependent upon the reaction conditions employed and the identity of the leaving group (F > Cl > NO_2). All three systems suffered from the reaction of the anhydride linkage with solvent (DMF) at higher temperature, and the nitro system was further complicated by reaction of the anhydride linkage with the sodium nitrite by-product. Using the fluoro system, yields of >85% were obtained for the phenoxyphthalic anhydrides.

As part of our continuing effort to understand the reaction of phenoxides with derivatives of nitro-substituted phthalic acids, we investigated the activating effect of the anhydride linkage in phthalic anhydrides. Previous results have shown that phenoxides react with nitro- and halo-substituted phthalimides,[1] nitro-substituted phthalonitriles,[2] and nitro-substituted phthalate esters.[3] The successful reaction of phenoxides with anhydride derivatives would give phenoxy-substituted phthalic anhydrides and would constitute a considerable improvement over existing syntheses (see eq 1 for an example[4]).

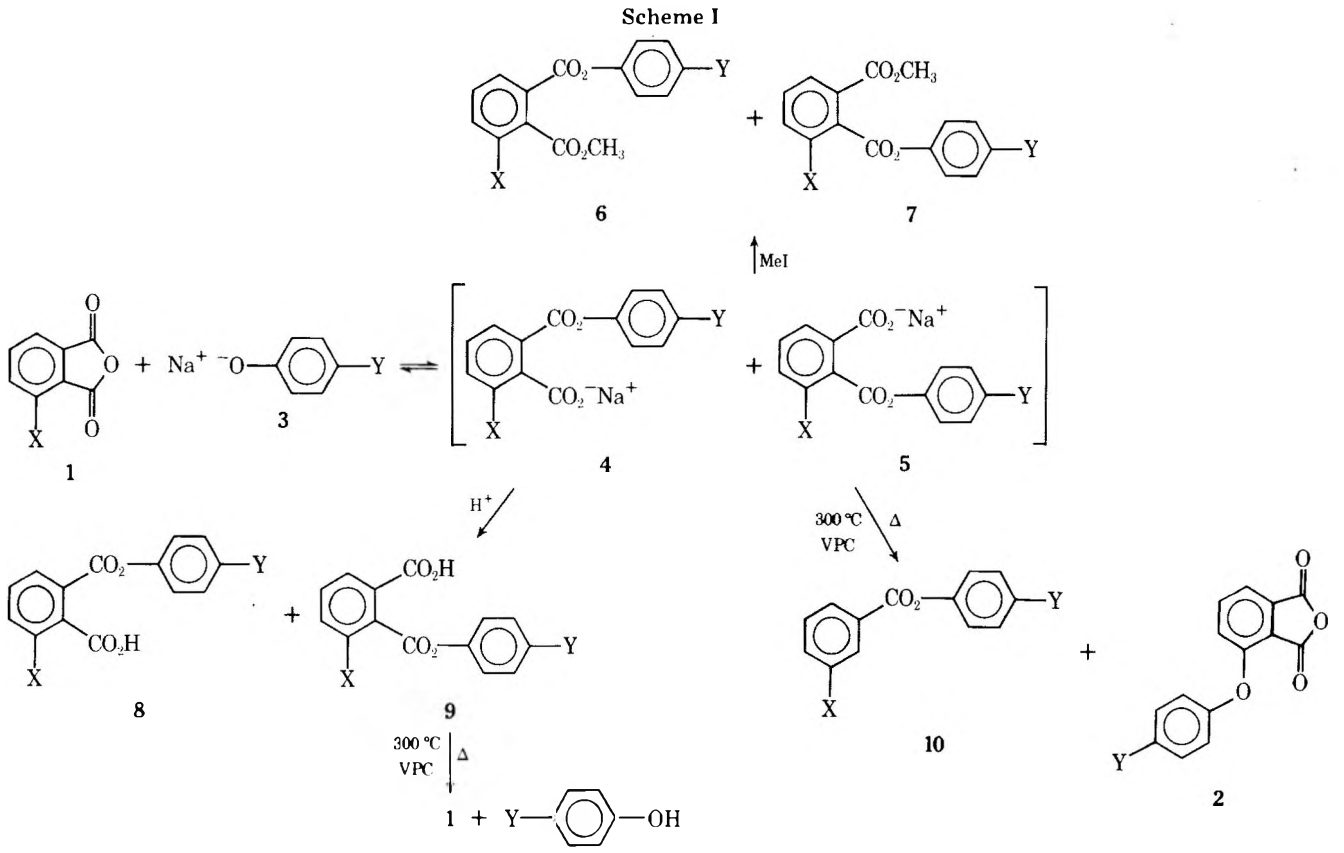


(1)

Results and Discussion

Reaction of Nitrophthalic Anhydrides. Reaction of 3-nitrophthalic anhydride (**1a**) with sodium phenoxide (Scheme I; X = NO_2, Y = H) in DMF at 25 °C produced a mixture of ring-opened acid ester salts **4** and **5** and *no* product (**2**) from nitro displacement. If, after 0.5 h at 25 °C, an equivalent amount of methyl iodide was added to the reaction mixture, the only products formed were the diesters **6** (21%) and **7** (79%) in excellent yield.[5] There was no trace of starting anhydride **1a** or displacement product **2a**. Therefore, in DMF at 25 °C, sodium phenoxide exclusively attacked the carbonyl carbons and, preferentially, the carbonyl α to the nitro group. In addition, because of the total absence of starting material, one can conclude that *if* there was an equilibrium between **1a**/**3** and **4**/**5** at room temperature, it was far to the right in favor of **4** and **5**.

Scheme I



When a reaction mixture containing **4** and **5** was acidified, the mixture of acid esters **8** and **9** was produced. However, VPC analysis of this mixture showed only starting anhydride **1a** and phenol, both of which were apparently formed from ring closure of **8** and **9** in the injection port of the VPC (300 °C). if, however, the initial homogeneous mixture of **4** and **5** in DMF was injected directly into the VPC injection port, then only **2a** and **10** were formed. There was no trace of starting anhydride **1a** or the other possible decarboxylation product phenyl *o*-nitrobenzoate (**11**) observed. Under these conditions, production of **2a** probably resulted from the displacement of the nitro group in **1a** by sodium phenoxide; both of these reagents could have been generated by the thermal ring closing of **4** and **5**.

Compounds **4** and **5** could also be generated by an alternate route. When a sample of the DMF reaction mixture, in which **6** and **7** were produced using CH_3I, was placed directly into the VPC injection port, not only **6** and **7** but also **2a** and **10** were observed. Since it had previously been found that only **6** and **7** were present in a workup involving a methylene chloride extraction of an identical DMF reaction mixture which had been diluted with aqueous HCl, products **2a** and **10** could not have orginated from unreacted salts **4** and **5** in the present example. Instead, we believe these salts were regenerated in the VPC by reaction of sodium iodide with the methyl group of each ester, **6** and **7**, to generate methyl iodide. These salts, **4** and **5**, then decomposed as previously described to give **2a** and **10**. When, in fact, a mixture of authentic samples of **6** and **7** and an equivalent amount of sodium iodide in anhydrous DMF was injected directly into the VPC, **6**, **7**, **2a**, and **10** were all observed. However, if this mixture was added to 1.2 N HCl, then extracted with methylene chloride, and these organic extracts were subjected to VPC analysis, only **6** and **7** were observed.

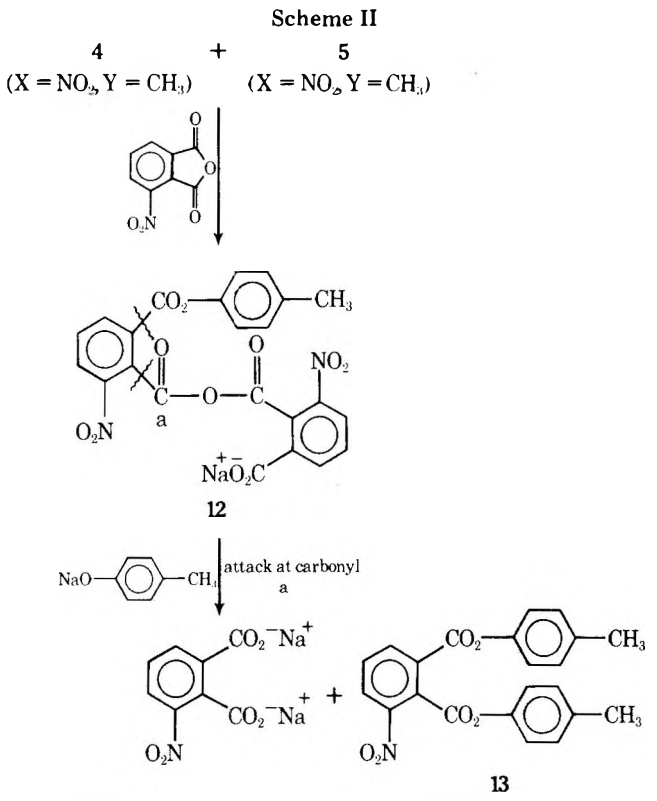
It is interesting to note that only the meta isomer **10** was formed from the decarboxylation of the mixture of **4** and **5** both during VPC analysis and at elevated temperature in solution. If the mixed ester **6** was stirred with an equivalent amount of sodium iodide in DMF and then injected directly into the VPC, ester **10** was formed as expected. However, when the experiment was repeated using pure **7**, instead of forming the ortho isomer **11**, only ester **10** was formed. Since the reaction of **7** with sodium iodide at 300 °C should have produced only **5** and no **4**, formation of **10** must have come about from the rearrangement of **5** to **4**. In both cases the yield of decarboxylated product was very low (17–18%), indicating perhaps that the decarboxylation process was not very efficient.[6] In addition, when a mixture of 80% of **9** and 20% of **8** was heated in quinoline with a copper catalyst, a 40% yield of only **10** was produced. This again indicated that a conversion between the salts (or the starting acids) could take place. These results are in agreement with reported literature findings for somewhat similar systems.[8,9]

The fact that **2a** was produced during VPC analysis suggested that the displacement reaction be tried in solution at elevated temperatures. Reaction of sodium phenoxide with **1a** in DMF at temperatures between 80 and 150 °C produced low yields of both **2a** and **10** as well as major amounts of salts **4** and **5**. Although this approach did produce **2a**, the yield was such (5–10%) that the reaction is of little synthetic value. In addition, at these higher temperatures, two other factors complicated the results: (1) reaction of the anhydride linkage with solvent; and (2) reaction of the anhydride linkage with sodium nitrite (vide infra).

The reaction of **1a** with sodium 4-methylphenoxide at room temperature gave very similar results to those described above, except the amount of attack by the nucleophile at the carbonyl α to the nitro group was slightly larger (84% vs. 79%). Repeating the reaction at 78 °C gave **2** (Y = CH_3) and **10** (Y = CH_3) as well as a new product **13**. This diester could result from initial formation of the intermediate **12**, followed by attack of the phenoxide at carbonyl a to give **13** (Scheme II).

Reaction of 4-nitrophthalic anhydride (**14a**) with sodium phenoxide in DMF at 25 °C gave the salts **15** and **16** (see Scheme III; X = NO_2, Y = H). When a homogeneous mixture of **15** and **16** was placed into the 300 °C injection port of a VPC, considerable amounts of starting material **14** were ob-

Scheme II



served. This suggests that ring closure of the salts in the 4 system may be considerably more favorable than closure in the 3 system (or the escape of 4-nitrophthalic anhydride from the reaction zone in which it was produced was more efficient). In addition, the amount of decarboxylated product, **19**,[10] was much smaller in this system. Methylation of the salts with methyl iodide produced the esters **17** and **18**. The isomers could not be separated on VPC columns, but ^{13}C NMR analysis indicated that two isomers were present in the approximate ratio of 56% (**17**) to 44% (**18**).[11] When the reaction was carried out at 150 °C, two unidentified minor products and a 17% yield of **20** were obtained.

While attempting to improve the yields of the ether products (**2** + **20**) in these reactions, a side reaction was discovered which was highly detrimental to the success of the nitro displacement. It was found that the nitrite ion produced from the displacement rapidly reacts with the anhydride linkage of the phthalic anhydride derivative to produce the corresponding phthalate salts.[12] Since this nitrite/anhydride reaction destroys the activating anhydride function of the starting materials (**1** and **14**), it interferes with the direct formation of phenoxyphthalic anhydrides by nitro displacement. We therefore became interested in the displacement of other leaving groups.

Reactions of Fluoro- and Chlorophthalic Anhydrides. Reaction of 3-fluorophthalic anhydride (**1b**) with sodium phenoxide in DMF at 25 °C gave the salts **4** and **5** (Scheme I; X = F, Y = H). Reaction of these salts with methyl iodide produced the diesters **7** and **6** in the ratio of 74:26, respectively.[13] The major isomer was assigned on the basis of its ^{13}C NMR and by analogy to the 3-nitro system. If, however, a homogeneous solution of **4** and **5** in DMF was injected into a VPC injection port at 300 °C, no decarboxylation product, **10**, was seen and starting material **1b** was regenerated quite efficiently. This suggested that if the reaction were carried out at a higher temperature, an equilibrium between **1c/3** and **4/5** could be established and displacement of the fluoro group could take place to give **2a**.

When a mixture of sodium phenoxide, **1b**, and DMF was heated in a 150 °C oil bath for 30 min, approximately an 85% yield (by VPC) of **2a** was formed. This reaction produced sodium fluoride which, unlike sodium nitrite, appeared to be inert under these reaction conditions. Unfortunately, at these higher temperatures, we found that the solvent, DMF, underwent a reaction with both **1b** and **2a** which slowly destroyed these materials. These results, which are contained in Table I, show that **1b** was much more susceptible to this reaction than **2a**. Although we know the reaction involves ring opening of the anhydride linkage, the resulting products have not yet been identified. However, a 1.2 N HCl workup was used in our control studies and the new product (or the intermediate leading to it) was not hydrolyzed back to the corresponding phthalic acid under these conditions. We are currently attempting to identify these products and determine if the corresponding dimethylamide derivatives are formed.[14] When the reaction between sodium phenoxide and **1b** was repeated in DMF at 150 °C for 20 min, an 87% yield of pure **2a** was isolated by direct precipitation of the reaction mixture into acidic water. This product, **2a**, was not contaminated with any of the corresponding diacid which could have formed from hydrolysis during workup.

Several ether derivatives were synthesized by fluoro dis-

Scheme III

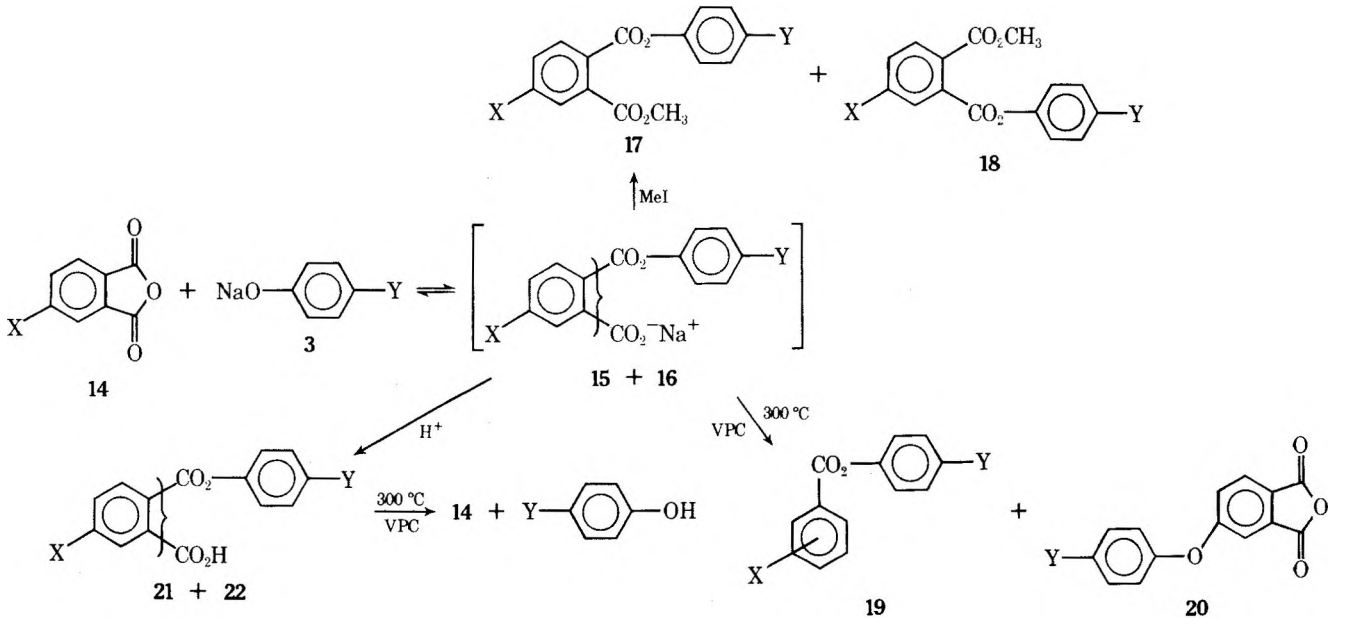
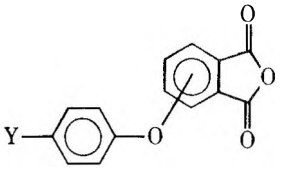


Table I. Destruction of Phthalic Anhydrides by DMF at Reflux

Reaction time, h	% destruction 1b	1c	2a
1	29	50	11
3	47	75	17
5	62	85	24
7	67	91	27
24	92	100	48

Table II. Synthesis of I by Fluoro Displacement



I

Compd (isomer)	Y	Yield, % (VPC)
2a (3)	H	85–95
2b (3)	CH_3	88–92
2c (3)	Cl	80–85
2d (3)	OCH_3	65–75
20b (4)	CH_3	85

placement (Table II). As can be seen from these results, use of this route allowed the synthesis of derivatives such as **2b** and **20b** containing groups which would be oxidized in conventional methods.[4]

Reaction of 3-chlorophthalic anhydride (**1c**) with sodium phenoxide in DMF at 25 °C, as in the fluoro and nitro cases, produced the mixture of salts, **5** and **4**, which upon methylation gave an 85:15 mixture of **7**/**6**[15] (Scheme I; X = Cl, Y = H). The isomer assignments were made again on the basis of the ^{13}C NMR data and by analogy to the nitro system. When the reaction was repeated at 150 °C for 5 h, the desired product, **2a**, was produced in 44% yield. The formation of **2a** by chloro displacement occurred more slowly and in lower yield than by fluoro displacement. However, under these reaction conditions, 24% of the product **2a** would have been destroyed by reaction with DMF (raising the possible yield of **2a** to 68%) and the remainder of unreacted **1c** (theoretically 32%) would have been completely destroyed by solvent reaction (see Table I). This argument is substantiated by the fact that we have isolated sodium chloride in yields of up to 73% of the theoretical amount. Production of sodium chloride from a route other than by the phenoxide displacement of the chloro group seems unlikely.

Attempts were made to find a solvent system in which **1c** and **2a** would not be destroyed, but in which displacement would occur. However, none of the solvents tried (DMAC, sulfolane, Me_2SO, HMPA, *N*-methylpyrrolidone, o-dichlorobenzene, acetonitrile, dimethyl sulfone, nitrobenzene, tributylamine, propylene carbonate, or a neat reaction) gave results as good as those in DMF. The use of potassium or lithium phenoxide did not increase the yield of **2a**.

Finally, the reaction of 4-chlorophthalic anhydride (**14c**) and sodium phenoxide was investigated. Reaction of **14** at 150 °C in DMF for 6 h resulted in a 33% yield of **20a** (Scheme III; X = Cl, Y = H). Since the 4 isomers are generally less reactive toward displacement than the 3 isomers in these systems,[1] it was not surprising to obtain this lower yield, since more of anhydride **14c** would have been destroyed by side reaction with DMF.

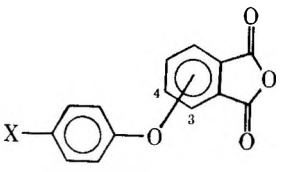
In conclusion, we found that the reaction between phenoxides and nitro-, chloro-, or fluorophthalic anhydrides was very dependent upon the reaction conditions employed and the leaving group. In all three systems, reaction with sodium phenoxide at room temperature resulted in opening of the anhydride ring to produce a mixture of acid ester salts (**4** and **5** for the 3 isomers, **15** and **16** for the 4 isomers). Upon heating of the reaction mixture, these salts either decarboxylated (X = NO_2) or ring closed to varying degrees (X = F, Cl > NO_2) to regenerate starting material. The starting material then underwent displacement with phenoxide to give the phenoxy ether derivative with varied success (F > Cl > NO_2). Using the fluoro system, yields of >85% were obtained for a variety of ether derivatives. All three systems suffered from the reaction of the anhydride linkage with solvent (DMF) at higher temperatures and the nitro system was further complicated by reaction of the anhydride linkages with the sodium nitrite by-product.

We are currently continuing our studies of the reactions of nucleophiles with nitro and halo phthalic acid derivatives in an attempt to better understand the role of the nitro group in such displacements.

Experimental Section

All ^1H NMR spectra were recorded with a Varian Associates T-60 NMR spectrometer using tetramethylsilane as an internal standard and deuteriochloroform or Me_2SO-d_6 as a solvent. Infrared spectra were taken on a Perkin-Elmer 457 grating infrared spectrophotometer in chloroform solution or as a KBr pellet. Mass spectra were deter-

Table III. Aryloxy-Substituted Phthalic Anhydride Derivatives[a]



Registry no.	Compd	X	Position of attachment	Mp, °C (solvent)	*m/e*
54738-86-2	**2a**	H	3	106–108 (hexane)	240
63181-77-1	**2b**	CH_3	3	117–118 (cyclohexane)	254
63196-07-6	**2c**	Cl	3	163–164 (benzene/hexane)	274[b]
63196-08-7	**2d**	OCH_3	3	108.5–109 (benzene/cyclohexane)	270
21345-01-7	**20a**	H	4	112–113 (hexane) (lit. 114–116)[4]	240
63196-09-8	**20b**	CH_3	4	89.5–90 (hexane)	254
63196-10-1	**20c**	Cl	4	118–118.5 (benzene)	274[b]
63196-11-2	**20d**	OCH_3	4	106–107.5 (benzene/cyclohexane)	270

[a] Satisfactory analytical data (±0.4% for C, H) were reported for all the compounds listed in the table. [b] One-chlorine molecular-ion cluster.

mined on a CEC 21-104 analytical mass spectrometer at 70 eV. Vapor-phase chromatography (VPC) was carried out on a Hewlett Packard 5750 research chromatograph using a 6 ft 10% UC-W98 on 80/100 Chromosorb W column with temperature programming between 150 and 250 °C at 10°/min, unless otherwise indicated. The injection port and detector were at 300 °C. Melting points were determined on a Thomas-Hoover instrument and are uncorrected.

The *N,N*-dimethylformamide (DMF) was either distilled from CaH_2 or purchased in the anhydrous state from Burdick and Jackson Laboratories. All other solvents were dried by standard methods and distilled prior to their use.

VPC yields were calculated as follows. In a typical run equivalent amounts of phenoxide and phthalic anhydride derivatives were mixed with an internal standard (o-terphenyl) in a given solvent (10 mL/g of anhydride) and the solution was heated under nitrogen. Aliquots were removed and added to a mixture of 1.2 N hydrochloric acid and chloroform. The mixture was shaken well, the layers were separated, and the chloroform solution was dried over anhydrous magnesium sulfate. The chloroform solution was subjected to VPC analysis and the yield was calculated from the relative peak areas of standard and product after correcting for detector response differences. Values for the peak areas were obtained by weighing Xeroxed copies of the peak traces.

The starting phthalic anhydride derivatives (**1** and **14**) were obtained as described previously.[1] The ^{13}C NMR spectra of these materials were obtained and are tabulated in the supplementary material (Table VI).

Preparation of Sodium Phenoxides. The sodium salts of the different phenol derivatives used in this study were prepared from the reaction of freshly prepared sodium methoxide in methanol with the desired phenol derivative.[1] The resulting salts were thoroughly dried and then were stored in a drybox under nitrogen. All salts were weighed in the drybox to avoid contact with oxygen and moisture.

Potassium Phenoxide. Potassium phenoxide was prepared from phenol and potassium *tert*-butoxide in a dimethylformamide/toluene mixture. The toluene and *tert*-butyl alcohol were removed by distillation.

Lithium Phenoxide. Lithium phenoxide was prepared from phenol and *n*-butyllithium in a mixture of benzene and hexane. Dimethylformamide was added and the hexane and benzene were removed by distillation.

Reaction of 3-Nitrophthalic Anhydride (1a) with Sodium Phenoxide. A. Room Temperature. A mixture of 12.46 g of sodium phenoxide, 28.74 g of **1a**, and 100 mL of anhydrous DMF was stirred at 25 °C under nitrogen. A dark orange color was initially present, but it quickly faded and a light yellow homogeneous solution was obtained. Analysis of this mixture by ^{13}C NMR indicated the absence of **1a**, displacement product **2a**, and decarboxylated material **10**, and the presence of two acid ester salts **4** and **5**.

If this homogeneous solution was injected directly into the VPC, two products were obtained. Collection of these materials by preparative VPC gave samples which were identified as **2a** and **10** by comparison to authentic samples (synthesis of these materials is described below).

An aliquot from this reaction mixture was added to a 1.2 N HCl solution and this mixture was extracted thoroughly with methylene chloride. The methylene chloride solution was dried and subjected to VPC analysis. This analysis showed only peaks corresponding to **1a** and phenol.

Another aliquot was removed from the reaction mixture and added to 1.2 N HCl, and this time the resulting precipitate was collected and dried to give a mixture of acid esters, **8** and **9**, in 88% yield. The assignment of structure was based on the ^{13}C NMR of this mixture, which also showed that no **1a**, **2a**, or **10** was present.

B. Room Temperature with Methyl Iodide. In order to determine the ratio of **4** to **5** (and **8** to **9**), the following experiment was carried out. A mixture of 1.989 g of sodium phenoxide, 3.31 g of **1a**, and 33 mL of DMF was stirred at 25 °C under nitrogen. After 30 min, 4.88 g of methyl iodide (2 equiv) was added and the clear yellow solution turned orange in color. This mixture was stirred for 2 h at 25 °C and then an aliquot was removed and added to a 1.2 N HCl solution and the entire mixture was extracted well with methylene chloride. The methylene chloride mixture was subjected to VPC analysis. This showed only a mixture consisting of 21% of **6** and 79% of **7**. The remainder of the reaction mixture was poured into 1.2 N HCl and the resulting precipitate was collected by filtration and dried to give 4.40 g (85%) of a mixture of esters **6** and **7**. The isomers were separated by preparative VPC and identified by comparison to authentic samples. The ^{13}C NMR spectrum (in Me_2SO-d_6) of the isolated mixture displayed all of the peaks for the major isomer (**7**) and all of the peaks of the protonated carbons of the minor isomer (**6**). Also, this ^{13}C NMR spectrum indicated that the mixture consisted of 23% of **6** and 77% of **7**.

C. Reaction at Elevated Temperature. In a typical run 1.16 g of sodium phenoxide, 1.93 g of **1a**, and 1.00 g of *o*-terphenyl (internal VPC standard) were heated at 150 °C in 20 mL of anhydrous DMF under a nitrogen atmosphere. Aliquots were removed at timed intervals (5 min to 16 h) from this dark black mixture and were worked up as described above. Analysis showed **2a** (5–10%), **10** (<5%), and a longer retention time material thought to be the product analogous to **13**. Other runs were made at temperatures between 80 and 150 °C and showed very little nitro displacement.

Reaction of Sodium 4-Methylphenoxide with 3-Nitrophthalic Anhydride.[16] A. At Room Temperature. Exactly 1.05 g (0.00808 mol) of sodium 4-methylphenoxide and 1.56 g (0.00808 mol) of **1a** were dissolved in 20 mL of DMF. A slight exotherm was noted initially. The ^{13}C NMR spectrum of the resulting solution was recorded and indicated that two acid/ester salts, **4** and **5**, had been produced. By analogy with the previous experiments with sodium phenoxide, it was assumed that the major isomer was **5**. An estimate (^{13}C NMR) for the ratio of isomers observed was 87 to 13. When the mixture of salts was converted to the corresponding methyl phenyl esters as has been previously described, then VPC analysis indicated an 84 to 16 ratio of products.[17]

The above reaction was repeated at 78 °C for 65 h to give upon workup and isolation 6% of **2b**, 1% of **10b**, and 6.5% of **13**. Products **2b** and **10b** were identified by comparison to authentic samples. The product **13** was identified from its mass spectrum (*m/e* 391) and ^{13}C NMR (see supplementary material).

Reaction of 4-Nitrophthalic Anhydride (14a) with Sodium Phenoxide. A. At Room Temperature. A mixture of 5.80 g of **14a** and 3.86 g of sodium phenoxide was stirred in 60 mL of DMF at room temperature under nitrogen for 0.5 h. Direct injection of this homogeneous reaction mixture into the VPC allowed the isolation of a small amount of the desired displacement product **20a**. In addition, a small amount of **19** contaminated with **20a** was collected. This material had identical retention time with both *m*- and *p*-nitrophenyl benzoate, which could not be separated under these conditions. Infrared analysis of this mixture (**19** and **20a**) showed the presence of a nitro group (1530 cm^{-1}) and an ester carbonyl (1745 cm^{-1}). The amount of **19** formed was much smaller than for the decarboxylation of the corresponding 3 isomer.

If the homogeneous reaction mixture was first added to a 1.2 N HCl solution, this mixture was extracted with ether, and the ether extracts were dried, then subjected to VPC analysis, no trace of **19** or **20a** was seen. However, there was a peak corresponding to starting material **14a**.

B. At Room Temperature with Methyl Iodide. The above reaction was repeated, except that after 4 h of stirring, 2 equiv of methyl idodide were added. The entire mixture was stirred for an additional 4 h. The mixture was worked up with 1.2 N $HCl/CHCl_3$ as described previously to give an 87% yield of **17** and **18**. VPC analysis showed only one peak for this mixture. However, ^{13}C NMR showed that two products were present in the ratio of 56:44. The major isomer has tentatively been assigned structure **17** for electronic reasons similar to those used as rationale for the observed product distribution in the 3 system.

C. At Elevated Temperature. A mixture of 5.80 g of **14a**, 3.86 g of sodium phenoxide, 2.50 g of *o*-terphenyl (internal standard), and 60 mL of DMF was stirred at room temperature under nitrogen. The mixture was quickly placed in an oil bath at 170 °C and aliquots were removed at timed intervals between 0.5 and 16 h. These aliquots were worked up with 1.2 N HCl/CH_2Cl_2 as described previously. VPC analysis indicated the maximum yield of desired product **20a** was 17% after 16 h. There was no trace of decarboxylated product(s) **19**.

Reaction of 3-Fluorophthalic Anhydride (1b) with Sodium Phenoxide. A. At Room Temperature. These reactions were run exactly as has been described for the nitro system.

B. At Elevated Temperatures. A mixture of 1.18 g of sodium phenoxide, 1.69 g of **1b**, and 22 mL of anhydrous DMF was heated at a bath temperature of 170 °C under nitrogen. The solution became homogeneous almost immediately, turned cloudy yellow, and after ca. 10 min turned orange and again became homogeneous. The solution was stirred at reflux for a total of 20 min and after brief cooling, it was added to a mixture of 200 mL of 1.2 N HCl/ice. The resulting white precipitate was removed by filtration and dried to give 2.12 g (87%) of **2a** (mp 102–104 °C). This material was identical in all respects with an authentic sample of **2a**. Analysis by ^{13}C NMR and IR showed no trace of the ring-opened diacid **23**. VPC analysis showed no trace of **1b**.

The reaction was repeated several times using *o*-terphenyl as an internal standard. Yields ranged from 85 to 95%. Typical results at 170 and 125 °C are as follows. 170 °C (time, % **2a**) 15 min, 76; 30 min, 85; 45 min, 84; 60 min, 78; 3 h, 79. 125 °C (time, % **2a**) 1 h, 51; 2 h, 56; 3 h, 60; 5 h, 54; 6.5 h, 47.

Reaction of Other Phenoxides with 1b. The solution salt of the phenoxide derived from *p*-chloro-, *p*-methyl-, and p-methoxyphenols was reacted with **1b** at 150 °C exactly as described above. In all cases, the products were isolated and found to be identical with authentic samples prepared by hydrolysis of the corresponding imide (vide infra). The yields of product were determined from VPC analysis using an alternal standard (*o*-terphenyl) (Table II).

Preparation of Authentic Samples. Phenyl *m*-Nitrobenzoate (10, Y = H; X = NO_2). A mixture of 1.88 g of phenol, 40 mL of pyridine, and 3.71 g of *m*-nitrobenzoyl chloride was stirred at room temperature under nitrogen. The solution was heated at 80 °C for 4 h, cooled to room temperature, and poured into ice water. The resulting white precipitate was collected and stirred vigorously with a 5% sodium carbonate solution. The solution was filtered to give 4.365 g of **10** (98% yield). Recrystallization from absolute ethanol gave a sample with mp 90–92 °C (lit.[18] mp 97 °C).

In a similar fashion phenyl *o*-nitrobenzoate (**11**), mp 50–52 °C (lit.[19] mp 52–53 °C), and phenyl *m*-chlorobenzoate, mp 57–58 °C (lit.[20] mp 53 °C), were prepared. ^{13}C NMR assignments for all three comounds are in the supplementary material.

Phenyl 2-Carbomethoxy-6-nitrobenzoate (7). Compound **7** was synthesized from methyl 2-carboxy-3-nitrobenzoate[21] in two steps. A mixture of 5.0 g of this acid was stirred with 50 mL of anhydrous DMF under a nitrogen atmosphere at room temperature. To this mixture was slowly added 2.82 g of oxalyl chloride and the solution was stirred for 4 h at room temperature. The solution was cooled in ice and 2.58 g of sodium phenoxide was added, and the mixture was gradually allowed to warm to room temperature. The mixture was stirred for 4 h and was then added to a 1.2 N HCl solution. The resulting oil was extracted well with methylene chloride and the methylene chloride solution was washed well with water, a sodium bicarbonate solution, and a saturated sodium chloride solution. After drying over magnesium sulfate, the solution was concentrated to give an oil which upon stirring with ethanol gave the desired product **7** as a white solid, mp 119–121 °C, in 55% yield. VPC analysis of this material showed only a single component having a different retention time from that of **6** (vide infra). The structure was confirmed by the ^{13}C NMR in Me_2SO-d_6. Mass spectral analysis of this material showed *m/e* at 270 (2%) for loss of methoxy and *m/e* at 208 (91%) for loss of phenoxy. There was no parent ion at *m/e* 301. Infrared analysis (KBr) of this sample showed strong absorptions at 1765, 1720, 1050, 980, and 890 cm^{-1}, which were absent in **6**.

Anal. Calcd for $C_{15}H_{11}O_6N$: C, 59.8; H, 3.7; N, 4.6. Found: C, 59.8; H, 3.9; N, 4.7.

Phenyl 2-Carboxymethoxy-3-nitrobenzoate (6). Compound **6** was synthesized from methyl 2-carboxy-6-nitrobenzoate[21] in two steps, exactly as was described for compound **7**. Starting with 9.54 g of methyl 2-carboxy-6-nitrobenzoate, we obtained a 60% yield of **6**, mp 105–107 °C. VPC analysis of this material showed only one compound, which had a different retention time from **7**. The structure was again confirmed by ^{13}C NMR spectroscopy in Me_2SO-d_6. Mass spectral analysis of this material showed *m/e* at 270 (5%), 208 (100%), and no parent ion at *m/e* 301. Infrared analysis (KBr) of this sample showed strong bands at 1745, 1735, 1260, 1070, and 955 cm^{-1} which were not present in **7**.

Anal. Calcd for $C_{15}H_{11}O_6N$: C, 59.8; H, 3.7; N, 4.6. Found: C, 59.9; H, 3.9; N, 4.7.

Synthesis of Phenoxy-Substituted Phthalic Anhydrides by Phthalimide Hydrolysis. The phthalimide derivatives were synthesized exactly as described in ref 1. Hydrolysis of the resulting 3 isomers required either the use of a higher boiling co-solvent or else higher temperatures (130 °C) under pressure. We believe this is due to the formation of a hindered amide acid intermediate from the 3 isomer which is more resistant to further hydrolysis. Higher temperatures could also be used with the 4 isomers to shorten the reaction time. The diacids from the hydrolysis were then ring closed in refluxing acetic acid/acetic anhydride to give the anhydride derivatives (see Table III for physical properties). ^{13}C NMR data for the diacids and dianhydrides are contained in the supplementary material in Tables IV and V. Representative examples for the hydrolysis and ring closures are given below.

3-(4-Methylphenoxy)phthalic Acid (24). To 200 mL of ethylene glycol and 40 mL of 25% aqueous NaOH was added 19.74 g (0.060 mol) of *N*-phenyl-3-(4-methylphenoxy)phthalimide. The system was heated at reflux (135 °C in solution) for 18 h and then added slowly to 2000 mL of 1 N HCl with stirring and cooling. The precipitated solid was filtered, washed with 0.1 N HCl, then with water, and dried in vacuo at 60 °C. The yield of 24 was 15.61 g (96%): ^1H NMR (Me_2SO-d_6) δ 2.30 (methyl, s, 3), 6.7–7.7 (aryl, m, 7), 9.2 (–COOH, br s, 2); IR (KBr) C=O 1688 (s) and 1708 (s), OH 2900 cm^{-1} (br); ^{13}C NMR was in accord with the assigned structure (see Table V).

3-(4-Methylphenoxy)phthalic Anhydride (2b). A solution of 54.5 g (0.20 mol) of **24**, 300 mL of acetic acid, and 40.8 g (0.40 mol) of acetic anhydride was heated at reflux for 2 h and then all solvent was removed in vacuo. The residue, after being recrystallized from cyclohexane, gave 39.6 g (78%) of **2b**: mp 117–118 °C; ^1H NMR ($CDCl_3$) δ 2.33 (methyl, s, 3), 6.7–7.7 (aryl, m, 7); IR (KBr) C=O 1782 (vs), 1840 cm^{-1} (s); ^{13}C NMR was in accord with the assigned structure (see Table IV); UV (Et_2O) λ_{max} 229 (ϵ 20 800), 333 nm (ϵ 5200), $\lambda_{shoulder}$ 324 nm (ϵ 4900).

Anal. Calcd for $C_{15}H_{10}O_4$: C, 70.9; H, 3.9; mol wt 254. Found: C, 70.8; H, 4.1; mol wt 254 (mass spectrum).

4-(4-Methylphenoxy)phthalic Acid (28). A mixture of 19.63 g (0.0596 mol) of *N*-phenyl-4-(4-methylphenoxy)phthalimide, 19.2 g of 50% NaOH, and 400 mL of H_2O was stirred and heated for 3 h at approximately 170 °C in a pressure bomb. The resulting yellow solution was extracted with ether and then acidified with 400 mL of 3 N HCl. The precipitated product was filtered, washed with a little H_2O, and dried in vacuo. In this way 15.53 g (96%) of **28** was obtained: ^1H NMR (Me_2SO-d_6) δ 2.35 (methyl, s, 3), 6.9–7.9 (aryl, m, 7), 10.9 (–COOH, br s, 2); ^{13}C NMR was in accord with the assigned structure (see Table V).

4-(4-Methylphenoxy)phthalic Anhydride (20b). A 13.51-g (0.0497 mol) sample of **28** was refluxed for 3 h with 10.2 g of acetic anhydride and 200 mL of acetic acid. Solvent was removed and the product was recrystallized from hexane to afford 10.87 g (86%) of **20b**: mp 89.5–90.0 °C; ^1H NMR (Me_2SO-d_6) δ 2.38 (methyl, s, 3), 6.9–8.1 (aryl, m, 7); IR ($HCCl_3$) C=O 1774 (s), 1847 cm^{-1} (m); ^{13}C NMR spectrum was in accord with the assigned structure (see Table IV).

Anal. Calcd for $C_{15}H_{10}O_4$: C, 70.9; H, 3.9; mol wt 254. Found: C, 70.9; H, 4.1; mol wt 254 (mass spectrum).

Acknowledgment. We would like to thank Dr. E. A. Williams and J. D. Cargioli for their assistance in obtaining and interpreting the ^{13}C spectra, which have been of great value to us in much of this study.

Registry No.—**1a**, 641-70-3; **1b**, 652-39-1; **1c**, 117-21-5; **5** (X = NO_2, Y = H), 63196-17-8; **5** (X = NO_2, Y = CH_3), 63196-18-9; **6**, 63196-23-6; **7** (X = NO_2, Y = H), 3196-19-0; **7** (X = F, Y + H), 63196-20-3; **7** (X = Cl, Y = H), 63196-21-4; **9** (X = NO_2, Y = H), 63196-22-5; **9** (X = NO_2, Y = CH_3), 63196-23-6; **10**, 1906-43-0; **11**, 31042-59-8; **13**, 63196-25-8; **14a**, 5466-84-2; **146**, 319-03-9; **i4c**, 118-45-6; **17**, 63196-26-9; **18**, 63196-27-0; **23**, 63196-12-3; **24**, 63181-80-6; **25**, 63196-13-4; **26**, 63196-14-5; **27**, 37951-15-8; **28**, 63196-15-6; **29**, 63196-16-7; **30**, 63196-14-5; sodium phenoxide, 139-02-6; sodium 4-methylphenoxide, 1121-70-6; sodium 4-chlorophenol, 1193-00-6; sodium 4-methoxyphenol, 1122-95-8; phenol, 108-95-2; *n*-nitrobenzoyl chloride, 121-90-4; methyl 2-carboxy-3-nitrobenzoate, 6744-85-0; methyl 2-carboxy-6-nitrobenzoate, 6744-85-0; ethylene glycol, 107-21-1; *N*-phenyl-3-(4-methylphenoxy)phthalimide, 63181-79-3; *N*-phenyl-4-(4-methylphenoxy)phthalimide, 63196-28-1; phenyl *n*-chlorobenzoate, 41998-17-8; *o*-nitrobenzoyl chloride, 610-14-0; *m*-chlorobenzoyl chloride, 618-46-2.

Supplementary Material Available. ^{13}C NMR assignments for all starting phthalic anhydrides, phenoxy-substituted phthalic acids, and phthalic anhydrides, and compounds **5**, **6**, **7**, **9**, **10**, **11**, **13**, **17**, and **18** (Tables IV–VII) (6 pages). Ordering information is given on any current masthead page.

References and Notes

(1) F. J. Williams and P. E. Donahue, *J. Org. Chem.*, this issue, companion paper.
(2) D. R. Heath and J. G. Wirth, U.S. Patent 3 787 475 (1974).
(3) F. J. Williams, H. M. Relles, J. S. Manello, and P. E. Donahue, *J. Org. Chem.*, this issue, companion paper.
(4) H. A. Vogel and H. T. Oien, U.S. Patent 3 431 240 (1969). For a similar synthetic approach using 3,4-dimethylphenol and *p*-chloronitrobenzene, see J. D. Seddon, British Patent 1 192 002 (1970).
(5) This ratio was obtained from VPC analysis correcting for detector response difference between the isomers. The ratio of products from ^{13}C NMR analysis was 23:77 (see Experimental Section).
(6) Decarboxylation of **4** would give only the carbanionic precursor of **10**; thus, a proton must have been supplied from some additional source to complete the transformation to **10**. The aldehydic proton of DMF might be such a source under these conditions. Since the *predominant*[7] fate of such a carbanion or one which could be a precursor to **11** is completely obscure,

any statement concerning the decarboxylation of **5** is meaningless at this time, even though none of **11** was observed and one would have predicted a priori that **4** should decarboxylate more readily than **5** (for both electronic and steric reasons).

(7) The amount of **2a** and **10** generated by this treatment corresponded to only a very small amount (20–30%) of the molar quantity of **4** and **5** placed into the VPC instrument.
(8) P. S. Mayuranathan, *J. Chem. Soc.*, 493 (1957).
(9) R. Goncalves and E. V. Brown, *J. Org. Chem.*, **19**, 4 (1954).
(10) We could not determine by VPC if this material was the meta or para isomer or a mixture of both.
(11) These assignments are tentative as they were not confirmed by independent chemical analysis.
(12) R. L. Markezich, O. S. Zamek, P. E. Donahue, and F. J. Williams, *J. Org. Chem.*, this issue, companion paper. We also found that when 2 equiv of sodium nitrite are stirred with **1a** in DMF at room temperature, an immediate reaction began (in the form of violent bubbling and a color change from clear to dark yellow) and a 71% yield of the disodium salt of 3-nitrophthalic acid was obtained.
(13) This ratio was obtained by VPC analysis, ignoring possible detector response differences between the isomers. The ratio of products from ^{13}C analysis was 64:36.
(14) It has been reported in the literature that DMF will react with anhydrides at elevated temperatures to give dimethylamides: see G. M. Coppinger, *J. Am. Chem. Soc.*, **76**, 1372 (1954); H. Schindlbauer, *Monatsh. Chem.*, **99**, 1799 (1968); H. Schindlbauer, *ibid.*, **100**, 1583 (1969); H. Schindlbauer, *ibid.*, **104**, 848 (1973). Preliminary examination by ^{13}C NMR of our reaction mixtures indicated the presence of other new compounds in addition to the dimethylamide derivatives.
(15) This ratio was obtained by VPC analysis, ignoring possible detector response differences between the isomers. The ratio of products from ^{13}C analysis was 74:26.
(16) All vapor-phase chromatographic (VPC) analyses carried out in this section were conducted with a $\frac{1}{8}$ in. × 6 ft 10% SE-30 column programmed from 150 to 290 °C at 10°/min.
(17) These numbers did not take into account possible detector response differences for the isomers.
(18) K. Nakayawa and S. Baba, *J. Pharm. Soc. Jpn.*, **75**, 378 (1955).
(19) R. A. Heacock and D. H. Hey, *J. Chem. Soc.*, 2481 (1954).
(20) "Dictionary of Organic Compounds," 4th ed, Oxford University Press, New York, N.Y., 1965.
(21) G. H. Hurst and M. L. Bender, *J. Am. Chem. Soc.*, **93**, 704 (1971).
(22) For an example of these types of calculations using a substituent parameter approach, see ref 3. For further examples, see: G. L. Nelson, G. C. Levy, and J. D. Cargioli, *J. Am. Chem. Soc.*, **94**, 3089 (1972); K. N. Scott, *ibid.*, **94**, 8564 (1972).
(23) This approach has been used successfully and tested using various pulse delays: see C. K. Sauers and H. M. Relies, *J. Am. Chem. Soc.*, **95**, 7731 (1973).
(24) G. C. Levy, private communication.

Reactions of Fluoride and Nitrite Ions with 4-Nitrophthalimides

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Received November 29, 1976

The reaction of 4-nitro-*N*-methylphthalimide with either fluoro or nitrite salts in an aprotic solvent affords up to a 78% yield of the diaryl ether, 4,4′-oxybis(*N*-methylphthalimide). When potassium fluoride is used in the reaction, 4-fluoro-*N*-methylphthalimide can also be isolated. The reaction of 4-fluoro-*N*-methylphthalimide with potassium nitrite affords the diaryl ether in 75% yield. A possible mechanism for the ether formation is discussed. The intermediate in this mechanism, 4-hydroxy-*N*-methylphthalimide, has been synthesized and shown to react with either 4-fluoro- or 4-nitro-*N*-methylphthalimide to afford the diaryl ether. In the reaction with 4-fluro-*N*-methylphthalimide, potassium fluoride was utilized as a base. Several other minor by-products were identified in the reaction; among them were *N*-methylphthalimide and 4-substituted phthalic acids. When Me_2SO is used as a solvent, 4-thiomethoxy-*N*-methylphthalimide is also formed.

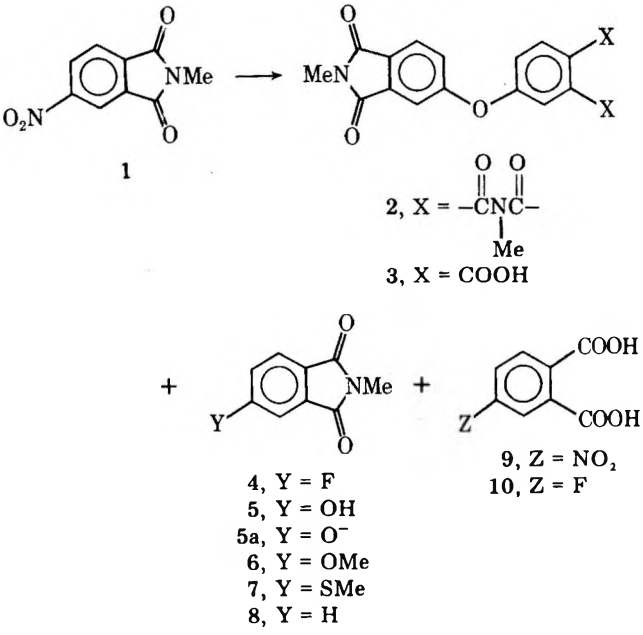
Recently[1] we reported the reaction of potassium fluoride with 4-nitrophthalic anhydride at elevated temperatures, in which a mixture of 4-fluorophthalic anhydride and dipotassium 4-nitrophthalate is produced. Reaction of 4-nitrophthalic anhydride with potassium nitrite produces dipotassium 4-nitrophthalate as the sole product. In this paper we describe the entirely different behavior of 4-nitro-*N*-methylphthalimide (**1**) with potassium fluoride and potassium nitrite.

Heating a solution of 4-nitro-*N*-methylphthalimide (**1**) with potassium fluoride in an aprotic solvent such as DMF, Me_2SO, or NMP at temperatures of 142–190 °C affords up to a 78% yield of 4,4′-oxybis(*N*-methylphthalimide) (**2**) (Scheme I). Instead of potassium fluoride, the use of potassium or sodium nitrite also affords good yields of the bisimide **2**. Examples are listed in Table I.

The reaction of nitro compounds to give diaryl ethers is not without precedent. It has been reported[2] that *p*-nitrobenzonitrile or *p*-chlorobenzonitrile will undergo a condensation reaction when treated with sodium nitrite in *N*-methylpyrrolidone to give 4,4′-oxybis(benzonitrile).

After isolation of the bisimide ether **2** by filtration, the filtrate was extracted with methylene chloride and the organic fractions were concentrated in vacuo. The components of this material were separated and identified by GC, GC/MS, and ^{13}C NMR analyses. The various products and their yields are listed in Table II.

Scheme I



Another compound identified in the reaction mixture when potassium fluoride was used was 4-fluoro-*N*-methylphthali-

Table I. Reaction of 4-Nitro-*N*-methylphthalimide (1) with Fluoride and Nitrite Salts

No.	Solvent	Salt	Equiv[a]	Time, h	Temp, °C	Yield of ether,[b] %
1	NMP	KF	1.6	8.5	190	72
2	NMP	KF	0.16	18	190	78
3	DMF	KF	1.0	16	153	69
4	Me_2SO	KF	0.9	18	142	42
5	Me_2SO	KF	1.0	19	142	61
6	Me_2SO	KF	2.0	28	142	52
7	Me_2SO	KF	4.0	28	142	47
8	DMF	NaF	1.0	16	153	<1
9	NMP	KNO_2	0.1	18	190	78
10	DMF	KNO_2	1.0	16	153	65
11	Me_2SO	KNO_2	1.0	18	142	50
12	DMF	$NaNO_2$	1.0	16	153	66

[a] Molar equivalents. [b] Isolated yield of 4,4′-oxybis(*N*-methylphthalimide) (2).

Table II. Yields[a] of Various Products Formed in the Reaction of 4-Nitro-*N*-methylphthalimide (1) with Fluoride and Nitrite Salts

		Compd yields, %										Total
No.[b]	Salt/solvent/time/temp	2[c]	1	4	5	7	8	9	3	6	10	yield, %
3	1.0 equiv KF/DMF/16 h/153 °C	70	7	7	1		1	6	1	Tr	1	94
4	0.9 equiv KF/Me_2SO/18 h/142 °C	39	7	22	3	3	1	4	1	Tr	Tr	80
7	4.0 equiv KF/Me_2SO/28 h/142 °C	45		8	1	13						67
10	1.0 equiv KNO_2/DMF/16 h/153 °C	65	5		2		3	14	4	Tr		93
11	1.0 equiv KNO_2/Me_2SO/18 h/142 °C	50	13		8	4	1	3	2	1		81
13[d]	1.1 equiv KNO_2/DMF/16 h/153 °C	75	4	4	4		4	6	1	Tr	Tr	98

[a] Absolute yields determined by ^{13}C NMR. [b] Experiment numbers are from Table I. [c] Yield of 2 was determined by isolation and VPC purity. [d] Reaction of 4-fluoro-*N*-methylphthalimide (4) with KNO_2.

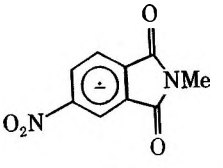
mide (4). This compound was not unexpected because treatment of 4-nitrophthalic anhydride with potassium fluoride afforded 4-fluorophthalic anhydride as the major product.[1] In one experiment, the methylene chloride extracts were distilled to afford an 8% yield of pure 4-fluoroimide (4). 4-Fluoro-*N*-methylphthalimide (4) was prepared in a 28% yield by heating neat 4-nitro-*N*-methylphthalimide (1) with potassium fluoride at 300 °C for 5 h and then distilling the product.

It is interesting at this point to compare the reactivity of 4-nitrophthalic anhydride with 4-nitro-*N*-methylphthalimide. Reaction of 4-nitrophthalic anhydride with potassium fluoride is complete within 25 min at 300 °C,[1] whereas 4-nitro-*N*-methylphthalimide requires more than 5 h under the same conditions and the yield of the 4-fluoro compound is much lower.

One of the more interesting compounds identified in the reaction mixture is 4-hydroxy-*N*-methylphthalimide (5). The phenol 5 is postulated as an intermediate in the formation of the bisimide 2 and will be discussed later. An authentic sample of 4-hydroxy-*N*-methylphthalimide (5) was prepared from 4-nitro-*N*-methylphthalimide by nitro displacement to afford a 74% yield of the methyl ether (6) followed by demethylation with boron tribromide to afford 5 in an 89% yield.

Another compound identified in the reaction mixture when Me_2SO was used as a reaction solvent was the thioether 7. An authentic sample of 7 was also prepared by nitro displacement. Treatment of 4-nitro-*N*-methylphthalimide (1) with the sodium salt of methyl mercaptan in DMF afforded a 76% yield of 4-thiomethoxy-*N*-methylphthalimide (7). It has been reported that the thermal decomposition of Me_2SO affords methyl mercaptan as one of the products.[3] Reaction of methyl mercaptan with either the 4-nitro compound 1 or the 4-fluoro compound 4 catalyzed by nitrite or fluoride salts would afford the methyl thioether 7.

4-Methoxy-*N*-methylphthalimide (6) was observed in most of the reactions, but it was formed in <1% yield and was not detectable by ^{13}C. Another compound produced in the reaction in small yield is *N*-methylphthalimide (8). It is probable that this compound is formed from the anion radical[4-6] 11 by loss of NO_2^- followed by hydrogen radical abstraction by the aryl radical.



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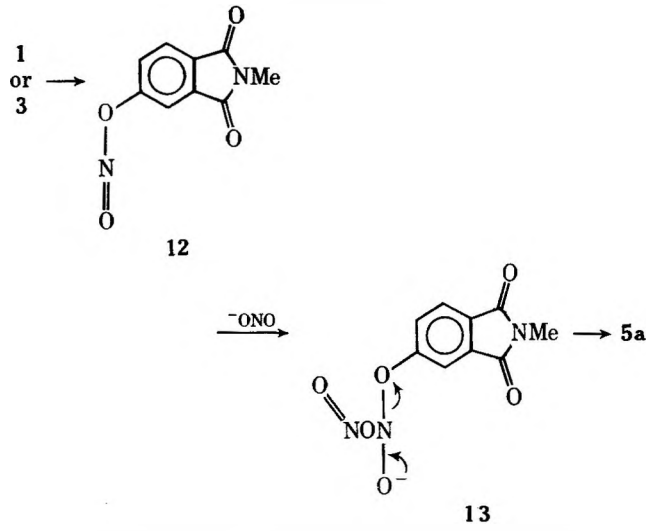
The diacids 3, 9, and 10 are also formed in the reaction of 4-nitro-*N*-methylphthalimide (1) with fluoride and nitrite salts. The formation of the diacids probably involve attack of nitrite ion on the carbonyl groups and then ring opening of the imide ring. We have shown that in the case of 4-nitrophthalic anhydride the only product of reaction with potassium nitrite is dipotassium 4-nitrophthalate.[1]

Reaction of 4-fluoro-*N*-methylphthalimide (4) with nitrite ion was also studied. Thus reaction of 4-fluoro-*N*-methylphthalimide (4) with potassium nitrite in DMF for 16 h at 153 °C gave a 74% yield of 4,4′-oxybis(*N*-methylphthalimide) (2). The other products identified in the reaction mixture are listed in Table II. Small amounts of 4-nitro-*N*-methylphthalimide (1) are observed, resulting from fluoro displacement by nitrite via nitrogen attack.

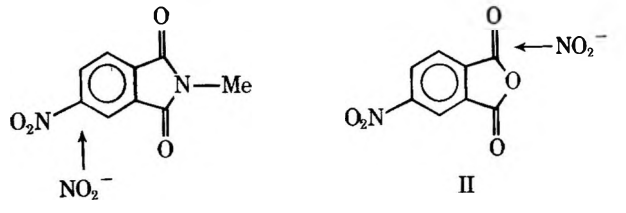
A possible mechanism for the formation of 4,4′-oxybis(*N*-methylphthalimide) (2) involves the intermediates 12 and 13 shown below. Nitrite ion has two potential reaction sites and can react by either oxygen or nitrogen attack.[7-9] Attack by oxygen on either 4-fluoro- or 4-nitro-*N*-methylphthalimide (4 or 1) gives the nitrite ester 12. Attack on 12 by another nitrite ion produces the phenoxide 5a and nitrogen oxides via the intermediate or transition state 13. Reaction of the phenoxide 5a with 4-fluoro- or 4-nitro-*N*-methylphthalimide (4 or 1) gives the ether 2.



This mechanism is supported by Parker and co-workers,[10,11] who studied the reaction of nitrite ion with nitrohalobenzene to give nitrophenols. Two moles of nitrite ion were consumed per mole of nitrophenol produced. They detected no radicals (via ESR) and believed that the decomposition of the nitrite ester involved nucleophilic attack by NO_2^- on the nitrogen of ArONO to displace ArO^- and form N_2O_3.

We observed small amounts of 4-hydroxy-*N*-methylphthalimide (**5**) in the reaction mixtures. It has been well documented[12-17] that nitrobenzenes substituted by electron-withdrawing groups readily undergo displacement of the nitro group with a wide variety of nucleophiles. Activated fluorobenzenes will also undergo nucleophilic displacement of the fluoro group.[18] So, it is quite reasonable to assume that the phenoxide **5a** will displace the nitro or fluoro group from the substituted imide to afford the ether **2**. As a proof we ran displacement reactions with the phenol **5**. Reaction of 4-hydroxy-*N*-methylphthalimide (**5**) with 4-fluoro-*N*-methylphthalimide (**4**) in DMF containing potassium fluoride[19] gives an 82% yield of the ether **2**. Preforming the phenoxide of **5** with sodium hydride and then reaction with 4-nitro-*N*-methylphthalimide (**1**) gave an 81% yield of the ether **2**.

As has been reported,[1] 4-nitrophthalic anhydride, when treated with potassium nitrite, affords the dipotassium salt of 4-nitrophthalic acid; no 4,4′-oxybis(phthalic anhydride) was detected. The difference in reactivity of nitrite ion with 4-nitro-*N*-methylphthalimide and 4-nitrophthalic anhydride is striking. The two extreme cases of reactivity are shown (I



and II). In the anhydride case, nitrite ion is trapped by reaction with the carbonyl groups to eventually give the diacid salt. In the *N*-methylimide case, the carbonyl groups being less reactive, nitrite ion is trapped by undergoing aromatic substitution to give a nitrite ester, which upon further reaction affords a phenoxide, which displaces a nitro group.

Experimental Section

General Procedures. All proton NMR spectra were measured on a Varian T-60 spectrometer with chemical shift values relative to tetramethylsilane. Carbon-13 NMR spectra were recorded on either a Varian XL-100-15 (25.2 MHz) or a Varian CFT-20 (20.0 MHz) NMR spectrometer operating in the Fourier transform (FT) mode with complete proton decoupling. Infrared spectra were measured on a Perkin-Elmer 457 grating infrared spectrophotometer. Mass spectra were obtained on a CEC 21-104 or a Varian MAT 311 spectrometer operating at 70 eV utilizing the direct inlet system. Vapor-phase chromatography (VPC) was carried out on a Hewlett-Packard 5700A gas chromatograph using a 6 ft × 1/8 in. 3% OV-17 on Chromosorb W column with temperature programming between 100 and 290 °C at 16°/min. Gas chromatography/mass spectroscopy was carried out on a Varian MAT 111 GC/mass spectrometer. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. All reactions were run under nitrogen unless otherwise noted. Anhydrous potassium fluoride was obtained from Alfa Chemicals.

Reaction of 4-Nitro-*N*-methylphthalimide (1) with Potassium Fluoride. In Me_2SO. A mixture of 22.421 g (109 mmol) of **1**, 14.757 g (254 mmol) of anhydrous KF, and 100 mL of dry Me_2SO was heated at 142 °C (bath temperature) with stirring for 27 h. The dark drown mixture, after cooling to room temperature, was poured into 900 mL of 0.2 M aqueous HCl to afford a brown precipitate. Filtration afforded 9.993 g (51% yield) of 4,4′-oxybis(*N*-methylphthalimide) (**2**) as a brown solid, mp 240–258 °C. Recrystallization from DMF afforded pale yellow prisms: mp 262–265 °C (lit.[24] mp > 250 °C]; ^{13}C NMR (Me_2SO-d_6) 23.2, 112.9, 123.7, 124.8, 128.1, 134.4, 160.1 ppm; ^1H NMR ($CDCl_3$) δ 3.18 (3 H, singlet), 7.3 (2 H, multiplet), 7.81 (1 H, apparent doublet, J = 8.5 Hz); IR (KBr) 1602, 1705, 1768, 1774 cm^{-1}; MS *m/e* 336 (100%, P^+), 308 (11%, P − CO), 292 (31%, P − CO_2).

Anal. Calcd for $C_{18}H_{12}N_2O_5$: 336.0746. Found: 336.0743.

The filtrate was extracted with dichloromethane and concentrated in vacuo to afford 6.383 g of a brown oil. Distillation gave 1.481 g (8% yield) of 4-fluoro-*N*-methylphthalimide (**4**) as a clear oil, bp 178–181 °C (30 mm), which solidified to a white solid on cooling, mp 99–100 °C.

The above reaction was repeated using 4.362 g (21.2 mmol) of **1**, 1.055 g (18.2 mmol) of anhydrous KF, and 40 mL of dry Me_2SO. This mixture was heated at 142 °C (bath temperature) with stirring for 18 h to afford 1.489 g (42% yield) of **2** as a light brown solid, mp 243–251 °C, 85% pure by VPC. The impurities were **1**, **4**, and **7**.

The filtrate was extracted twice with dichloromethane and concentrated in vacuo to afford 1.621 g of a brown oil. The ^{13}C NMR showed this oil to contain 54% **4**, 17% **1**, 10% **9**, 8% **5**, 5% **7**, 3% **8**, 2% **3**, and 1% **2**. The identity of these compounds was confirmed by GC/MS, which also showed the presence of **6** and **10**.

In DMF. The above reaction was repeated using DMF as a solvent. Heating a mixture of 5.177 g (25 mmol) of **1**, 1.536 g (26 mmole) of anhydrous KF, and 25 mL of dry DMF at reflux (153 °C) for 16 h afforded 2.900 g (69% yield) of **2** as a tan solid, mp 254–259 °C, >99% pure by VPC.

The filtrate was extracted with ethyl acetate and concentrated in vacuo to afford 1.247 g of a brown solid. The ^{13}C NMR spectrum showed it to consist of 30% **4**, 28% **1**, 24% **9**, 6% **8**, 4% **2**, 3% **5**, 3% **3**, and 2% **10**. The identity of these compounds was confirmed by GC/MS, which also showed the presence of **6**.

In NMP. A mixture of 10.227 g (50 mmol) of **1**, 4.559 g (79 mmol) of anhydrous KF, and 50 mL of dry NMP was heated at 190 °C (bath temperature) with stirring for 8.75 h. The dark brown mixture, after cooling to room temperature, was poured into 0.2 M aqueous HCl to afford 4.992 g (72% yield) of **2** as a tan solid, mp 259–263 °C.

Reaction of 4-Nitro-*N*-methylphthalimide (1) with Potassium Nitrite. In DMF. A mixture of 5.283 g (25.6 mmol) of **1**, 2.231 g (26.2 mmol) of potassium nitrite, and 25 mL of dry DMF was heated at reflux (153 °C) with stirring for 16 h. After cooling to room temperature the reaction mixture was poured into 100 mL of 0.2 M aqueous HCl to afford a tan precipitate. Filtration afforded 2.819 g (65% yield) of 4,4′-oxybis(*N*-methylphthalimide) (**2**) as a tan solid, mp 247–255 °C, >98% pure by VPC.

The filtrate was extracted twice with dichloromethane and concentrated in vacuo to afford 1.421 g of a brown oil. The ^{13}C NMR showed the oil to consist of 51% **9**, 20% **1**, 13% **8**, 9% **3**, and 8% **5**. The identity of these compounds was confirmed by GC/MS, which also showed the presence of **6** and **2**.

In Me_2SO. The above reaction was repeated using Me_2SO as a solvent. Heating a mixture of 4.013 g (19.5 mmol) of **1**, 1.644 g (19.3 mmol) of potassium nitrite, and 40 mL of dry Me_2SO at 142 °C (bath temperature) for 18 h afforded 1.638 g (50% yield) of **2** as a tan solid, mp 220–236 °C, 88% pure by VPC. The impurities were **1** and **7**.

The filtrate was extracted twice with dichloromethane and concentrated in vacuo to afford 1.241 g of a brown oil. The ^{13}C NMR showed the oil to contain 36% **1**, 25% **5**, 11% **9**, 10% **7**, 7% **2**, 4% **3**, 3% **8**, and 3% **6**. The identity of these compounds was confirmed by GC/MS.

Reaction of 4-Fluoro-*N*-methylphthalimide (4) with Potassium nitrite. A mixture of 1.674 g (9.4 mmol) of **4**, 0.840 g (9.9 mmol) of potassium nitrite, and 20 mL of dry DMF was heated at reflux (153

°C) with stirring for 16 h. After cooling to room temperature the reaction mixture was poured into 100 mL of 0.2 N aqueous HCl to afford a tan precipitate. Filtration afforded 1.164 g (74% yield) of 4,4′-oxybis(*N*-methylphthalimide) (2) as a light tan solid, mp 258–262 °C, >99% pure by VPC.

The filtrate was extracted with dichloromethane and concentrated in vacuo to afford 0.375 g of a brown gum. The ^{13}C NMR spectrum showed the mixture to consist of 25% **9**, 19% **5**, 19% **1**, 16% **4**, 16% **8**, 3% **2**, and 3% **3**. The identity of these compounds was confirmed by GC/MS, which also showed the presence of **10**.

4-Fluoro-*N*-methylphthalimide (4). A mixture of 21.30 g (103 mmol) of **1** and 12.02 g (207 mmol) of anhydrous KF was heated at 300 °C (bath temperature) for 5 h. After cooling to ~250 °C a still head was attached and the mixture distilled to afford 5.20 g (28% yield) of **4** as a clear liquid, bp 183–188 °C (60 mm), which on cooling solidified to an off-white solid: mp 98–100 °C; ^{13}C NMR ($CDCl_3$) 24.0, 110.4, 111.4, 120.4, 121.3, 125.4, 125.7, 128.2, 128.3, 135.0, 135.4, 161.3, 167.2, 171.5 ppm; ^1H NMR ($CDCl_3$) δ 3.20 (3 H, singlet), 7.2–8.0 (3 H, multiplet); IR ($CHCl_3$) 1612, 1713, 1769 cm^{-1}; MS *m/e* 179 (100%, P^+), 178 (16%), 151 (18%, P − CO), 135 (18%, P − CO_2), 122 (52%, P − CO − NMe).

Anal. Calcd for $C_9H_6NO_2F$: 179.0383. Found: 179.0386.

The pot residue (17.90 g) was placed in a Soxhlet extractor and extracted for 2 days with chloroform to afford 4.611 g of a brown solid. GC/MS analysis showed that this solid consisted of a mixture of **4**, **1**, and **2**.

4-Methoxy-*N*-methylphthalimide (6). To a mixture of 20.00 g (97 mmol) of **1** in 100 mL of dry Me_2SO was added 5.34 g (99 mmol) of sodium methoxide and the reaction stirred at room temperature for 1 h and then at 60–70 °C for 3 h. After cooling to room temperature, the mixture was poured into water and the precipitate filtered to afford 13.63 g (74% yield) of **6** as a tan solid. Recrystallization of a sample from ethyl acetate/hexane afforded tan needles; mp 153–155 °C (lit.[25] mp 153 °C); ^{13}C NMR ($CDCl_3$) 23.4, 55.5, 107.5, 118.9, 123.6, 123.6, 134.3, 164.0, 167.6 ppm; ^1H NMR ($CDCl_3$) δ 3.14 (3 H, singlet), 3.90 (3 H, singlet), 7.07 (1 H, doublet, J = 8 Hz), 7.22 (1 H, doublet, J = 2 Hz), 7.64 (1 H, quartet, J = 2 and 8 Hz); IR ($CHCl_3$) 1710, 1767 cm^{-1}; MS *m/e* 191 (100%, P^+), 190 (10%), 163 (18%, P − CO), 147 (36%, P − CO_2), 134 (30%, P − CO − NCH_3).

Anal. Calcd for $C_{10}H_9NO_3$: 191.0582. Found: 191.0585.

4-Hydroxy-*N*-methylphthalimide (5). To a mixture of 10.409 g (41.6 mmol) of boron tribromide in 50 mL of dichloromethane was added dropwise 1.596 g (8.4 mmol) of **6** in 50 mL of dichloromethane and the reaction mixture stirred overnight at room temperature. Water (~ 5 mL) was then added to hydrolyze the boron complexes and the dichloromethane was removed on a rotary evaporator. Filtration afforded 1.309 g (89% yield) of **5** as a light brown solid, mp 225–234 °C. Recrystallization of a sample from ethanol gave tan prisms: mp 244–246 °C [lit.[25] mp 250 °C); ^{13}C NMR (Me_2SO-d_6) 23.5, 109.7, 120.0, 122.0, 124.8, 134.5, 163.2, 167.8 ppm; ^1H NMR (Me_2SO-d_6) δ 3.00 (3 H, singlet), 7.1 (2 H, multiplet), 7.70 (1 H, apparent doublet, J = 8.5 Hz); IR (KBr) 1600, 1620, 1682, 1761 cm^{-1}; MS *m/e* 177 (100% P^+), 176 (13%), 149 (20%, P − CO), 133 (27%, P − CO_2).

Anal. Calcd for $C_9H_7NO_3$: 177.0426. Found: 177.0426.

4-Thiomethoxy-*N*-methylphthalimide (7). Into a 250-mL round-bottom flask fitted with a magnetic stirrer and nitrogen inlet was placed 4.332 g (102 mmol) of 56.8% NaH oil dispersion. After washing with hexane, 100 mL of dry DMF was added, and then methyl mercaptan was bubbled into the mixture until hydrogen evolution ceased. To this was added 20.00 g (97 mmol) of **1** and the reaction was stirred at room temperature overnight. The reaction mixture was then poured into water and filtered to afford 15.542 g (76%) of **7** as a light tan solid, mp 141–143 °C. Recrystallization of a sample from ethyl acetate/hexane afforded pastel yellow prisms: mp 142–144 °C; ^{13}C NMR ($CDCl_3$) 14.9, 23.6, 119.1, 122.8, 127.8, 129.8, 132.9, 147.6, 167.7 ppm; ^1H NMR ($CDCl_3$) δ 2.55 (3 H, singlet), 3.13 (3 H, singlet), 7.5 (3 H, multiplet); IR ($CHCl_3$) 1604, 1702, 1769 cm^{-1}; MS *m/e* 207 (100%, P^+), 163 (32%, P − CO_2).

Anal. Calcd for $C_{10}H_9NO_2S$: 207.0354. Found: 207.0349.

Reaction of 4-Hydroxy-*N*-methylphthalimide (5) with 4-Fluoro-*N*-methylphthalimide (4). A mixture of 0.931 g (5.3 mmol) of **5**, 0.965 g (5.4 mmol) of **4**, 0.332 g (5.7 mmol) of anhydrous KF, and 20 mL of dry DMF was stirred and heated at reflux (153 °C) for 16 h. After cooling to room temperature the reaction mixture was poured into 100 mL of 0.2 M aqueous HCl to give a tan precipitate. Filtration afforded 1.461 g (82% yield) of 4,4′-oxybis(*N*-methylphthalimide) (2) as a tan solid, mp 265–267.5 °C, >99% pure by VPC.

Reaction of 4-Hydroxy-*N*-methylphthalimide (5) with 4-Nitro-*N*-methylphthalimide (1). Into a round-bottom flask was placed 1.064 g (6.04 mmol) of **5**, 0.689 g (6.14 mmol) of potassium *tert*-butoxide, and 20 mL of dry DMF. After stirring at room temperature for 30 min to form the phenoxide, 1.288 g (6.25 mmol) of **1** was added. The reaction mixture was stirred and heated at reflux (153 °C) for 16 h. After cooling to room temperature the reaction mixture was poured into 100 mL of 0.2 M aqueous HCl to give a tan precipitate. Filtration afforded 1.651 g (81% yield) of 4,4′-oxybis(*N*-methylphthalimide) (2) as a tan solid, mp 266–268 °C, >99% pure by VPC.

Registry No.—**1**, 41663-84-7; **2**, 27507-54-6; **3**, 63196-43-0, **4**, 63196-44-1; **5**, 4112-65-6; **6**, 63196-45-2; **7**, 63196-46-3; **8**, 550-44-7; **9**, 610-27-5; **10**, 320-97-8; KF, 7789-23-3; NaF, 7681-49-4; KNO_2, 7758-09-0; $NaNO_2$, 7632-00-0; sodium methoxide, 124-41-4; methyl mercaptan, 74-93-1.

References and Notes

(1) R. L. Markezich, O. S. Zamek, P. E. Donahue, and F. J. Williams, *J. Org. Chem.*, this issue; companion paper.
(2) German Patent 2 037 781.
(3) V. J. Traynelis and W. L. Hergenrother, *J. Org. Chem.*, **29**, 221 (1964).
(4) N. Kornblum, *Angew. Chem., Int. Ed. Engl.*, **14**, 734 (1975).
(5) J. F. Bunnett, *J. Chem. Educ.*, **51**, 312 (1974).
(6) J. K. Kim and J. F. Bunnett, *J. Am. Chem. Soc., Soc.*, **92**, 7463 (1970).
(7) N. Kornblum, P. A. Smiley, P. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955).
(8) D. H. Rosenblatt, W. M. Dennis, and R. D. Goodin, *J. Am. Chem. Soc.*, **95**, 2133 (1973).
(9) R. Gomppa, *Angew. Chem., Int. Ed. Engl.*, **3**, 560 (1964).
(10) T. J. Broxton, D. M. Muir, and A. J. Parker, *J. Org. Chem.*, **40**, 2037 (1975).
(11) T. J. Broxton, D. M. Muir, and A. J. Parker, *J. Org. Chem.*, **40**, 3230 (1975).
(12) J. R. Beck, *J. Org. Chem.*, **38**, 4086 (1973).
(13) J. R. Beck and J. A. Yahmer, *J. Org. Chem.*, **39**, 3440 (1974).
(14) J. R. Beck, R. L. Sobczak, R. G. Suhr, and J. A. Yahmer, *J. Org. Chem.*, **39**, 1839 (1974).
(15) J. R. Beck, *J. Org. Chem.*, **37**, 3224 (1972).
(16) L. R. Caswell and T. L. Kao, *J. Heterocycl. Chem.*, **3**, 333 (1966).
(17) N. Kornblum, L. Cheng, R. C. Kerber, M. M. Kestner, B. N. Newton, H. W. Pinnick, R. G. Smith, and P. A. Wade, *J. Org. Chem.*, **41**, 1560 (1976).
(18) R. G. Fowler, L. R. Caswell, and L. I. Sue, *J. Heterocycl. Chem.*, **10**, 407 (1973).
(19) The ability of potassium fluoride to serve as a base has been well documented; see ref 20–23.
(20) L. Rand, J. V. Swisher, and C. J. Cronin, *J. Org. Chem.*, **27**, 3505 (1962).
(21) L. Rand, D. Haidukewych, and R. J. Dolinski, *J. Org. Chem.*, **31**, 1272 (1966).
(22) J. W. ApSimon, J. W. Hooper, and B. A. Laishes, *Can. J. Chem.*, **48**, 3064 (1970).
(23) British Patent 1 348 630.
(24) British Patent 1 192 147 (1968).
(25) W. Flitsch, *Chem. Ber.*, **94**, 2494 (1961).

Notes

Reactions of 4-Nitrophthalic Anhydride with Potassium Fluoride and Potassium Nitrite

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Received November 29, 1976

The recent communication by Ishikawa and co-workers[1] on the preparation of 3- and 4-fluorophthalic anhydride from the corresponding nitro compound by fluorodenitration[2,3] prompts us to report our findings in the same area. Ishikawa reports that heating 4-nitrophthalic anhydride (1) with 3 mol of potassium fluoride affords 4-fluorophthalic anhydride (2). The yields are around 56%, but the authors fail to answer the question of the fate of almost half of the substituted phthalic anhydride.

We find that 3 mol are not necessary; 1 mol will give similar results. We have also elucidated the fate of all the substituted phthalic anhydrides. Nitrite ion produced in the reaction is trapped by the anhydride present, thus lowering the apparent overall yield of the reaction.

Heating 4-nitrophthalic anhydride (1) with at least 1 equiv of potassium fluoride at 230–240 °C produced 4-fluorophthalic anhydride (2) with the evolution of a red-brown gas. Distillation afforded up to a 62% yield of 4-fluorophthalic anhydride (2).

After distillation of the 4-fluorophthalic anhydride, a tan solid remained in the distillation pot. This material was insoluble in organic solvents, but dissolved readily in water. Acidification of an aqueous solution of this solid with hydrochloric acid and extraction with ethyl acetate afforded 4-nitrophthalic acid. The recovery of the 4-substituted phthalic acid was 34%; thus, the overall yield of the exchange reaction was >90%.

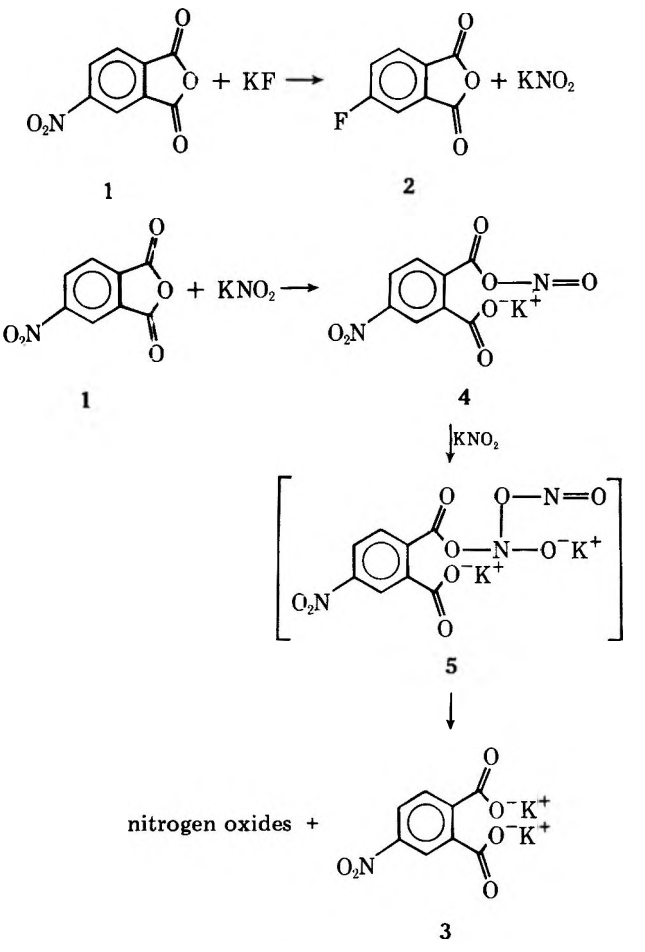
Sodium fluoride failed to give any reaction; heating a mixture of 4-nitrophthalic anhydride and 2 equiv of sodium fluoride for 18 h at 230–260 °C did not produce fluoro compound.

While a 220 °C temperature was necessary to give reaction of potassium fluoride with 4-nitrophthalic anhydride in the melt, the use of an aprotic solvent, such as dimethyl sulfoxide, greatly lowered the temperature required. Thus, reaction of 4-nitrophthalic anhydride with 2 equiv of potassium fluoride in dimethyl sulfoxide was complete within 20 min at 142 °C.

Fluoride exchange will also occur in acetonitrile solvent at 80 °C using the crown ether 2,3:11,13-dibenzo-1,4,-7,10,13,16-hexaoxacyclooctadeca-2,11-diene (dibenzo-18-crown-6) to solubilize the potassium fluoride. The use of crown ethers to solubilize potassium fluoride in acetonitrile and reactions of "naked" fluoride as a nucleophile have been reported.[4] Thus, reaction of 4-nitrophthalic anhydride with potassium fluoride in acetontrile containing dibenzo-18-crown-6 for 43 h afforded the 4-fluorophthalic anhydride, which was isolated as the diacid. Without the crown ether present, no 4-fluoro material was produced.

A possible mechanism for the formation of 4-nitrophthalic acid is shown in Scheme I. Exchange of potassium fluoride with 4-nitrophthalic anhydride affords 4-fluorophthalic anhydride and potassium nitrite. Nitrite ion has two potential reaction sites, and can react by either oxygen or nitrogen attack. Attack by oxygen on 4-nitrophthalic anhydride gives the

Scheme I. Mechanism for Formation of 4-Nitrophthalic Acid



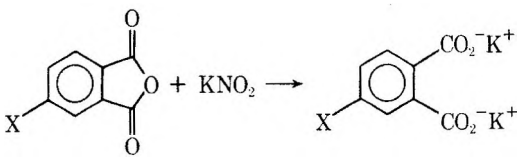
aroyl nitrite 4. Attack on 4 by another nitrite ion produces the dipotassium salt of 4-nitrophthalic acid and nitrogen oxides via the intermediate or transition state 5.

This mechanism is supported by several observations. The dipotassium salt of 4-nitrophthalic acid is formed. The infrared spectrum of the gases given off during the exchange reaction showed bands corresponding to the absorption bands of NO_2. Also, assuming the mechanism in Scheme I, the maximum yield of 4-fluorophthalic anhydride should only be 67%.

The ambifunctional nature of the nitrite ion has been well documented.[5-7] Nitrite ion reacts with alkyl halides to give a mixture of alkyl nitrites and nitroalkanes.[5] It has also been reported[8] that the solvolysis of acetic anhydride is markedly catalyzed by nitrite ions. The rate-determining step involves nucleophilic attack by nitrite ion on the anhydride molecule to produce an intermediate, believed to be acetyl nitrite, which undergoes relatively instantaneous decomposition in the buffered solvent to regenerate nitrite ion.

The reaction of nucleophiles with nitrite ester has been reported by Kornblum and co-workers.[9] In the reaction of primary nitroparaffins with a nitrite ester and sodium nitrite to give carboxylic acids, the sodium nitrite functions as a base to produce the nitro stabilized anion. Nucleophilic attack of this anion on the nitrite ester affords an alkoxide and a nitrosated nitro compound, which breaks down to form a carboxylic acid.

Table I. Reaction of 4-Substituted Phthalic Anhydrides with Nitrite



X	Registry no.	KNO_2/ anhydride (molar ratio)	% yield[a]
–H	85-44-9	2	96
$-NO_2$	5466-84-2	2	71
$-NO_2$		1	35
–F	319-03-9	2	74
–Cl	118-45-6	2	84
$-CH_3$	19438-61-0	2	90

[a] Isolated yield of dipotassium salt of the 4-substituted phthalic acid.

The reaction of potassium nitrite with anhydrides is not limited to 4-nitrophthalic anhydride. Table I lists the results of the reaction of various 4-substituted phthalic anhydrides with nitrite in DMF solution at room temperature. In all cases, there is obtained in good yields the dipotassium salt of the corresponding phthalic acid. In one case, when only 1 mol of potassium nitrite is used, the yield is greatly reduced.

As would be expected, the rate of nitrite attack on the anhydride seems to be determined by the electron-withdrawing ability of the group in the 4 position. Thus in the potassium fluoride exchange reaction, >99% of the attack of nitrite occurs on 4-nitrophthalic anhydride.

Experimental Section

General Procedures. Carbon-13 NMR spectra were recorded on either a Varian XL-100-15 (25.2 MHz) or a Varian CFT-20 (20.0 MHz) NMR spectrometer operating in the Fourier transform (FT) mode with complete proton decoupling. Infrared spectra were measured on a Perkin-Elmer 457 grating infrared spectrophotometer. Mass spectra were obtained on a CEC 21-104 or a Varian-MAT 311 spectrometer operating at 70 eV utilizing the direct inlet system. Vapor-phase chromatography (VPC) was carried out on a Hewlett-Packard 5700A gas chromatograph using a 6 ft × 1/8 in. 3% OV-17 on Chromosorb W column with temperature programming between 100 and 290 °C at 16°/min. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Anhydrous potassium fluoride was obtained from Alfa Chemicals.

Reaction of 4-Nitrophthalic Anhydride with Potassium Fluoride. A flask containing 9.944 g (51.5 mmol) of 4-nitrophthalic anhydride and 6.618 g (114.1 mmol) of anhydrous potassium fluoride was fitted with a distilling head, receiver, and nitrogen inlet and placed into an oil bath at 135 °C. The bath temperature was raised to 235–240 °C and held at this temperature for 60 min. Distillation afforded 5.101 g (60% yield) of 4-fluorophthalic anhydride, bp 205–206 °C (160 mm) [lit.[6] bp 148 °C (20 mm)], as a clear liquid which solidified to give a white solid, mp 74–76 °C (lit.[6] mp 75 °C): IR ($CHCl_3$) 1780, 1856 cm^{-1}; mass spectrum *m/e* 166 (43%, P^+), 122 (100%, $-CO_2$), 94 (100%, $-CO_2 - CO$).

Using only 1 equiv of potassium fluoride at 220 °C for 120 min afforded a 62% yield of distilled 4-fluorophthalic anhydride.

The above reaction was repeated with 34.954 g (0.181 mol) of 4-nitrophthalic anhydride and 21.611 g (0.373 mol) of potassium fluoride to give a 58% yield of the fluoro compound 2. In the distillation pot was left 33.394 g of a pale tan solid. Carbon-13 NMR showed the organic component of this material to be 3, the dipotassium salt of 4-nitrophthalic acid. This solid was dissolved in 100 mL of water and extracted with ethyl acetate (2 × 100 mL) to afford 0.197 g of a yellow oil (containing 4-nitro- and 4-fluorophthalic anhydride). The aqueous solution was acidified to pH 1 with concentrated HCl (16 mL, 0.192 mol) and extracted with EtOAc (5 × 150 mL) and ether (2 × 150 mL) to afford 14.190 g (37% recovery) of 4-nitrophthalic acid, mp 163–165 °C (lit.[12] mp 165–166 °C). VPC analysis showed the material to be 95% 4-nitrophthalic acid and 5% 4-fluorophthalic acid. The recovery in this reaction was 95.2%.

Reaction of 4-Nitrophthalic Anhydride (1) with Potassium Fluoride in Me_2SO. A mixture of 3.351 g (17.4 mmol) of 4-nitrophthalic anhydride (1), 2.083 g (35.9 mmol) of anhydrous potassium fluoride, and 8 mL of dry Me_2SO was heated at 142 °C for 35 min under nitrogen. VPC analysis of an aliquot showed that the reaction was over after 20 min. After cooling to room temperature, the reaction mixture was poured into dilute aqueous HCl and extracted with ethyl acetate to afford 3.188 g of a pale yellow solid. The ^{13}C NMR spectrum showed that the material contained 48% 4-fluorophthalic acid, 9% 4-fluorophthalic anhydride, and 43% 4-nitrophthalic acid. Distillation of this material afforded 1.007 g (35% yield) of 4-fluorophthalic anhydride, bp 200–208 °C (160 mm).

Reaction of 4-Nitrophthalic Anhydride (1) with Potassium Fluoride in Acetonitrile Containing Dibenzo-18-crown-6. A mixture of 2.008 g (34.6 mmol) of anhydrous potassium fluoride, 0.458 g (1.3 mmol) of dibenzo-18-crown-6,[10] and 20 mL of dry acetonitrile was refluxed (82 °C) for 30 min under nitrogen and then 3.011 g (15.6 mmol) of 4-nitrophthalic anhydride (1) was added and the refluxing continued. After refluxing for 43 h, the mixture was cooled to room temperature, methylene chloride was added, and the mixture filtered to remove 3.330 g of a solid material. Concentration of the filtrate under vacuum afforded 2.000 g of a mixture containing 82% 4-fluorophthalic anhydride and 18% dibenzo-18-crown-6. To remove the dibenzo-18-crown-6, the material was dissolved in aqueous KOH, extracted with ethyl acetate, and acidified with concentrated HCl to pH 1. Extraction with ethyl acetate afforded 1.195 g (42% yield) of pure (>99% by VPC) 4-fluorophthalic acid, mp 148–150 °C (lit.[11] mp 152–153 °C): IR (KBr) 1706 cm^{-1} (s); mass spectrum *m/e* 184 (16%, P^+), 167 (41%, – OH), 166 (10%, $-H_2O$), 140 (100%, $-CO_2$). Exact mass calcd for $C_8H_5O_4F$: 184.0171. Found 184.0170.

The methylene chloride insoluble material was dissolved in water, extracted with ethyl acetate, and acidified with concentrated hydrochloric acid to pH 1. Extraction with ethyl acetate yielded 1.117 g (33.9% recovery) of 4-nitrophthalic acid as a tan solid, mp 163–166 °C (lit.[12] mp 165–166 °C). The ^{13}C NMR showed the material to be >95% 4-nitrophthalic acid.

Reaction of Potassium Nitrite with Substituted Phthalic Anhydride. The following procedures are representative: A mixture of 1.93 g (0.01 mol) of 4-nitrophthalic anhydride, 1.70 g (0.02 mol) of potassium nitrite, and 19 mL of anhydrous DMF was stirred under a nitrogen atmosphere at room temperature. After stirring for 16 h, the reaction mixture was added to 200 mL of diethyl ether, and the resulting precipitate was collected and dried to give 1.32 g (71% yield) of the dipotassium salt of 4-nitrophthalic acid. The material was identified from its ^{13}C NMR (D_2O).

A mixture, 4.0 g (27 mmol) of phthalic anhydride and 4.6 g (54 mmol) of potassium nitrite, was heated up to 200–230 °C over a 110-min period. A brown gas was evolved after heating for 160 min at 200–230 °C; the ^{13}C NMR spectra showed the material to be the dipotassium salt of phthalic acid.

Registry No.—KNO_2, 7758-09-0; KF, 7789-23-3; 4-nitrophthalic acid dipotassium salt, 63196-42-9; 4-nitrophthalic acid, 610-27-5; 4-fluorophthalic acid, 320-97-8; dibenzo-18-crown-6, 14187-32-7; phthalic acid dipotassium salt, 4409-98-7; 4-fluorophthalic acid dipotassium salt, 63196-39-4; 4-chlorophthalic acid dipotassium salt, 63196-40-7; 4-methylphthalic acid dipotassium salt, 63196-41-8.

References and Notes

(1) N. Ishikawa, T. Tanake, and D. Hayashi, *Bull. Chem. Soc. Jpn.*, **48**, 359 (1975).
(2) G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc.*, **78**, 6034 (1956).
(3) G. Vartoli, A. Latrofa, F. Naso, and P. E. Todesco, *J. Chem. Soc., Perkin Trans. 1*, 2671 (1972).
(4) C. L. Liotta and H. P. Harris, *J. Am. Chem. Soc.*, **96**, 2250 (1974).
(5) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955).
(6) D. H. Rosenblatt, W. M. Dennis, and R. D. Goodin, *J. Am. Chem. Soc.*, **95**, 2133 (1973).
(7) R. Gomppa, *Angew. Chem., Int. Ed. Engl.*, **3**, 560 (1964).
(8) E. B. Lees and B. Saville, *J. Chem. Soc.*, 2262 (1958).
(9) N. Kornblum, R. K. Blackwood, and D. D. Mooberry, *J. Am. Chem. Soc.*, **78**, 1501 (1956).
(10) Aldrich Chemical Company. 2,3,11,12-Dibenzo-1,4,7,10,13,16-hexaoxacyclooctadeca-2,11-diene.
(11) G. Valkansas and H. Hopff, *J. Chem. Soc.*, 3475 (1963).
(12) "Handbook of Chemistry and Physics", 54th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1973, p 432.

Direct Fluorination of 2,2,4,4-Tetramethylpentane. Sterically Protected Residual Protons?

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Received September 20, 1976

The low-temperature direct-fluorination technique is used to control the reaction of fluorine gas under precisely regulated conditions with an organic or inorganic compound. This technique has been shown to be useful for making a wide variety of fluorine-containing compounds ranging from perfluoro carbons[1] to perfluoro ethers[2] and to unusual compounds such as partially fluorinated carboranes,[3] perfluoroganmetallic compounds,[4] and perfluoro sulfur–nitrogen ring compounds.[5]

In reactions where fluorine is used to replace hydrogen atoms, it has been found that, as the reaction proceeds, the remaining hydrogen atoms become progressively harder to replace. The reasons for this behavior are not definitely known, though the increasing acidity of the remaining protons as well as the increasing steric protection of their sites, due to the larger fluorine atoms becoming bonded to adjacent sites (convalent radius of F = 0.71 Å, of H = 0.37 Å),[6] would seem to be the most likely causes. The present work was initiated to determine if steric effects were strong enough to allow a molecule containing hydrogen atoms on hindered sites to become otherwise completely fluorinated, except for the hindered protons. The compound chosen for this study was 2,2,4,4-tetramethylpentane, because the two hydrogens on the center carbon atom were surrounded by two *tert*-butyl groups.

The expected products from this reaction are interesting in themselves and because they also have potential for use as fluorocarbon blood substitutes. Their highly branched structures are desirable, since branched molecules tend to form more stable water emulsions than unbranched molecules.[7] Furthermore, their molecular weights are such that their expected oxygen-dissolving capabilities and their expected volatilities are within the range necessary for a blood substiutute.[8]

Results and Discussion

The first series of reactions resulted in the formation of the perfluoro, monohydro and dihydro compounds in ratios of about 0.20 to 0.66 to 0.14 (Figure 1) with a total yield of about 70%. The second series of reactions, run under the same conditions except that the time interval with pure fluorine was increased from 36 to 85 h, gave the same ratios of the perfluoro, monohydro, and dihydro products, but the total yield was increased to about 95%. The third series of reactions, which were identical to the second except that half the amount of starting material was used, gave the same results as the second series.

The first set of fluorination conditions were nearly identical to those used in the fluorination of hexamethylethane. The latter reaction resulted in a 9.8% yield of perfluorohexamethylethane,[1] while the 2,2,4,4-tetramethylpentane reaction resulted in a combined yield of the monohydro, dihydro, and perfluoro compounds of about 70%. Hexamethylethane and 2,2,4,4-tetramethylpentane have quite similar structures and volatilities, so that the large differences in the yields of the fluorinated products are unexpected.

The observations that the length of time of the tetramethylpentane reaction and the amount of fluorine used did not affect the product distribution, as well as the fact that the dihydro product was unchanged after being exposed to pure fluorine for 72 h, show that (at −78 °C) the fluorine reaction with the protons located on the central carbon atom of the molecule apparently stopped after the methyl groups became fully fluorinated. This is assumed to be primarily a steric effect from the bulky CF_3 groups shielding the hydrogens on the center carbon atom from further fluorine attack. It is not primarily an electronic effect (from the increasing acidity of the remaining hydrogen atoms). If this were the case, it would be expected that compounds with one or two hydrogens remaining on the methyl groups, and with the center carbon atom completely fluorinated, would be found.

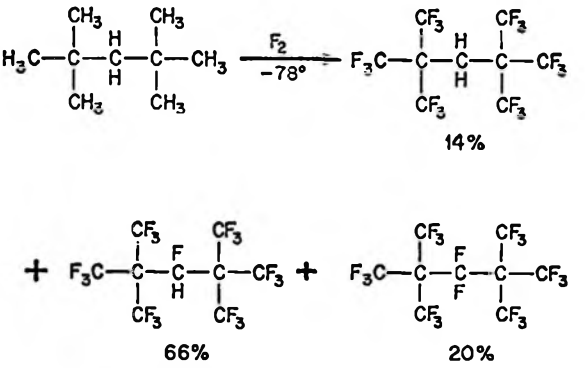

Figure 1. Reaction scheme.

Experimental Section

Mass spectra were measured on a Hitachi RMU 6D mass spectrometer at 70 eV. NMR spectra were taken on a Perkin-Elmer R20-B spectrometer at 60 MHz for protons and 56.4 MHz for fluorine. Gas chromatography was done on a Bendix gas chromatograph equipped with a cryogenic controller and a thermal-conductivity detector. A 25-ft × 3/8-in. column packed with 10% SE 30 on Chromosorb P and a 10-ft × 0.25-in. column packed with 15% dinonyl phthalate on Chromosorb P were used. Analyses were done by Schwarzkopf Micronalytical Laboratory. Infrared data were collected on a Beckman IR 20A instrument. All experiments were carried out in a four-zone cryogenic reactor system, described previously.[1]

Fluorination of 2,2,4,4-Tetramethylpentane. The fluorination system was flushed with helium for 12 h, and then the first two zones of the reactor were cooled to −78 °C and the 2,2,4,4-tetramethylpentane was injected. Three sets of fluorination conditions were used. For the first set of reactions, the helium flow was set to 20 cm^3/min and the fluorine flow was set to 1.5 cm^3/min. After 18 h, zones two and three were cooled and the helium flow was reduced to 8 cm^3/min. After an additional 24 h, zones three and four were cooled and the helium flow was terminated. The reaction was then allowed to continue for an additional 36 h. In the second series of reactions, the conditions were the same as above for the initial 42 h, but the final conditions, when zones three and four were cooled, were held for 85 h, not 36. The last series of reactions was run with conditions identical with those of the second series, except that only 0.8 g of starting material was used. The reaction was ended by flushing the system for 12 h with helium, then warming the reactor and transferring the volatile products to a liquid-nitrogen-cooled trap.

The products from the trap were initially separated on the SE-30 column at 30 °C. 3,3-Dihydrooctadecafluoro-2,2,4,4-tetramethylpentane had a retention time of 15 min, while the monohydro and perfluoro compounds both had a retention time of 24 min. The latter two materials were then separated on the dinonyl phthalate column held at 10 °C. Perfluoro-2,2,4,4-tetramethylpentane had a retention time of 10 min and 3-hydrononadecafluoro-2,2,4,4-tetramethylpentane had a retention time of 12 min.

3,3-Dihydrooctadecafluoro-2,2,4,4-tetramethylpentane. Anal. Calcd: C, 23.89; H, 0.44; F, 75.66. Found: C, 23.69; H, 0.39; F, 75.64. The ^{19}F NMR consisted of a singlet at −11.7 ppm from an external trifluoroacetic acid reference. The ^1H NMR consisted of a singlet at τ 7.18. The gas-phase infrared spectrum contained bands at (cm^{-1}) 3025 (w), 1460 (w), 1315 (s), 1295 (vs), 1260 (s), 1215 (w), 1185 (m), 1095 (m), 1045 (s), 990 (m), 740 (m), 695 (m). The mass spectrum at 70 eV contained a peak at m/e of 433 assigned to the parent minus fluorine. The melting point was between −38 and −39 °C.

3-Hydrononadecafluoro-2,2,4,4-tetramethylpentane. Anal. Calcd: C, 22.98; H, 0.21; F, 76.81. Found: C, 22.93; H, 0.18; F, 76.72.

The ^{19}F NMR consisted of a doublet (from the CF_3 groups) centered at −13.8 ppm from an external trifluoroacetic acid reference. The coupling constant, J_{FF}, was 15.9 Hz. The signal from the fluorine on the center carbon atom would be expected to be a doublet of two 19 line multiplets, split by the hydrogen and the CF_3 groups, respectively, hut was of too low an intensity to be observed. The ^1H NMR spectrum consisted of a doublet centered at τ 4.34. The coupling constant, J_{FH}, was 36.6 Hz. The gas-phase infrared spectrum contained bands at (cm^{-1}) 1440 (w), 1365 (m), 1300 (vs), 1290 (vs), 1265 (s), 1225 (w), 1195 (m), 1165 (w), 1080 (w), 1045 (s), 995 (s), 975 (w), 795 (w), 775 (m), 745 (m), 715 (m). The mass spectrum at 70 eV contained no peaks above m/e 381($C_8F_{15}^+$). The melting point was between −33 and −34 °C.

Perfluoro-2,2,4,4-tetramethylpentane. Anal. Calcd: C, 22.13; F, 77.87. Found: C, 22.58; F, 77.63. The ^{19}F NMR spectrum consisted of triplet (from the CF_3 groups) centered at −17.1 ppm from an external trifluoroacetic acid reference. The coupling constant, J_{FF}, was 14.9 Hz. The signal from the two fluorines on the center carbon atom would be expected to be a 19-line multiplet, but was of too low intensity to be observed. The gas-phase infrared spectrum contained bands at (cm^{-1}) 1300 (vs), 1285 (vs), 1270 (s), 1235 (w), 1195 (s), 1175 (w), 1150 (w), 1095 (w), 1025 (w), 990 (s), 815 (m), 750 (m), 740 (s), 715 (m). The mass spectrum at 70 eV contained a peak at m/e 469, assigned to the parent minus fluorine. The melting point was between −24 and −25 °C.

Fluorination of 3,3-Dihydrooctadecafluoro-2,2,4,4-tetramethylpentane. The fluorination system was flushed with helium for 12 h, and then the first two zones of the reactor were cooled to −78 °C and 0.5 g of 3,3-dihydrooctadecafluoro-2,2,4,4-tetramethylpentane was injected. The helium flow was terminated and the fluorine flow was set to 1.5 cm^3/min. After 24 h, reactor zones 3 and 4 were cooled to −78 °C and the first two zones were warmed to room temperature. After an additional 48 h, the reaction was terminated and the product was collected. The product was found to consist entirely of the starting material.

Registry No.—2,2,4,4-Tetramethylpentane, 1070-87-7; 3,3-dihydrooctadecafluoro-2,2,4,4-tetramethylpentane, 41296-82-6; 3-hydrononadecafluoro-2,2,4,4-tetramethylpentane, 62375-53-5; perfluoro-2,2,4,4-pentamethylpentane, 62375-54-6.

References and Notes

(1) N. J. Maraschin, B. D. Catsikis, L. H. Davis, G. Jarvinen, and R. J. Lagow, *J. Am. Chem. Soc.*, **97**, 513 (1975).
(2) J. L. Adcock and R. J. Lagow, *J. Org. Chem.*, **38**, 3617 (1973); *J. Am. Chem. Soc.*, **96**, 7588 (1974); J. L. Adcock, R. A. Beh, and R. J. Lagow, *J. Org. Chem.*, **40**, 3271 (1975).
(3) J. L. Margrave and R. J. Lagow, *J. Inorg. Nucl. Chem.*, **35**, 2084 (1973); N. J. Maraschin and R. J. Lagow, *Inorg. Chem.*, **14**, 1855 (1975).
(4) E. Liu and R. J. Lagow, *J. Am. Chem. Soc.*, **98**, 8270 (1976).
(5) N. J. Maraschin and R. J. Lagow, *J. Am. Chem. Soc.*, **94**, 8601 (1972).
(6) J. E. Huheey, in "Inorganic Chemistry", Harper and Row, New York, N.Y. 1972, p 84.
(7) J. W. Sargent and R. J. Seffl, *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **29**, 1699 (1970); M. Hill, *Chem. Ind. (London)*, 118 (1975).
(8) L. C. Clark, Jr., F. Becattini, and S. Kaplan, *Ala. J. Med. Sci.*, **9**, 16 (1971).

Conversion of Virescenol A into Virescenol B

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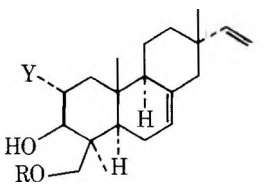
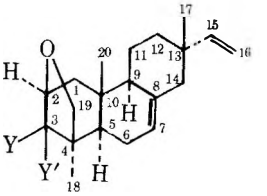
Received April 12, 1977

In connection with a study of the chemistry of virescenol A (**1a**), the aglycone of several of the fungal, virescenoside metabolites,[1] the tetrahydrofuran **2a** has been encountered frequently and now has been utilized for the conversion of virescenol A into B (**1b**).[2]

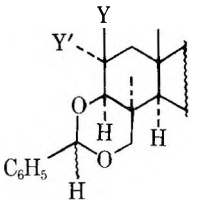
Treatment of virescenol A (**1a**) with benzaldehyde and zinc chloride yielded the benzylidene derivative **3a**,[3] whose reduction with lithium aluminum hydride in the presence of aluminum chloride led to ether **1e**. Attempted tosylation of the latter in pyridine solution gave the hydroxy ether **2a**, presumably by sequential formation of **1f** and the oxonium salt **4**, followed by pyridine debenzylation of the latter.



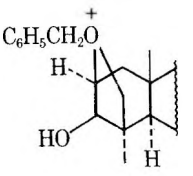
1a, R = H; Y = OH
b, R = Y = H
c, R = Ts; Y = OH
d, R = Ts; Y = OTs
e, R = $CH_2C_6H_5$; Y = OH
f, R = $CH_2C_6H_5$; Y = OTs
g, R = H; Y = OTs



2a, Y = OH; Y′ = H
b, Y + Y′ = O
c, Y = H; Y′ = OH



3a, Y = H; Y′ = OH
b, Y + Y′ = O
c, Y = OH; Y′ = H



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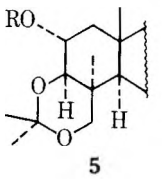

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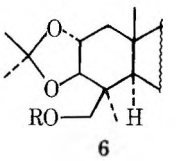
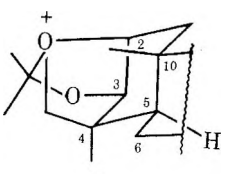


6

a, R = H
b, R = Ts

Treatment of virescenol A (**1a**) with acetone and cupric sulfate produced the isopropylidene derivatives **5a**[4] and **6a**, whose tosylation afforded sulfonic esters **5b** and **6b**, respectively. Even though the latter was stable, tosylate **5b** was converted into the ether **2a** on standing or on exposure to silica gel in benzene. This transformation may be the consequence of displacement of the tosylate by a ketal oxygen (cf. **7**), followed by hydrolysis, or prior hydrolytic formation of dihydroxytosylate **1g** and subsequent internal displacement.



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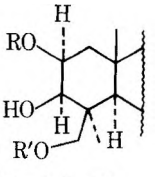
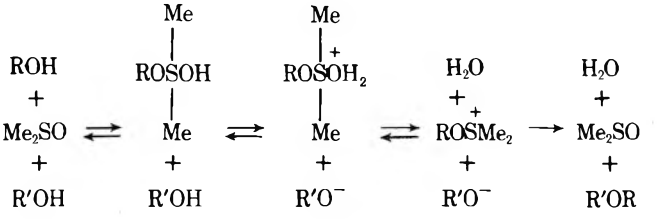


8a, R = R′ = H
b, R = (−); R′ = $^+SMe_2$

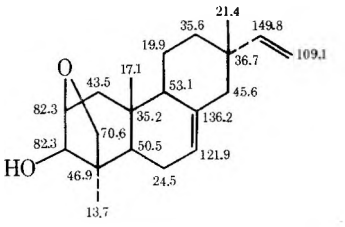
Collins oxidation of the hydroxy acetal **3a** and sodium borohydride reduction of the resultant ketone **3b** gave the isomeric hydroxy acetal **3c**, whose acid hydrolysis yielded 2-



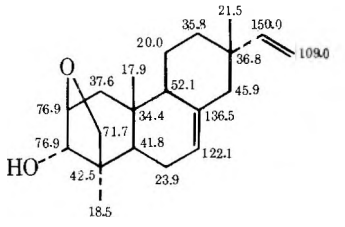
epivirescenol A (**8a**). In analogy with previous reports of tetrahydrofuran formation,[5] heating of a dimethyl sulfoxide solution of **8a** led to a high yield of hydroxy ether **2a**, presumably by way of the mechanism below and hence via intermediate **8b**. Even thermolysis of virescenol A (**1a**) itself in dimethyl sulfoxide produced **2a**, albeit in low yield.

Collins oxidation of hydroxy ether **2a**, thus prepared by a variety of paths from virescenol A (**1a**) (vide supra), yielded ketone **2b**, whose reduction in liquid ammonia with lithium and ethanol yielded virescenol B (**1b**) along with tetrahydrofurans **2a** and **2c**. The latter was also the product of sodium borohydride reduction of ketone **2b** in analogy with the stereoselective hydride reductions of bicyclo[3.2.1]octan-8-ones.[6] The C(3) stereochemistry of the two hydroxytetrahydrofurans was confirmed by ^{13}C NMR spectroscopy.

The carbon shifts of **2a** and **2c** are based on those of isopimaradiene[7] and virescenol B (**1b**)[8] and are listed on formulas **9** and **10**, respectively. The strong shielding of C(1) and C(5)



9



10

in **2c** (**10**) indicates the ring A axiality of the 3-hydroxy group in this isomer. Similarly, the shielding of the 4-methyl group in **2a** reveals a closer proximity of the methyl function to its neighboring hydroxy group in **2a** than in **2c**. These facts confirm the ring A stereochemistry of the two isomeric alcohols.

Experimental Section

Melting points were determined on a Reichert micro hotstage and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 167 spectrophotometer. ^1H NMR spectra of $CDCl_3$ and CCl_4 solutions (Me_4Si, $\delta = 0$) were recorded on a Jeol H-60 spectrometer, while the ^{13}C NMR spectra were produced on a Varian XL-100-15 spectrometer operating at 25.2 MHz in the Fourier transform mode.

3-*O*,19-*O*-Benzylidenevirescenol A (3a). A mixture of benzaldehyde (16 g), zinc chloride (4.0 g), and virescenol A (3.2 g) was stirred at room temperature for 12 h. It then was poured into ice water and extracted with chloroform. The extract was washed in water, dried (Na_2SO_4), and concentrated and the excess benzaldehyde (13 g) was removed by distillation. Chromatography of the residue (6.4 g) on silica and elution with petroleum ether yielded benzaldehyde (1.5 g). Continued elution with 1:1 petroleum ether/ether gave 2.8 g (65%) of **3a:** mp 172–174 °C (methanol); IR ($CHCl_3$) 3580 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.86, 1.03, 1.48 (s, 9, Me_3), 3.40 (d, 1, J = 10 Hz, H-3), 3.63, 4.23 (dd, 2, J = 11 Hz, H-19), 4.46 (m, 1, H-2), 5.70 (s, 1, benzyl H), 7.1–7.6 (m, 5, aromatic Hs).

Anal. Calcd for $C_{27}H_{36}O_3$: C, 79.37; H, 8.88. Found: C, 79.24; H, 8.96.

19-*O*-Benzylvirescenol A (1e). A solution of 0.15 g of 3a in 10 mL of anhydrous tetrahydrofuran was added dropwise to a stirring suspension of 0.12 g of lithium aluminum hydride and 0.20 g of aluminum chloride in 10 mL of tetrahydrofuran under nitrogen and the mixture refluxed for 3 h. $Na_2SO_4 \cdot 10H_2O$ was added cautiously; the mixture was shaken and then filtered. Evaporation of the filtrate gave a residue (0.14 g) which was chromatographed on silica. Elution with 9:1 benzene/ethyl acetate gave 0.10 g (67%) of oily diol **1e:** IR ($CHCl_3$) 3560 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.86, 0.90, 1.30 (s, 9, Me_3), 3.04 (d, 1, J = 10 Hz, H-3), 3.42, 3.98 (dd, 2, J = 10 Hz, H-19), 3.69 (m, 1, H-2), 4.48 (s, 2, benzyl H), 7.3 (m, 5 H, aromatic Hs).

Anal. Calcd for $C_{27}H_{38}O_3$: C, 78.98; H, 9.33. Found: C, 78.74; H, 9.25.

2β,19-*O*-Dehydrovirescenol B (2a). A solution of 0.9 g of **1e** and 0.6 g of tosyl chloride in 10 mL of pyridine was stirred at room temperature for 48 h. It then was poured into ice water and extracted with chloroform. The extract was washed with 1 N hydrochloric acid and water, dried, and concentrated. Chromatography of the residue (1.1 g) on silica and elution with 99:1 chloroform/methanol gave 0.3 g (45%) of **2a:** mp 166–168 °C; IR (CCl_4) 3610 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.88, 1.02, 1.12 (s, 9, Me_3), 3.51 (s, 1, H-3), 3.45, 3.97 (dd, 2, J = 9 Hz, H-19), 4.17 (m, 1, H-2).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.22; H, 10.15.

Isopropylidene Derivatives of Virescenol A (5a and 6a). A mixture of **1a** (0.45 g) and copper sulfate (1.1 g) in 15 mL of acetone was stirred at room temperature for 3 h. It then was filtered and evaporated, and the residue (0.55 g) was chromatographed on Florisil. Elution with benzene gave a fraction (0.15 g, 28%) whose crystallization from methanol yielded **6a:** mp 173–175 °C; IR ($CHCl_3$) 3545 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.85, 0.93, 1.23, 1.43, 1.46 (s, 15, Me_5), 3.16 (d, 1, J = 10 Hz, H-3), 3.33, 4.13 (dd, 2, J = 11 Hz, H-19), 3.80 (m, 1, H-2).

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.38; H, 10.25.

Continued elution with 9:1 benzene/ethyl acetate gave 0.15 g (28%) of oily **5a:** IR ($CHCl_3$) 3560 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.86, 0.96, 1.33, 1.43, 1.53 (s, 15, Me_5), 3.16 (d, 1, J = 10 Hz, H-3), 3.33, 4.13, (dd, 2, J = 12 Hz, H-19), 4.16 (m, 1, H-2).

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.50; H, 10.35.

Further eluction with 4:1 benzene/ethyl acetate gave 0.14 g of starting triol **1a.**

3-*O*,19-*O*-Isopropylidenevirescenol A Tosylate (5b). A solution of 0.20 g of **5a** and 0.15 g of tosyl chloride in 5 mL of pyridine was stirred at room temperature for 48 h. It then was poured into ice water and extracted with chloroform. The extract was washed with 1 N hydrochloric acid and water, dried, and concentrated. Chromatography of the residue (0.3 g) on silica and elution with benzene gave 0.22 g (73%) of oily **5b:** NMR ($CDCl_3$) δ 0.81, 1.00 (s, 6, Me_2), 1.23 (s, 9, Me_3), 2.40 (s, 3, aromatic Me), 3.13 (d, 1, J = 16 Hz, H-3), 3.33, 3.93 (dd, 2, J = 11 Hz, H-19), 4.93 (m, 1, H-2), 7.1, 7.8 (dd, 4, J = 10 Hz, aromatic Hs).

Anal. Calcd for $C_{30}H_{42}O_5S$: C, 70.01; H, 8.23. Found: C, 70.32; H, 8.02.

A mixture of **5b** (0.1 g) and silica gel (1.0 g) in benzene (5 mL) was stirred at room temperature for 2 h. It was filtered and the filtrate concentrated under vacuum. The residue (80 mg) was chromatographed on silica and elution with 9:1 benzene/ethyl acetate gave pure **2a** (vide supra).

2-*O*,3-*O*-Isopropylidenevirescenol A Tosylate (6b). The same treatment of 0.2 g of **6a** and workup gave 0.2 g (70%) of oily **6b:** NMR ($CDCl_3$) δ 0.86, 0.90, 1.13, 1.33, 1.36 (s, 15, Me_5), 2.43 (s, 3, aromatic Me), 3.06 (d, 1, J = 10 Hz, H-3), 3.52 (m, 1, H-2), 4.20 (br s, 2, H-19), 7.15, 7.85 (dd, 4, J = 10 Hz, aromatic Hs).

Anal. Calcd for $C_{30}H_{42}O_5S$: C, 70.01; H, 8.23. Found: C, 70.20; H, 8.07.

Keto Ketal 3b. A solution of **3a** (0.3 g) in methylene chloride (5 mL) was added dropwise (15 min) to a suspension of Collins reagent (1.0 g) in anhydrous methylene chloride (15 mL) and the mixture was stirred at room temperature for 15 min. It was filtered and the filtrate was washed with 10% acetic acid solution. The combined organic solutions were washed with 5% sodium hydroxide, dried, and evaporated. Chromatography of the residue on silica and elution with chloroform gave 0.2 g (68%) of oily ketone **3b:** IR ($CHCl_3$) 1718 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.87, 1.00, 1.60 (s, 9, Me_3), 3.61, 4.15 (dd, 2, J = 11 Hz, H-19), 4.30 (s, 1, H-3), 5.97 (s, 1, benzyl H), 7.2–7.7 (m, 5 H, aromatic Hs).

Anal. Calcd for $C_{27}H_{34}O_3$: C, 79.76; H, 8.43. Found: C, 80.00; H, 8.20.

3-*O*,19-*O*-Benzylidene-2-epivirescenol A (3c). Sodium borohydride (85 mg) was added to a solution of **2b** (0.25 g) in tetrahydrofuran (15 mL) and the mixture was stirred at room temperature for 5 min. Then a 0.1 N sulfuric acid solution (50 mL) was added and the mixture was extracted with chloroform. The extract was washed with saturated sodium bicarbonate solution, dried, and concentrated under vacuum. The residue (0.2 g) was crystallized from 3:2 petroleum ether/benzene, giving 0.15 g (44%) of crystalline **3c:** mp 168–170 °C;

IR ($CHCl_3$) 3575 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.90, 1.16, 1.41 (s, 9, Me_3), 3.50 (d, 1, J = 3Hz, H-3), 3.58, 4.62 (dd, 2, J = 11 Hz, H-19), 6.49 (s, 1, benzyl H), 7.2–7.7 (m, 5 H, aromatic Hs).

Anal. Calcd for $C_{27}H_{36}O_3$: C, 79.37; H, 8.88. Found: C, 79.50; H, 8.58.

2-Epivirescenol A (8a). A mixture of 0.25 g of **3c** and 5 mL of 0.1 N methanolic sulfuric acid in 5 mL of chloroform was refluxed for 5 h. It was diluted with water and extracted with chloroform. The extract was washed with water, dried, and concentrated under vacuum. Chromatography of the residue (90 mg) on silica and elution with 6:1 benzene/ethyl acetate gave 0.13 g (65%) of a solid whose crystallization from 1:1 benzene/petroleum ether yielded crystalline **8a**: mp 168–170 °C; IR ($CHCl_3$) 3570 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.85, 1.05, 1.20 (s, 9, Me_3), 3.38 (m, 1, H-3), 3.48, 4.63 (dd, 2, J = 11 Hz, H-19).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.62; H, 10.30.

A solution of **8a** (0.20 g) in Me_2SO (5 mL) was stirred under nitrogen at 160 °C for 4 h. It then was poured into water and the mixture was extracted with chloroform. The extract was washed with water, dried, and concentrated under vacuum. Chromatography of the residue (0.16 g) on silica and elution with 6:1 benzene/ethyl acetate gave 0.14 g of **2a** (vide supra).

A solution of virescenol A (**1a**) (0.20 g) was treated in the same manner. The same workup gave 50 mg of **2a** (vide supra).

Keto Ether 2b. A solution of hydroxy ether **2a** (0.2 g) in methylene chloride (5 mL) was added dropwise (10–15 min) to a suspension of Collins reagent (0.7 g) in anhydrous methylene chloride (10 mL). The mixture was allowed to stir for an additional 15 min and filtered. The dark filtrate was washed successively with 1 N sulfuric acid and water and concentrated under vacuum. The light brown residue was purified by chromatography on silica. Elution with chloroform led to 0.2 g (100%) of oily **2b**: IR (CCl_4) 1762 cm^{-1} (C=O); NMR ($CDCl_3$) δ 0.91, 1.00, 1.30 (s, 9, Me_3), 3.78, 4.39 (dd, 2, J = 11 Hz, H-19), 4.04 (d, 1, J = 6 Hz, H-2).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.15; H, 9.17.

Reduction of Keto Ether 2b. To a solution of **2b** (0.40 g) in methanol (20 mL) was added a solution of sodium borohydride (90 mg) in 6 mL of 50% aqueous methanol. The mixture was stirred at room temperature for 10 min and then 50 mL of 0.5 N sulfuric acid solution was added thereto. It was extracted with chloroform and the extract was washed with saturated sodium bicarbonate solution, dried, and concentrated under vacuum. Chromatography of the residue on silica and elution with 50:1 chloroform/methanol gave 0.38 g (94%) of oily **2c**: IR (CCl_4) 3650 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.83, 0.88, 1.04 (s, 9, Me_3), 3.36, 3.96 (dd, 2, J = 9.5 Hz, H-19), 3.76 (d, 1, J = 6 Hz, H-3), 4.10 (m, 1, H-2).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.35; H, 9.85.

A solution of 0.16 g of ketone **2b** in 10 mL of 9:1 tetrahydrofuran/ethanol was added over a 10-min period to a solution of lithium (15 mg) in 30 mL of liquid ammonia and the reaction mixture was stirred at −40 °C for 10 min. A few drops of bromobenzene were added to the mixture, the ammonia was evaporated in a stream of nitrogen, and 20 mL of a 0.5 N sulfuric acid solution was added to the residue. The resulting mixture was extracted with chloroform and the extract combined, washed with water, dried, and concentrated under vacuum. Chromatography of the residue (0.12 g) on silica and elution with 9:1 benzene/ethyl acetate gave 25 mg of **2c** (vide supra). Elution with 6:1 benzene/ethyl acetate gave 35 mg of **2a** (vide supra) and 30 mg of virescenol B (**1b**), identical in all respects with an authentic sample.[1]

Tosylation of Virescenol A (1a). A solution of 0.96 g of **1a** and 0.70 g of tosyl chloride in 10 mL of pyridine was stirred at room temperature for 72 h. It was poured into ice water and extracted with chloroform. The extract was washed with 1 N hydrochloric acid and water, dried, and concentrated. Chromatography of the residue (1.2 g) on silica and elution with 9:1 benzene/ethyl acetate gave 0.25 g (13%) of virescenol A 2,19-ditosylate (**1d**) [IR ($CHCl_3$) 3540 cm^{-1} (OH); NMR ($CDCl_3$) δ 0.86 (s, 6, Me_2), 1.03 (s, 3, Me), 2.43 (s, 6, aromatic Me_2), 3.26 (d, 1, J = 10 Hz, H-3), 3.96 (s, 2, H-19), 4.73 (m, 1, H-2), 7.1–7.8 (m, 8, aromatic Hs)], 0.18 g (19%) of tetrahydrofuran **2a** (vide supra), and 0.40 g (28%) of virescenol A 19-tosylate (**1c**) [IR ($CHCl_3$) 3575 cm^{-1} (OH); NMR (CCl_4) δ 0.84 (s, 6, Me_2), 1.50 (s, 3, Me), 2.38 (s, 3, aromatic Me), 7.3–7.6 (dd, 4 H, J = 8 Hz, aromatic Hs)].

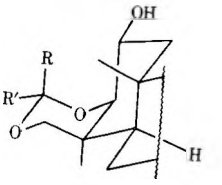
Registry No.—**1a**, 22343-46-9; **1b**, 22343-47-1; **1c**, 63089-00-9; **1d**, 63089-01-0; **1e**, 63089-02-1; **2a**, 63089-03-2; **2b**, 63089-04-3; **2c**, 63121-82-4; **3a**, 63089-05-4; **3b**, 63089-06-5; **5a**, 63089-07-6; **5b**, 63089-08-7; **6a**, 63089-09-8; **6b**, 63089-10-1; **8a**, 63089-11-2; benzaldehyde, 100-52-7.

References and Notes

(1) N. Cagnoli Bellavita, P. Ceccherelli, M. Ribaldi, J. Polonsky, and Z. Baskevitch, *Gazz. Chim. Ital.*, **99**, 1354 (1969); P. Ceccherelli, N. Cagnoli Bellavita, J. Polonsky, and Z. Baskevitch, *Tetrahedron*, **29**, 449 (1973).

(2) The $\Delta^{8(9)}$ isomer of **2a** has been shown previously to accompany the tosylates $\Delta^{8(9)}$-**1c** and $\Delta^{8(9)}$-**1d** as a product of the derivatization of isovirescenol A ($\Delta^{8(9)}$-**1a**) [J. Polonsky, Z. Baskevitch, N. Cagnoli Bellavita, and P. Ceccherelli, *Bull. Soc. Chim. Fr.*, 1912 (1970)].

(3) This substance probably possesses the benzylic β-hydrogen configuration, depicted in conformational structure i.



i, R = H; R′ = C_6H_5
ii, R = R′ = Me

(4) This ketal can be represented by structure ii, in which an energetically unfavorable, 1,3-diaxial, nonbonded interaction exists between the ketal β-methyl group and the C(2)–C(3) bond. This may be responsible for the production of two ketals, but only one acetal.

(5) B. T. Gillis and P. E. Beck, *J. Org. Chem.*, **28**, 1388 (1963); P. R. Jefferies and C. A. Henrick, *Chem. Ind. (London)*, 1801 (1963).

(6) E. Wenkert and Z. Kumazawa, *Chem. Commun.*, 140 (1968).

One-Vessel Synthesis of 4-Hydroxyproline from Glyoxal and Oxaloacetic Acid[1]

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Received April 20, 1977

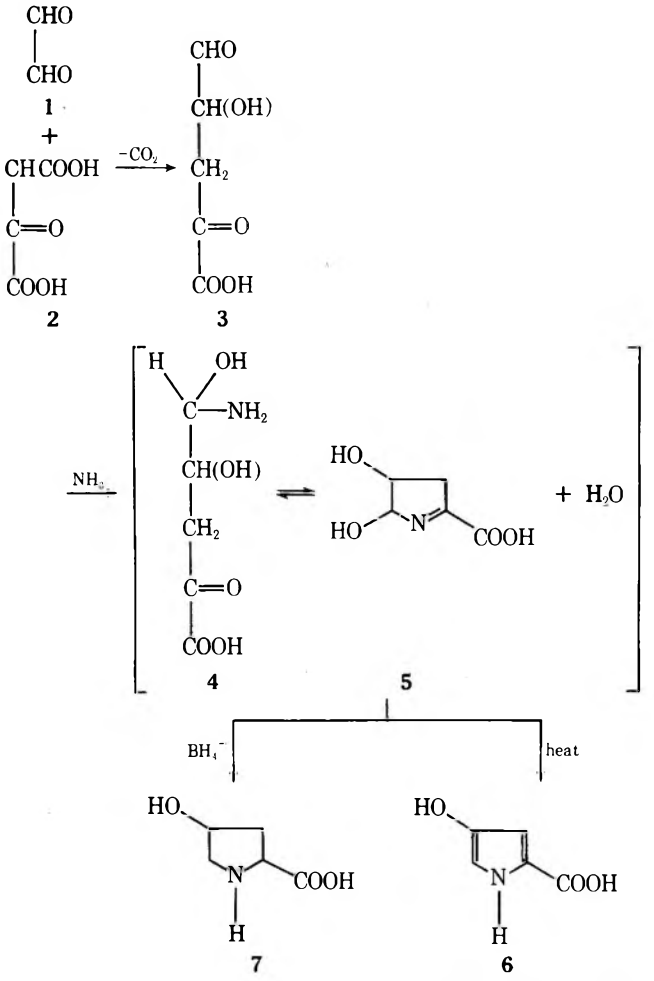
4-Hydroxyproline, obtained initially by isolation from gelatin hydrolyzates,[2] was first synthesized by Leuchs,[3] and subsequently by a variety of other procedures. Some of these were variants of the Leuchs method involving a valerolactone intermediate;[4–8] others were based on different routes,[9–12] but generally required rather complex reaction sequences, commercially unavailable starting materials, or necessitated the isolation of intermediates.

We report here a new synthesis of the mixed racemates of 4-hydroxyproline, obtained in good yield from the commercially available starting compounds, glyoxal and oxaloacetic acid. Although this procedure was briefly cited earlier[13] in connection with the use of one of the intermediates (**3**, Scheme I), no details were presented. The entire reaction sequence is carried out in a single vessel, the yield is approximately 40% (mixture of racemates), and the starting materials have the advantage that at least one can be obtained readily in radioactive form,[14] since the goal in synthesizing 4-hydroxyproline is usually to obtain the radioactive (especially, the ^{14}C) product.

Results and Discussion

In outline, this procedure involves simply the reaction of equimolar glyoxal and oxaloacetic acid in aqueous solution at room temperature and neutral pH, and the subsequent addition, successively, of excess NH_4OH and sodium borohydride. Our speculation concerning intermediate steps is outlined in Scheme I, as supported by previous reports of analogous synthetic steps, involving the condensation of glyoxylic acid and oxaloacetic acid to form 4-hydroxy-2-ketoglutaric acid[15,16] (in analogy with **3**, Scheme I), the formation of pyrrole-2-carboxylic acid[17] (in analogy with **6**, Scheme I),

Scheme I



or the conversion of 2-ketoglutaric semialdehyde to proline[17,18] (in analogy with the conversion of **3** to **7**, Scheme I).

The rather involved series of column purification steps described below were aimed at establishing the products as crystalline *trans*- and *cis*-4-hydroxyproline. For the isolation of radioactive products on a small scale, it would seem sufficient simply to carry out the first desalting step (Dowex 50 H^+ chromatography) followed by separation of the two diastereomeric forms on an amino acid analyzer type column.

Experimental Section

Starting materials were glyoxal trimeric dihydrate and oxaloacetic acid (both from Sigma Chemical Co.). Sodium borohydride was a British Drug House product, 4-hydroxy-L-proline and allo-4-hydroxy-D-proline were purchased from Sigma Chemical Co. [2-^{14}C]-4-Hydroxy-DL-proline (4×10^7 dpm/μmol) was purchased from Amersham Searle Corp. Resins used were Dowex 50-W X-8, 100–200 mesh (Sigma); AG-1-X8, 100–200 mesh, and AG-50W X12, 400 mesh, both from BioRad Laboratories.

Paper electrophoresis was carried out at pH 1.85 at 260 V/cm.[19] Amino acid analysis was carried out by the methods and with the buffer system described earlier;[20] by this method, *trans*-4-hydroxyproline and *cis*-4-hydroxyproline are eluted at approximately 65–70 and 80–85 min, respectively. Colorimetric analysis for 4-hydroxyproline utilized a modification of the procedure of Cleary and Saunders.[21] NMR spectra were obtained at room temperature with a Jeolco 60-MHz instrument. Optical rotation was measured in a Bendix NPL polarimeter.

Reaction Mixture. Equal amounts of glyoxal trimeric dihydrate and oxaloacetic acid, usually 0.5 to 0.6 mmol, were dissolved in water; the solution was adjusted to pH 7.5 with 1 N NaOH, brought to a final volume of 10 mL, and kept at 20–25 °C for 24 h, then treated with 0.75 mL of concentrated NH_4OH. After 10 min, sodium borohydride (0.4 g) was added, and after a further 10 min, the reaction mixture was acidified to pH 1 (pH paper) with 6 N HCl. Aliquots of the reaction mixture, assayed for hydroxyproline, showed yields ranging from 26 to 41%.

Estimation of *cis*- and *trans*-4-Hydroxyproline and Other Amino Acids. After addition of [^{14}C]-*trans*-4-hydroxyproline as a tracer, an aliquot of the reaction mixture was desalted by passage through Dowex-50 H^+ (1 × 33 cm column) and elution with 0.23 N NH_4OH; recovery of both radioactively and chemically determined hydroxyproline was close to 100%. The NH_3 was removed by flash evaporation and the dry residue was taken up in dilute HCl (pH 1.5). Amino acid analysis showed equal amounts of *cis*- and *trans*-4-hydroxyproline as the major peaks. Small peaks in the positions of aspartic acid, serine, and alanine were also present, the peak consistent with aspartic acid (approximately one-sixth the molar quantity of hydroxyproline) being the major impurity. Oxaloacetic acid was apparently responsible for these side products, since its omission from the reaction mixture prevented their appearance, while the omission of glyoxal alone did not.

Purification, Separation of Cis and Trans Racemates, and Crystallization. A large-scale reaction mixture, identical with that described above, utilized 6 mmol each of glyoxal trimeric dihydrate and oxaloacetic acid. It was treated exactly as noted and yielded 1.7 mmol (28%) of hydroxyproline. [^{14}C]-*trans*-Hydroxyproline was added as a tracer, the reaction mixture was evaporated to dryness, and, to remove a large proportion of the salt present, the dry residue was extracted twice by stirring with 30 mL of 80% ethanol for 1 h at 5 °C. Ethanol was removed by flash evaporation; the residue was taken up in 10 mL of water and passed through a column of Dowex 1 acetate (AG-1 × 8, 3 × 25 cm) to remove aspartic acid. The effluent was evaporated to dryness, taken up in 5 mL of water, acidified to pH 2, applied to a Dowex 50 H^+ column (3 × 25 cm), and eluted with 0.23 N NH_4OH.

Separation of the cis and trans forms followed a scaled-up modification of the method of Piez et al.[22] utilizing a heated column (55 °C, 1.6 × 70 cm) of AG 50 W × 12, 400-mesh resin;[23] only one-third of the pooled eluates from the Dowex 50 column above was chromatographed at a time. In each run, *trans*-hydroxyproline, coincident with the radioactive tracer, was eluted as a separate peak (125–150 mL) followed closely by *cis*-hydroxyproline. Corresponding peaks were pooled from the three runs and represented 470 μmol of *trans*-hydroxyproline and 520 μmol of *cis*-hydroxyproline, about 60% recovery of the sample loaded. Each pool was evaporated to dryness and again desalted by adsorption to Dowex 50 H^+ as above and elution with 0.23 N NH_4OH. The eluates were pooled, dried, and dissolved with heating in a small volume of 90% ethanol. Crystals appeared after several days at 5 °C. On drying, these first crops weighed 30 (trans form) and 24 mg (cis form).

Identity and Purity of the Crystalline Racemates. Samples of each crystalline product were run on paper electrophoresis, on the amino acid analyzer, and from each, NMR spectra were obtained in D_2O. Amino acid analysis indicated that each sample was eluted in the expected position and was free of other ninhydrin-reactive peaks. Paper electrophoresis showed that each sample migrated with the authentic reference isomer. NMR spectra indicated identity with the corresponding reference standard, hydroxy-L-proline or allohydroxy-D-proline; the spectra agreed with those reported earlier.[25] As expected for this synthetic route, solutions of the trans and cis forms of hydroxyproline gave zero rotation, indicating each as the racemate.

Acknowledgments. The authors wish to thank Dr. K. A. Rosler (University of Maryland School of Pharmacy) for help in obtaining NMR spectra and Dr. C. D. Gutsche (Washington University) for his comments on the manuscript.

Registry No.—Glyoxal, 107-22-2; oxaloacetic acid, 32842-7; *cis*-4-hydroxyproline, 49761-17-3; *trans*-4-hydroxyproline, 618-28-0.

References and Notes

(1) This investigation was supported by PHS Grant GM 11105 and NSF Grant BMS 74-21153.
(2) E. Fischer, *Ber.*, **35**, 2660 (1902).
(3) H. Leuchs, *Ber.*, **38**, 1937 (1905).
(4) J. Capková-Jirku, J. V. Kostir, and M. Vondracek, *Chem. List*, **44**, 19 (1950).
(5) E. Hammarsten, *C. R. Trav. Lab. Carlsberg*, **11**, 223 (1916).
(6) H. McIlwain and G. M. Richardson, *Biochem. J.*, **33**, 44 (1939).
(7) R. Gaudry and C. Godin, *J. Am. Chem. Soc.*, **76**, 139 (1954).
(8) Y. K. Lee and T. Kaneko, *Bull. Chem. Soc. Jpn.*, **46**, 2914 (1973).
(9) R. Kuhn and G. Osswald, *Chem. Ber.*, **89**, 1423 (1956).
(10) B. Witkop and T. Beiler, *J. Am. Chem. Soc.*, **78**, 2882 (1956).
(11) C. Eguchi and A. Kakuta, *Bull. Chem. Soc. Jpn.*, **47**, 1704 (1974).
(12) T. Wieland, and U. Wintermeyer, *Chem. Ber.*, **90**, 1721 (1957).
(13) E. Adams, and G. Rosso, *J. Biol. Chem.*, **242**, 1802 (1967).
(14) Although [^{14}C]glyoxal or [^{14}C]oxaloacetic acid are not presently available

from standard commercial sources, variously labeled forms of [^{14}C]oxaloacetic acid are readily obtained from correspondingly labeled [^{14}C]-aspartic acid, a commonly offered commercial product (cf. A. Goldstone and E. Adams, *J. Biol. Chem.*, **240**, 2077 (1965)).
(15) A. Ruffo, E. Testa, A. Adinolfi, and G. Pelizza, *Biochem. J.*, **85**, 588 (1962).
(16) E. Adams, *Methods Enzymol.*, **17B**, 273 (1971).
(17) R. M. M. Singh and E. Adams, *J. Biol. Chem.*, **240**, 4352 (1965).
(18) R. Schwyzer, U.S. Patent 2 917 519 (1959).
(19) J. C. Sheehan and J. G. Whitney, *J. Am. Chem. Soc.*, **85**, 3863 (1963).
(20) R. M. Gryder, M. Lamon and E. Adams, *J. Biol. Chem.*, **250**, 2470 (1975).
(21) J. Cleary and R. A. Saunders, *Clin. Chim. Acta*, **57**, 217 (1974).
(22) K. A. Piez, F. Irreverre and H. L. Wolff, *J. Biol. Chem.*, **223**, 687 (1956).
(23) For large-scale preparative purposes, fractional crystallization either of the copper salts,[2] or of free hydroxyproline itself,[24] is a more practical way of separating the diasteromeric racemates; we chose ion-exchange separation in order to maximize the purity of the products.
(24) D. S. Robinson and J. P. Greenstein, *J. Biol. Chem.*, **195**, 383 (1952).
(25) R. J. Abraham and K. A. McLauchlan *Mol. Phys.*, **5**, 195 (1962).

A Convenient Synthesis of 3- and 4-Methylphthalonitrile

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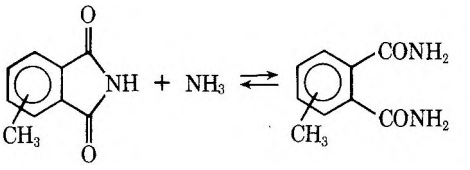
Received March 25, 1977

Recent interest in more soluble derivatives of N-donor chelating ligands, such as phthalocyanine[1,2] and 1,3-bis(2-pyridylimino)isoindoline,[3,4] made desirable a facile synthesis for precursor alkyl-substituted phthalonitriles. Although 3- and 4-methylphthalonitrile were first prepared many years ago, the multi-step synthesis is time consuming and deficient in overall yield.[5-8] More recently, alternate syntheses for alkyl-substituted phthalonitriles have been reported, but they rely upon less readily available starting materials.[9-11] We report here a convenient high yield synthesis of 3- and 4-methylphthalonitrile from the commercially available phthalic anhydrides. 3- and 4-alkylphthalic anhydrides are particularly suitable starting materials because alkyl-substituted phthalic anhydrides are obtainable from dehydrogenation of Diels–Alder adducts of maleic anhydride and the appropriately substituted butadienes.[12]

Results and Discussion

Although unsubstituted phthalic anhydride may be readily converted to phthalonitrile via phthalimide and phthalamide intermediates, this chemical reaction sequence fails when applied to the synthesis of alkyl-substituted phthalonitriles. 3- and 4-methylphthalic anhydride **1** are readily converted to the corresponding imide **2** in high yield. However, unlike phthalimide itself, which reacts with ammonium hydroxide to form phthalamide in good yield, 3- and 4-methylphthalimide **2** react with ammonium hydroxide under identical conditions to form a water-soluble product characterized as the ammonium half-salt of the acid amide **4** (probably a mixture of the the two possible positional isomers). The infrared and elemental analyses are consistent with the presence of carboxylate and amide groups. Treatment of the salt **4** with thionyl chloride or heat resulted in reconversion to the starting imide **2**; treatment of salt **4** with dilute acid afforded the corresponding phthalic acid **5**.

Conversion of 3- or 4-methylphthalimide **2** to the diamide **3** was possible upon treatment of the imide with dry ammonia; up to 80% conversion was obtained and unreacted imide could be recycled. The difference in reactivity between unsubstituted phthalimide and 3- or 4-methylphthalimide **2** may be associated with the imide–amide equilibrium (eq 1), which is



apparently less favorable for 3- or 4-methylphthalamide than it is for unsubstituted phthalamide.

3-Methylphthalamide (**3**) was more easily converted to the nitrile **6** than was the 4-methyl derivative. With acetic anhydride the yield of 3-methylphthalonitrile was only 15%, but with $SOCl_2$/DMF at 0 or −12 °C the yield was as high as 80%. With acetic anhydride the yield of 4-methylphthalonitrile was considerably less than 15% and with $SOCl_2$/DMF at 0 °C the yield was still negligible (in the latter case the imide was the only major product observed). However, reducing the temperature of the $SOCl_2$/DMF reaction to −12 °C or using reverse addition resulted in yields of 4-methylphthalonitrile as high as 84%. The beneficial effect of lower temperatures on the $SOCl_2$/DMF dehydration of aromatic amides was reported earlier by Thurman.[13]

The convenient three-step sequence presented here allowed formation of 3-methylphthalonitrile in 60% and 4-methylphthalonitrile in 62% overall yield from commercially available starting materials.

Experimental Section

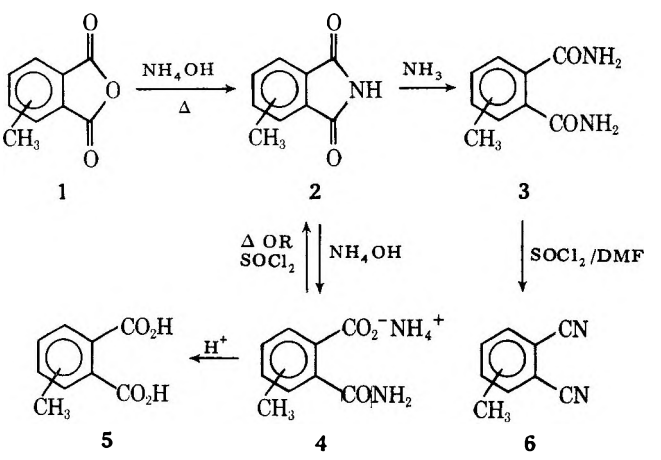
3- and 4-methylphthalic anhydride were obtained from Eastman Chemicals and used as obtained. Infrared spectra were recorded from KBr pellets on a Perkin-Elmer Model 457 spectrophotometer; only pertinent absorption bands are reported. NMR spectra were recorded where solubility permitted with tetramethylsilane as an internal standard. Melting points are reported uncorrected. Microanalyses were performed by Central Laboratory Services of the Ford Motor Company.

3-Methylphthalimide. The imide was prepared from 3-methylphthalic anhydride according to the general procedure of Noyes and Potter.[14] The 3-methylphthalimide was conveniently purified by Soxhlet extraction with benzene and was obtained in 98% yield as white crystals, mp 186–187 °C (lit.[8] 189–190 °C).

4-Methylphthalimide. This imide was obtained by the same method as white crystals in 93% yield, mp 195–196 °C (lit.[6] 196 °C).

Reaction of 3-Methylphthalimide with Ammonium Hydroxide. A flask was charged with 0.22 g of 3-methylphthalimide, 5 mL of ethanol, and 8 mL of aqueous ammonia. The mixture was stirred at 24 °C for 40 h. After the solvent was evaporated under a stream of N_2, the residue was recrystalized from methanol–ethyl acetate to yield

Scheme I



0.10 g of off-white crystalline powder: mp 137–139 °C; IR (KBr) 3380 (m), 3170 (m), 1650 (s), 1590 (m-s), 1560 (s), 1468 (m), 1440 (m), 1390 (s) cm^{-1}.

Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 53.73; H, 6.64; N, 12.92. Material obtained from other runs of this reaction likewise failed to give good C, H, and N analyses; attempts at further purification of the salt resulted in decomposition.

Reaction of 4-Methylphthalimide with Ammonium Hydroxide. When 4-methylphthalimide was treated with NH_4OH as described above, an off-white powder was obtained. Recrystallization of the powder from water–ethanol afforded white crystals: mp 172–173 °C (melting point was not consistent from batch to batch); IR (KBr) 3420 (m-s), 3180 (m-s), 1710 (w), 1670 (m), 1620 (m-s), 1578 (m), 1538 (m-s), 1410 (m-s), 1390 (m-s) cm^{-1}.

Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.17; N, 14.28. Found: C, 54.84; H, 6.15; N, 14.29.

A sample of the salt was treated with 10% hydrochloric acid. After the solvent had evaporated the residue was extracted with ethyl acetate. Addition of heptane to the extract induced crystallization of 4-methylphthalic acid: mp 156–157 °C (lit.[7] 152 °C); IR (KBr) ν_{CO} 1690 (s, br) cm^{-1}.

To a slurry of the salt (1.0 g) in 12 mL of DMF which was cooled to ca. −10 °C was added dropwise 1.7 mL of thionyl chloride. After the addition was complete, the temperature was allowed to rise to 24 °C and stirring was continued for 16 h. The reaction mixture was poured over 50 mL of ice and then filtered to collect 0.82 g (90%) of a white powder, spectroscopically identical with an authentic sample of 4-methylphthalimide.

A 50-mg sample of the salt was heated in an evacuated glass vessel for 15 min at 196 °C. Recrystallization of the cool melt from benzene–heptane afforded 33 mg (79%) of white powder: mp 194–195.5 °C (lit.[6] 196 °C), spectroscopically identical with 4-methylphthamide.

3-Methylphthalamide. A 3-oz glass pressure vessel was charged with 4.01 g (24.9 mmol) of 3-methylphthalimide and 4 mL of dry DMF. The suspension was cooled to 0 °C and the ammonia gas was bubbled in for 30 min. The vessel was pressurized to 50 psi and then heated for 8 h at 45 °C. After cooling to room temperature the pressure was carefully released. Acetonitrile (20 mL) was added with stirring and the mixture was suction filtered. After vacuum drying (70 °C) 3.38 g of 3-methylphthalamide (76% yield) was obtained as a white powder: mp 225 °C; IR (KBr) 3420 (m-s), 3330 (m), 3200 (m), 1680 (m), 1655 (s), 1610 (m-s), 1582 (w-m) cm^{-1}.

Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.34; H, 5.72; N, 15.75.

3-Methylphthalimide (1.07 g) was recovered from the filtrate and could be recycled.

4-Methylphthalamide. A 3-oz glass pressure vessel was charged with 4.01 g of 4-methylphthalimide and 40 mL of absolute ethanol. After the mixture was cooled to 0 °C, ammonia was bubbled into the suspension for 30 min. The reaction mixture was pressurized with ammonia until a pressure of 50 psi was maintained, and the mixture was then heated for 18 h at 50 °C. After cooling to room temperature, the pressure was carefully released and the mixture was filtered. Pure 4-methylphthalamide, 3.56 g (80% yield), was obtained: mp 188 °C (lit.[7] 188 °C); IR (KBr) 3435 (m-s), 3235 (m), 3200 (m), 1690 (m), 1655 (s), 1630 (sh), 1605 (m-s), 1582 (w-m) cm^{-1}.

3-Methylphthalonitrile. Method A. A flask was charged with 1.00 g of 3-methylphthalamide, 15 mL of dry DMF, and a magnetic stir bar, and was capped with a rubber septum and cooled to 0 °C (ice bath). Thionyl chloride (1.49 g) was added with stirring over a 30-min period (via syringe). The reaction mixture was allowed to slowly warm to room temperature and was then poured over 80 g of ice. The water-insoluble product was collected by filtration, washed with water, and dried. The yield of 3-methylphthalonitrile was 0.638 g (80%): mp 143 °C (lit.[8] 143 °C); IR (KBr) ν_{CN} 2230 cm^{-1}.

Method B. A suspension of 3.77 g (21.2 mmol) of 3-methylphthalamide in 20 mL of dry DMF was added to a solution of 3.9 mL (53 mmol) of thionyl chloride in 9 mL of DMF which had been cooled to 0 °C. The addition was made over a 30-min period; after an additional 30 min, the reaction mixture was poured over ice (150 g). The product was collected by filtration and dried to afford 1.18 g (39%) of the dinitrile.

4-Methylphthalonitrile. Method A. A flask was similarly charged with 1.00 g of 4-methylphthalamide, 15 mL of dry DMF, and a magnetic stir bar, and was capped with a rubber septum and cooled to −12 °C (NaCl–ice bath). Thionyl chloride (1.48 g) was added (via syringe) with stirring over a 30-min period. The reaction mixture was allowed to warm to room temperature and stirring was continued for ca. 16 h. The reaction mixture was poured over 83 g of ice and the insoluble product was collected by filtration, washed with water, and dried. The yield of 4-methylphthalonitrile was 0.39 g (48%): mp 120 °C (lit.[6] 120 °C); IR (KBr) ν_{CN} 2255 cm^{-1}.

Method B. A suspension of 3.90 g (21.9 mmol) of 4-methylphthalamide in 20 mL of dry DMF was added to a solution of 4.0 mL (55 mmol) of thionyl chloride in 20 mL of DMF which had been cooled to 0 °C. The addition was carried out over a 20-min period, after which the mixture was allowed to warm to room temperature. The reaction mixture was poured over ice and the product collected by filtration. A white powder (mp 122 °C) was obtained in 84% yield (2.62 g).

Registry No.—3-methyl-**2**, 7251-82-3; 4-methyl-**2**, 40314-06-5; 3-methyl-**3**, 63089-46-3; 4-methyl-**3**, 63089-47-4; 3-methyl-**4**, 63089-48-5; 4-methyl-**4**, 63089-49-6; 4-methyl-**5**, 4316-23-8; 3-methyl-**6**, 36715-97-6; 4-methyl-**6**, 63089-50-9.

Acknowledgment. The authors gratefully acknowledge inspiration and encouragement from Dr. Lee R. Mahoney.

References and Notes

(1) E. A. Luk'yanets, S. A. Mikhalenko, and E. I. Kovshev, *Zh. Obshch. Khim.*, **41**, 934 (1971).
(2) K. Chiba, E. Endo, and K. Yamaka, *Bull. Chem. Soc. Jpn.*, **48**, 743 (1975).
(3) W. O. Siegl, *J. Organomet. Chem.*, **107**, C27 (1976).
(4) W. O. Siegl, *J. Org. Chem.*, **42**, 1872 (1977).
(5) G. Glock, *Ber.*, **21**, 2659 (1888).
(6) S. Niementowski, *Monatsch. Chem.*, **12**, 624 (1891).
(7) W. Findeklee, *Ber.*, **38**, 3542 (1905).
(8) Gabriel and Thieme, *Ber.*, **52**, 1082 (1919).
(9) R. Helder and H. Wynberg, *Tetrahedron Lett.*, 605 (1972).
(10) S. A. Mikhalenko, S. A. Gladyr, and E. A. Luk'yanets, *Zh. Org. Khim.*, **8**, 341 (1972).
(11) H. Suzuki and T. Hanafusa, *Synthesis*, 53 (1974).
(12) D. Colaitis, *C. R. Acad. Sci.*, **250**, 328 (1960).
(13) J. C. Thurman, *Chem. Ind. (London)*, 752 (1964).
(14) W. A. Noyes and P. K. Potter, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1941, p 457.

The Bimolecular Elimination of *trans*-2-Methylcycloocytl Tosylate. A Reinvestigation

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Received February 17, 1977

Our continuing interest in the synthetically useful reactions of eight-membered rings[1a–c] has recently led us to reinvestigate the elimination reaction of *trans*-2-methylcyclooctyl tosylate. In 1966, Brown and Klimisch published preliminary results[2] on that reaction as part of a study of E2 eliminations in a series of *trans*-2-methylcycloalkyl tosylates, using potassium *tert*-butoxide in *tert*-butyl alcohol. For the five-, six-, and seven-membered rings, they obtained a 99:1 ratio of 3-methylcycloalkene to the 1-methyl isomer. However, this expected selectivity (based on the well-documented stereoelectronic requirement for an anti-periplanar transition state

Table I

Conditions[a]	cis-1-Methylcyclooctene	*cis*-3-Methylcyclooctene
Literature[2]	1	1
50 °C, 3 h, KO-*t*-Bu, *t*-BuOH	2	1
50 °C, 3 h, Na_2CO_3, *t*-BuOh	2.5	1
25 °C, 30 min, KO-*t*-Bu, Me_2SO	1	23

[a] Both alkenes are stable to these reaction conditions.

in such reactions) was not followed by the eight-membered tosylate, which afforded a 1:1 ratio of olefins.

We were intrigued by this anomolous behavior of the cyclooctane ring, and especially by the possibility that the 1-methyl iosmer could have resulted from a trans elimination toward the methyl group, giving *trans*-1-methylcyclooctene,[3] which the reported acidic workup might well have isomerized to the observed *cis*-1-methylcyclooctene. However, repetition of the experiment followed by a careful, nonacidic workup yielded no such trans olefin.

It has long been known that the introduction of sp^2 centers into a saturated eight-membered ring significantly relieves nonbonded interaction (I-strain) in the ring;[4] it seemed possible that such an effect could so favor an E1 process[5] as to render it competitive with the E2 reaction. Accordingly, a series of experiments was run (summarized in Table I) including a solvolysis where *trans*-1-methylcyclooctyl tosylate was treated in *tert*-butyl alcohol with heterogeneous carbonate as the only base.[6] Under conditions identical with the butoxide experiments (50 °C, 3 h), a product ratio of 2.5:1 (1-methylcyclooctene to 3-methylcyclooctene, respectively) was obtained in high yield. In one repetition of the original experiment, we observed a rate qualitatively equal to that reported,[2] but a product ratio favoring the 1-methyl isomer. Given these results, it appears likely that the observed 1-methycyclooctene actually results from a solvolytic, E1 reaction with a rate comparable to that of the bimolecular elimination being studied. To test this hypothesis, a reaction was run with potassium *tert*-butoxide in dimethyl sulfoxide at room temperature, since these conditions should favor the E2 mechanism at the expense of E1; indeed, after 30 min a nearly quantitative yield of alkenes was obtained with 3-methylcyclooctene highly favored (>20:1).

In conclusion, we feel that cyclooctyl sulfonates do not provide an exception to the anti-periplanar rule; thus, for synthetic purposes, the direction of bimolecular eliminations in these systems can be predicted with the same confidence as for other alkyl tosylates.

Experimental Section

Elimination Reaction Using Carbonate and *tert*-Butyl Alcohol. To a 0.32 M solution of *trans*-2-methylcyclooctyl tosylate[2] in dry *tert*-butyl alcohol was added 1 equiv of solid sodium carbonate (to bind any tosyl acid formed). This heterogeneous solution was stirred under nitrogen at 50 °C for 3 h. The resulting mixture was diluted with water and extracted three times with pentane. The combined pentane extracts were dried with 4-Å molecular sieves and concentrated (by distilling the pentane at 760 mm) to give the crude product, analyzed by gas chromatography (Carbowax 20 M). The gas chromatogram showed two peaks, in the ratio of 2.5:1, whose retention times were identical with those for authentic samples of *cis*-1-methylcyclooctene and *cis*-3-methylcyclooctene, respectively. The combined yield was >95% (GC).

Elimination Reaction Using Potassium *tert*-Butoxide in Me_2SO. *trans*-2-Methylcyclooctyl tosylate was dissolved in dry dimethyl sulfoxide and 2.5 equiv of solid potassium *tert*-butoxide was added under nitrogen (the resulting solution was 0.5 M in base). The reaction mixture immediately became dark green and slightly warm. After 30 min, isolation was effected as above. The yield of *cis*-3-methylcyclooctene, identified by NMR (^1H and ^{13}C), was determined to be 93%, while *cis*-1-methylcyclooctene was produced in 4% yield.

Elimination Reaction Using Potassium *tert*-Butoxide in *tert*-Butyl Alcohol. A solution of *trans*-2-methylcyclooctyl tosylate and 2.5 equiv of potassium *tert*-butoxide in dry *tert*-butyl alcohol (0.26 M in tosylate, 0.65 M in base) was stirred under nitrogen at 50 °C for 3 h. Isolation as before provided a 2:1 ratio of the 1-methyl- to 3-methylcyclooctene in a combined yield of 65%.

Acknowledgment. Financial support of this research by the Robert A. Welch Foundation is gratefully acknowledged.

Registry No.—*trans*-2-Methylcyclooctyl tosylate, 6597-13-3; *cis*-3-methylcyclooctene, 15840-65-0; *cis*-1-methylcyclooctene, 15840-64-9.

References and Notes

(1) (a) J. K. Whitesell and P. D. White, *Synthesis*, 602 (1975); (b) J. K. Whitesell and R. S. Matthews, *J. Org. Chem.*, **40**, 3312 (1975); (c) J. K. Whitesell, R. S. Matthews, and P. A. Solomon, *Tetrahedron Lett.*, 1549 (1976).
(2) H. C. Brown and R. L. Klimisch, *J. Am. Chem. Soc.*, **88**, 1430 (1966).
(3) E. Vedejs, K. A. J. Snobler, and P. L. Fuchs, *J. Org. Chem.*, **38**, 1178 (1973).
(4) A. C. Cope, M. M. Martin, and M. A. McKervey, *Q. Rev., Chem. Soc.*, **20**, 119 (1966).
(5) The incursion of E1 components into E2 processes is by no means a new phenomenon; see T. H. Brownlee and W. H. Saunders, Jr., *Proc. Chem. Soc.*, 314 (1961); E. D. Hughes and J. Wilby, *J. Chem. Soc.*, 4094 (1960).
(6) H. C. Brown and R. L. Klimisch, *J. Am. Chem. Soc.*, **88**, 1425 (1966).

A Novel Intramolecular C Alkylation Involving a 1,4-Benzoquinone Derivative

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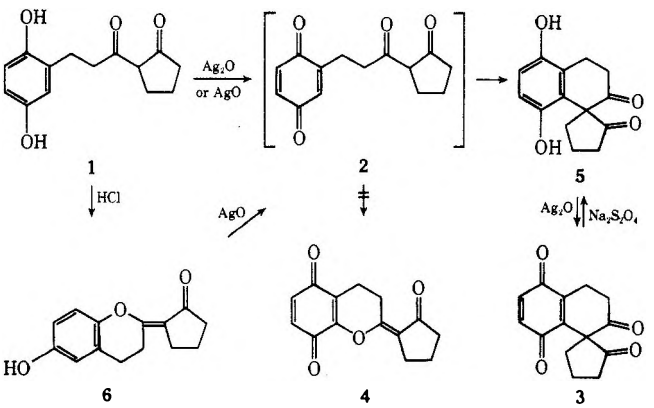
Received February 28, 1977

Part of our investigations, related to the synthesis of substituted 1,4-benzoquinones,[1] dealt with the oxidation of 2-[3-(2,5-dihydroxyphenyl)-1-oxopropyl]cyclopentanone (1)[2] with 1 equiv of silver(I) oxide (Ag_2O). In this reaction two products, a quinone (A), mp 86–87 °C, and a white crystalline compound (B), mp 230–232 °C, were obtained in 26 and 35% yield, respectively. When 2 equiv of silver oxide was used, only A was obtained in 60% yield. The formation of the expected 1,4-benzoquinone, **2**, was ruled out by the fact that reduction of compound A with sodium dithionite did not produce the starting hydroquinone **1**, but gave a hydroquinone identical to compound B. Elemental analysis and the mass spectrum (*m/e* 244) of A indicated the molecular formula to be $C_{14}H_{12}O_4$. The ^1H NMR spectrum exhibited a sharp singlet at δ 6.70 which integrated to two benzoquinone protons.

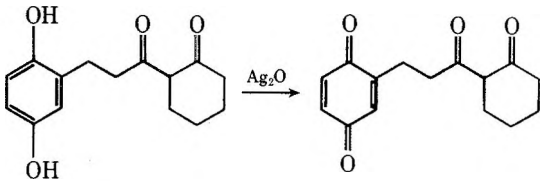
The analytical data indicate intramolecular O or C alkylation of the 1,4-benzoquinone by the 1,3-diketone side chain. In order to differentiate between the C-alkylation product **3** and the O-alkylation product **4**, the catalytic hydrogenation of A was attempted. In this reaction only B was obtained, indicating an absence of a double bond in A. Further evidence was provided by ^{13}C NMR spectroscopy. The ^{13}C NMR spectrum of A exhibited two different carbonyl carbon signals at 212.44 and 204.59 ppm, which were assigned to a cyclopentanone (213.9 ppm) and a cyclohexanone (208.8 ppm)



moiety, respectively.[3] All evidence indicates that the sole oxidation product A of 1 is the intramolecular C-alkylation product **3**, and compound B is its reduction product **5**.

The mechanism of this reaction involves the intermediate formation of **2**, followed by cyclization to give the hydroquinone **5**, which is further oxidized to the final oxidation product **3**. The hydroquinone derivative 1 undergoes cyclodehydration at room temperature in the presence of strong mineral acids, such as hydrochloric acid, to give 6-hydroxy-2-(2′-oxocyclopentylidene)benzopyran (**6**) in virtually quantitative yield. The formation of **3** from **6** involves initial oxidative dealkylation to give **2**, which undergoes cyclization and further oxidation. This mechanism is supported by the fact that hydroquinone dimethyl ethers undergo oxidative demethylation with silver(II) oxide to give the corresponding 1,4-benzoquinones.[4] Furthermore, oxidation of 1 with silver(II) oxide also produced **3** in approximately 40% yield. No other quinones could be isolated.

The C alkylation of 1,4-benzoquinones is a well-known reaction; however, more drastic conditions and a Lewis acid catalyst are always required.[5] The observed facile C alkylation is surprising and prompted us to test the generality of this reaction. The cyclohexanone analogue of 1, compound **7**, was synthesized by the procedure used in the preparation of 1.[6] Oxidation of **7** with both silver(I) oxide and silver(II) oxide



7 **8**

produced solely the 1,4-benzoquinone derivative **8** in quantitative yield. No cyclization of **7** was observed even with anhydrous zinc chloride both at room temperature and at 90 °C. The difference in the stability of the 1,4-benzoquinone derivatives **8** and **2** can only be explained by the acidity differences between the two diketones. The ionization constants of 2-acetylcyclopentanone and 2-acetylcyclohexanone are reported to be 1.5×10^{-8} and 8.1×10^{-11}, respectively.[7] Thus, 2-acetylcyclopentanone is a stronger acid by about 2 pK_a units, which may be sufficient to explain the difference in reactivity of **2** and **8**.

Experimental Section

Infrared spectra were recorded on a Beckman AccuLab 5. ^1H NMR spectra were obtained on a Varian T-60 spectrometer and ^{13}C NMR were obtained on a Varian CFT-20 spectrometer. Mass spectra were obtained on a Varian CH-5 mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. The melting points are uncorrected.

Oxidation of 2-[3-(2,5-dihydroxyphenyl)-1-oxopropyl]-cyclopentanone (2). Silver(I) Oxide (Ag_2O). A solution of 1 (5.0 g, 20 mmol) in 150 mL of ethyl acetate was suspended with Ag_2O (5.0 g, 21 mmol) and anhydrous sodium sulfate (5.6 g, 39 mmol) and stirred. After 18 h, the insolubles were filtered and TLC (6:4 chloroform–ether, silica gel plates) examination showed that it contained one *p*-benzoquinone component. The unconverted starting **2** was removed as a copper complex by stirring with a hot solution of cupric acetate, which amounted to 2.7 g. From the organic layer, after washing with 1 N H_2SO_4, followed by water, and drying (anhydrous $MgSO_4$), 2.2 g of brown viscous liquid was isolated. TLC (6:4 chloroform–ether, silica gel plate) examination revealed that it contained two components. This liquid was chromatographed over 75 g of silica gel (Biosil A, 100–200 mesh). With chloroform was isolated 0.6 g (26%) of **3** as a yellow solid, mp 84–86 °C. After recrystallization from methanol it melted at 86–87 °C: ^1H NMR ($CDCl_3$) δ 2.0–3.2 (m, 10, aliphatic protons of two fused rings), 6.70 (s, 2, *p*-benzoquinone); IR ($CHCl_3$) 1655 cm^{-1} (C=O, benzoquinone), 1700 cm^{-1} (C=O cyclohexanone), 1735 cm^{-1} (C=O cyclopentanone); mass spectrum *m/e* 244 (M^+).

Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.91; H, 5.06.

Further elution with chloroform–ether (6:4) gave a brown liquid which when triturated with ether gave 0.8 g (35%) of **5**, mp 230–232 °C. It was once recrystallized from *n*-hexane–ethyl acetate: mp 234–236 °C; ^1H NMR (acetone-d_6) δ 1.90–3.20 (m, 10), 6.56 (s, 2, aromatic), 7.40 (br s, 2, phenolic OH); IR (KBr) 1698 cm^{-1} (C=O cyclohexanone), 1725 cm^{-1} (C=O cyclopentanone); mass spectrum *m/e* 246 (M^+).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.37; H, 5.68.

When the oxidation was carried out with 2 equiv of Ag_2O (10.0 g, 42 mmol) for 5 days, 3.0 g (60%) of **3** was isolated by similar work-up.

Oxidation of 1 with Silver(II) Oxide (AgO). To a suspension of AgO (1.7 g, 13.7 mmol) in 40 mL of THF (freshly distilled over CaH_2) containing 1 (1.0 g, 4 mmol) was added 4 mL of 6 N HNO_3 under stirring and after 5 min diluted with 160 mL of chloroform and 40 mL of water. Evaporation of the organic layer gave a liquid which partly solidified. Chromatography over 45 g of silica gel using benzene as solvent yielded 0.4 g (40%) of **3**, mp 84–86 °C (mixture melting point and IR spectral comparison with that of **3** from Ag_2O oxidation of 1).

Reduction of (6-Oxo-5,6,7,8-tetrahydro-1,4-naphthoquinone)-5,1′-(2′-oxocyclopentane) (3) with Sodium Dithionite. A solution of **3** (0.5 g) in 100 mL of ethyl acetate was shaken with an aqueous solution of a sodium dithionite (5%) and instantly the quinone was reduced as evidenced by a change in color from light orange to colorless. The organic layer was separated, washed with water, dried (anhydrous $MgSO_4$), and evaporated to give 0.5 g of **5** (100% yield), mp 230–232 °C.

Preparation of 6-Hydroxy-2-(2′-oxocyclopentylidene)benzopyran (6). To 1 (5.0 g, 20 mmol) was added 25 mL of concentrated HCl. The solution turned yellow and solidified. After 5 min, it was diluted with ice-cold water and the resulting white solid was filtered, washed with excess water, and dried to give 4.5 g (97%) of **6**, mp 204–206 °C. It melted at 207–209 °C after one recrystallization from ethyl acetate.

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 73.58; H, 6.40.

Oxidation of 6 with Silver(II) Oxide (AgO). The oxidation of **6** (0.9 g, 3.9 mmol) was conducted similarly to the AgO oxidation of 1, to give 0.4 g (41%) of **3**, identical with the quinone isolated in the oxidation of 1 (mixture melting point and IR spectral comparison).

Oxidation of 2-[3-(2,5-Dihydroxyphenyl)-1-oxopropyl]cyclohexanone (7)[6] with Silver(I) Oxide (Ag_2O). The diketone 7 (2.0 g, 7.6 mmol) in 100 mL of ethyl acetate was stirred with Ag_2O (5.1 g, 21 mmol) and anhydrous sodium sulfate (5.6 g, 20 mmol) for 18 h. The reaction mixture was filtered and TLC (6:4 chloroform–ether, silica gel) showed that it contained one component. Evaporation of the solvent gave 2.0 g (100%) of orange-brown solid, mp 85–87 °C. It was recrystallized from 2-propanol to give orange needles of **8**: mp 87–88 °C; ^1H NMR ($CDCl_3$), δ 6.50–6.65 (m, 1, benzoquinone H adjacent to side chain), 6.70 (s, 2, benzoquinone).

Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20. Found: C, 69.50; H, 6.58.

Reduction of **8** with sodium dithionite gave the starting material **7**.

Oxidation of 7 with Silver(II) Oxide. The oxidation of **7** (1.0 g, 3.8 mmol) was carried out in a manner similar to that of 1 with AgO. The resulting quinone (100% yield) was identical with **8** obtained by Ag_2O oxidation.

Registry No.—**1**, 50714-97-1; **2**, 63216-56-8; **3**, 63250-61-3; **5**, 63216-57-9; **6**, 63216-58-0; **7**, 63216-59-1; **8**, 63216-60-4.

References and Notes

(1) D. V. Rao, H. Ulrich, and A. A. R. Sayigh, *J. Org. Chem.* **40**, 2548 (1975).
(2) H. Bader and A. C. Mehta, U.S. Patent 3,772,368 (*Chem. Abstr.*, **80**, 2695ln (1974)).
(3) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., p 112.
(4) C. D. Snyder and H. Rapoport, *J. Am. Chem. Soc.* **94**, 227 (1972); *ibid.*, **96**, 8046 (1974).
(5) J. H. Wood, C. S. Colburn, Jr., L. Cox, and H. C. Garland, *J. Am. Chem. Soc.* **66**, 1540 (1944); J. A. D. Jeffreys, *J. Chem. Soc.*, 2153 (1959); T. J. King and C. E. Newall, *J. Chem. Soc.*, 974 (1965).
(6) The diketone **7** was prepared following the procedure given in reference **2**. It was purified by the copper complex method, mp 108–110 °C. The spectral data are in agreement with the structure.
(7) R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.* **75**, 2439 (1953).

Improved Reduction of Nitrimines to Nitramines Using Sodium Borohydride and Acetic Acid

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Received April 1, 1977

Imines can generally be reduced efficiently with sodium borohydride, lithium aluminum hydride, catalytic hydrogenation, or dissolving metal reductions. However, in the presence of many functional groups (e.g., esters, ketones, nitro groups, and double bonds), these methods often cannot be employed for imine reduction due to concomitant reduction of the functional group.[1] In such cases, sodium borohydride is usually the reagent of choice,[2] but even it will not always reduce nitro-substituted imines in good yield.

The present study provides a significant improvement in the reduction of nitrimines to nitramines by the addition of acid to the reaction mixture (Table I). The procedure is simple and general, yet provides greatly improved yields over the usual sodium borohydride reduction procedures. When 3β-acetoxy-5α-chloro-6-nitriminocholestane (**1**) was treated with sodium borohydride in dioxane and ethanol, the nitramine **2** was obtained in only 15% yield regardless of reaction time; no nitrimine was recovered. Addition of glacial acetic acid to the reaction mixture dramatically increased the yield of recrystallized product to 76%. Similarly, sodium borohydride reduction of 3-chloro-3-methyl-2-nitriminobutane (**3**) without acid gave only a trace of the nitramine **4**, but when the reduction was run in the presence of acetic acid, the yield of nitramine again jumped to 76%. Although a mechanistic study of the role of acetic acid was not undertaken, the presumed reducing agent is an acyloxyborohydride species formed by the initial reaction of acetic acid and sodium borohydride. Sodium triacetoxyborohydride is known to reduce aldehydes under mild conditions.[3]

That this reduction is general for a variety of structurally different nitrimines and can be accomplished without concomitant reduction of the nitro moiety is illustrated by the reduction of 1-nitrimino-9-chloro-10-methyldecalin (**5**) and 1-chloro-1-(α-nitriminoethyl)cyclohexane (**7**) to their corresponding nitramines **6** and **8**, respectively, in good yield.

Sodium borohydride has been used in acidic media to reduce aldehydes,[3] oxazines,[4] and indoles.[5] These examples generally require the reaction medium itself to be acidic, whereas in the present study only a relatively small amount of acetic acid is required, not enough to acidify the reaction mixture.

Experimental Section

All melting points were uncorrected. NMR spectra were recorded on a Varian A-60 spectrometer using Me_4Si as an internal standard. Infrared spectra were recorded on a Perkin Elmer 137 spectrometer.

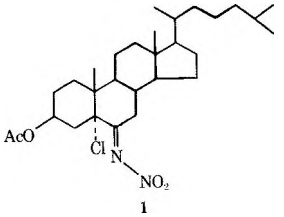
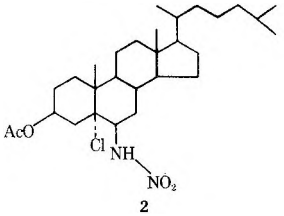
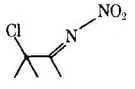
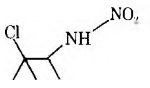
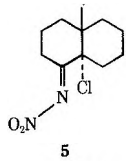
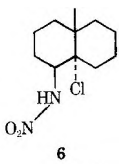
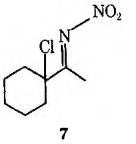
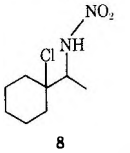
General Procedure for Nitramine Reduction. a solution of 23.2 mmol of nitrimine in 165 mL of dioxane, 165 mL of ethanol, and 0.5 mL of glacial acetic acid was stirred at 0 °C while 229 mmol of sodium borohydride was added as fast as possible while still controlling frothing. The mixture was stirred for 30 min at 0 °C, and 1.5 mL of glacial acetic acid was added (total of 35.0 mmol of HOAc). After stirring for 1 h at 0 °C followed by 1 h at room temperature, the mixture was diluted with 700 mL of 3% aqueous acetic acid and extracted with methylene chloride. The extracts were washed with water, dried, and concentrated in vacuo to give the crude nitramine which was either recrystallized or distilled.

3β-Acetoxy-5α-chloro-6β-nitraminocholestane (2). Sodium borohydride reduction as above of **1**[6] gave a white solid which was recrystallized from acetone to give a 76% yield of **2**: mp 206–206.5 °C (dec); IR (Nujol) 5.85 (s) and 6.20 (s) μm; NMR ($(CD_3)_2SO$) δ 5.50–4.90 (m, 1 H, –COOCH<), 2.28–0.72 (m, 30 H, aliphatic), 1.99 (s, 3 H, CH_3CO–), 1.19 (s, 3 H, C-19 methyl), 0.90 (br s, 6 H, C-26 and C-27 methyls), 0.80 (br s, 3 H, C-21 methyl), and 0.69 (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{49}N_2O_4Cl$: C, 66.32; H, 9.50; N, 5.33; Cl, 6.75. Found: C, 66.40; H, 9.29; N, 5.16; Cl, 6.83.

3-Chloro-3-methyl-2-nitriminobutane (3). A solution of 200 g (2.85 mol) of 2-methyl-2-butene in 1200 mL of methylene chloride was stirred at 0 °C while nitrosyl chloride was slowly bubbled into the solution for 1.3 h. The resultant blue solution was stirred for 1.5 h at 0 °C and concentrated in vacuo without heating to give ca. 200 g of 3-chloro-3-methyl-2-butanone oxime as an oily blue-green solid. Further purification was not attempted.

Table I. Reduction of Nitrimines with Sodium Borohydride and Acetic Acid[a]

Nitrimine	Nitramine	Yield, %	mp or bp, °C
 1	 2	76	mp 206 (dec)
 3	 4	76	bp 60/0.15 mm
 5	 6	70	mp 126–127
 7	 8	41	mp 84–85

[a] Registry numbers: **1**, 31239-36-8; **2**, 63215-89-4; **3**, 63215-90-7; **4**, 63215-91-8; **5**, 63215-92-9; **6**, 63215-93-0; **7**, 28042-44-6; **8**, 28042-46-8.

The 200 g of 3-chloro-3-methyl-2-butanone oxime in 1600 mL of methylene chloride was stirred at 0 °C while nitrosyl fluoride was slowly bubbled into the solution for 1.25 h. The green solution was stirred at 0 °C for 3.5 h, followed by 1.5 h at room temperature. The mixture was slowly poured into saturated aqueous sodium carbonate and washed with saturated aqueous sodium carbonate, water, and brine. The organic layer was dried, filtered, and concentrated in vacuo to give a blue oil which was distilled giving 21.00 g (0.128 mol, 4% overall) of 3-chloro-3-methyl-2-nitriminobutane: bp 48–50 °C/0.5 mm; IR (neat) 6.17, 6.36 (s) and 6.92 μm; NMR ($CDCl_3$) δ 2.24 (s, 3 H, $-(CH_3)C{=}N-$) and 1.83 (s, 6 H, $-((CH_3)_2)CCl$).

Anal. Calcd. for $C_5H_9N_2O_2Cl$: C, 36.49; H, 5.51; N, 17.02; Cl, 21.54. Found: C, 36.30; H, 5.59; N, 17.27; Cl, 21.51.

3-Chloro-3-methyl-2-nitraminobutane (4). Sodium borohydride reduction as above of **3** gave a yellow liquid which was distilled giving a 76% yield of **4** as colorless liquid: bp 60 °C/0.1 mm; IR ($CHCl_3$) 6.35 and 6.88 μm; NMR ($CDCl_3$) δ 8.55 (br m, 1 H, >NH), 4.44 (br q, 1 H, J = 6.5 Hz, $>CH-NHNO_2$), 1.67 (s, 3 H, $>(CH_3)CCl$), 1.64 (s, 3 H, $>(CH_3)CCl$), and 1.39 (d, 3 H, J = 6.5 Hz, $>(CH_3)CNH-$).

Anal. Calcd for $C_5H_{11}N_2O_2Cl$: C, 36.05; H, 6.66; N, 16.81; Cl, 21.28. Found: C, 36.09; H, 6.52; N, 16.28; Cl, 21.49.

1-Oximino-9-chloro-10-methyldecalin and 1-Nitrimino-9-chloro-10-methyldecalin (5). A solution of 58.0 g (0.387 mol) of 10-methyl-$\delta^{1,9}$-octalin[7,8] in 1 L of methylene chloride at 0 °C was stirred while nitrosyl chloride was slowly bubbled in for 20 min. The reddish-brown solution was stirred at 0 °C for 3 h and concentrated in vacuo to give a light-green solid which was washed with cold hexane and filtered giving 22.73 g (0.105 mol, 27%) of 1-oximino-9-chloro-10-methyldecalin, mp 128–132 °C (dec). The filtrate was concentrated in vacuo to give a dark oil which was chromatographed on a 6.5 × 34.5 cm column of silicic acid (Mallinckrodt, Silic Ar, CC-7) slurry packed in 10% chloroform in hexane. Elution in 500-mL fractions gave fraction 1, 1.38 g of unidentified oil, and fractions 2–4, 25.05 g (0.102 mol, 26%) of **5**: NMR ($CDCl_3$) δ 3.30–1.00 (m, 14 H, aliphatic) and 1.11 (s, 3 H, methyl); IR ($CHCl_3$) 6.19, 6.38, and 6.90 μm.

Anal. Calcd for $C_{11}H_{17}N_2O_2Cl$: C. 53.99; H, 7.00; N, 11.45. Found: C, 54.22; H, 7.16; N, 11.11.

1-Nitrimino-9-chloro-10-methyldecalin (5). A solution of 22.73 g (0.105 mol) of 1-oximino-9-chloro-10-methyldecalin in 1.5 L of methylene chloride at 0 °C was stirred while nitrosyl chloride was slowly bubbled in for 30 min. The reddish-brown solution was stirred at 0 °C for 5.5 h, poured into water, washed with water and brine, dried, filtered, and concentrated in vacuo to give a yellow oil which was chromatographed on a 3.5 × 39.5 cm column of silicic acid (Mallinckrodt, Silic AR, CC-7) slurry packed in 10% chloroform in hexane. Elution in 200-mL fractions gave fraction 1, nil, fractions 2–5, 14.49 g (0.059 mol, 56%) of **5**, and fraction 6, 160 mg.

A small sample of **5** was recrystallized from ethanol, yielding white crystals which melted at 61–62 °C.

1-Nitramino-9-chloro-10-methyldecalin (6). Sodium borohydride reduction as above of **5** gave a white solid which was washed with hexane, filtered, and vacuum dried giving a 70% yield of **6** as a white solid: mp 136 °C (dec); NMR ($CDCl_3$) δ 9.10–8.50 (br m, 1 H >NH), 4.76–4.49 (br m, 1 H, $>CH-NHNO_2$), 2.68–0.84 (m, 14 H, aliphatic), and 1.20 (s, 3 H, methyl); IR ($CHCl_3$) 6.24, 6.38, 6.74, and 6.84 μm.

Anal. Calcd for $C_{11}H_{19}N_2O_2Cl$: C, 53.55; H, 7.76; N, 11.35; Cl, 12.97. Found: C, 53.52; H, 7.62; N, 11.30; Cl, 12.99.

1-Chloro-1-(α-nitraminoethyl)cyclohexane (8). Sodium borohydride reduction as above of **7**[1] gave a yellow oil which crystallized from hexane. Recrystallization from hexane afforded a 41% yield of **8** as a white solid: mp 84–85 °C (lit.[1] mp 91–92.5 °C). Both NMR and IR were in agreement with reported spectra.[1]

Registry No.—Acetic acid, 64-19-7; sodium borohydride, 16940-66-2; 2-methyl-2-butene, 513-35-9; nitrosyl chloride, 2696-92-6; 3-chloro-3-methyl-2-butanone oxime, 3238-16-2; 10-methyl-$\Delta^{1,9}$-octalin, 13942-77-6; 1-oximino-9-chloro-10-methyletacalin, 63215-94-1.

References and Notes

(1) C.-Y. Shiue and L. B. Clapp, *J. Org. Chem.*, **36**, 1169 (1971).
(2) (a) G. A. Boswell, *J. Org. Chem.*, **33**, 3699 (1968); (b) J. P. Freeman, *ibid.*, 26, 4190 (1961).
(3) G. W. Gribble and D. C. Ferguson, *Chem. Commun.*, 535 (1975).
(4) A. I. Meyers and A. Nabeya, *Chem. Commun.*, 1163, (1967).
(5) G. W. Gribble, P. D. Lord, J. Skotnicki, S. E. Dietz, J. T. Eaton, and J. L. Johnson, *J. Am. Chem. Soc.*, **96**, 7812 (1974).
(6) Y. Komeichi, S. Tomioka, T. Iwasaki, and K. Watanabe, *Tetrahedron Lett.*, 4677 (1970).
(7) J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2501 (1964).
(8) J. A. Marshall and A. R. Hochstetler, *J. Org. Chem.*, **31**, 1020 (1966).

Total Synthesis of (±)-Damsin

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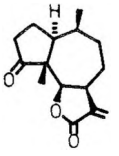
Received April 6, 1977

Among the many isolated sesquiterpene lactones[2a] the nonisoprenoid hydroazulenic pseudoguaianolides[2b] represent the largest family. Several synthetic approaches[3–5] to these compounds have appeared, recently culminating in the total syntheses of (±)-damsin[6] (**1**) and (±)-confertin[7] (**2**). In this



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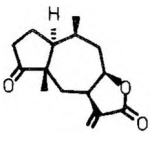

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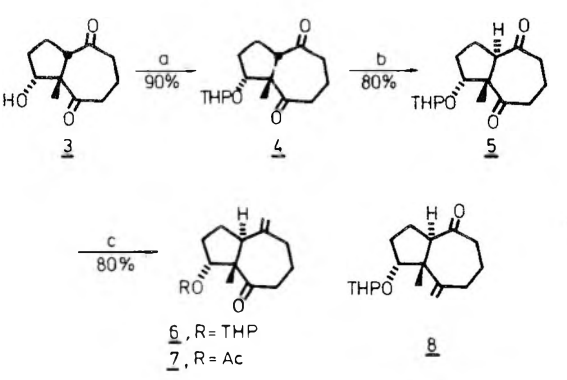
paper we report an independent synthesis of (±)-damsin and describe some transformations of synthon **3** which could be of value for the synthesis of other pseudoguaianolides.

Our synthetic plan centers about the hydroazulenic dione **3**, which we prepared via oxidative cleavage of a tricyclo[5.3.0.$0^{6,10}$]decanetriol.[5,8] This intermediate seems ideally suited for further transformation to pseudoguaianolides. The necessary trans ring fusion of the natural representatives is favored in an equilibrium isomerization process.[9] The two carbonyl functions are expected to be easily differentiated due to a marked difference in steric environment. The hydroxyl group allows for further functionalization of the cyclopentane ring; its α-orientation could, however, disturb the exercise of the stereochemical control by the angular methyl group.[4,10]

The isomerization of compound **4** could easily be achieved in alkaline medium (Scheme I). The equilibrium (85% trans, 15% cis) is largely in favor of the trans ring-fused product, which can be separated from the contaminating dione **4** by crystallization. The presence of a cis-fused γ-butyrolactone in many pseudoguaianolides, e.g., in damsin (**1**), demands alkylation in the 5 position after protection or transformation of the 2-carbonyl function. It has been suggested[4] that the alkylation of similar trans-fused hydroazulenic ketones with methyl bromoacetate proceeds poorly, unless one or more additional trigonal centers are present in the enolate, thereby lowering the steric congestion of the seven-membered ring. These considerations coupled with the anticipated formation of a β-methyl group on catalytic hydrogenation of an *exo*-methylene function led us to synthesize ketone **6**. Under the

Scheme I[a]



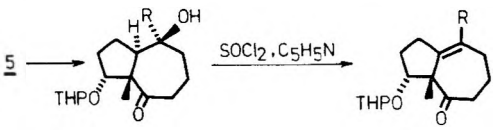
3 **4** **5**

6, R = THP
7, R = Ac

8

[a] a, DHP, *p*-TsOH; b, NaOH, MeOH; c, $(C_6H_5)_3P{=}CH_2$, THF.

given reaction conditions (Scheme I) the olefin **6** was obtained from diketone **5** in high yield and as the sole product. When Me_2SO was used as solvent, attack at the more hindered 6-ketone function, leading to product **8**, also occurred.[11] In



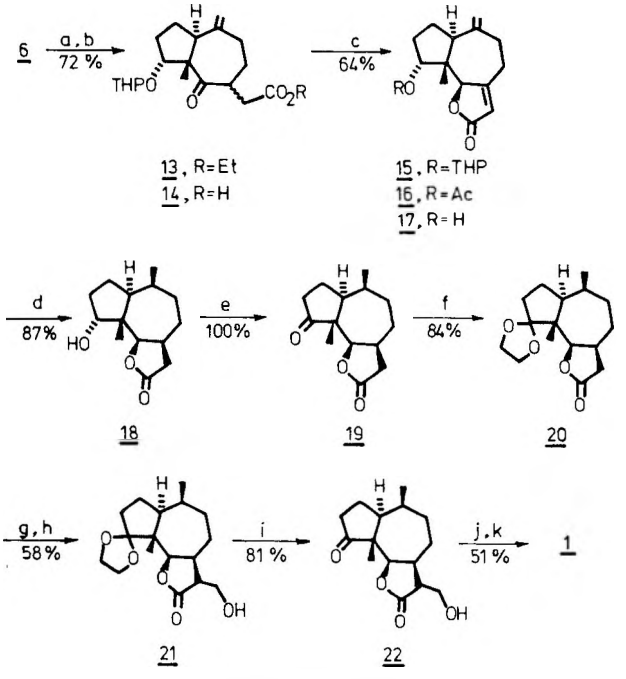
9, R = Me
10, R = H

11, R = Me
12, R = H

preliminary experiments a regioselective methyllithium reaction on **5**, followed by dehydration, was attempted. The reaction with methyllithium, although mostly regioselective, gave a low yield of the tertiary alcohol **9**; it is interesting to note that subsequent dehydration with thionyl chloride–pyridine gave nearly exclusively the tetrasubstituted olefin **11**, indicating a quasi-trans-diaxial relationship between the ring fusion hydrogen and the hydroxyl group.[12] A similar result was obtained when the alcohol **10**, from the reduction of **5** with lithium tri-*tert*-butyloxyaluminum hydride, was treated with thionyl chloride–pyridine.

The further conversion of ketone **6** to damsin (**1**) was performed in a straightforward way (Scheme II). Following the concept of Marshall[4,7] we decided to introduce the thermodynamically less favored orientation of the ester side chain through catalytic hydrogenation of the butenolide **15**. This product was obtained in a three-step sequence, involving alkylation of unsaturated ketone **6** with ethyl bromoacetate, saponification of the resulting epimeric mixture **13** to the keto acids **14**, and finally, treatment with acetic anhydride–sodium acetate.[13] Analysis of the ^1H NMR spectra of the corresponding alcohol **17** and its acetate **16** clearly shows butenolide **15** being stereohomogeneous (except for the chirality present in the protective ether group); the stereochemistry shown at C-6 could not be established at this point. In order to minimize

Scheme II[a]



13, R = Et
14, R = H

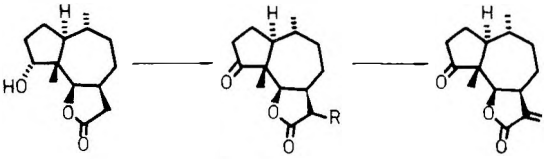
15, R = THP
16, R = Ac
17, R = H

18 **19** **20**

21 **22**

[a] a, LDA, $BrCH_2CO_2Et$, HMPA; b, KOH, MeOH; c, Ac_2O, NaOAc; d, H_2, Pt/C(10%), EtOH; e, H_2CrO_4, acetone; f, $(CH_2OH)_2$, *p*-TsOH; g, NaH, HCO_2Et; h, $NaBH_4$, MeOH; i, 3 M HCl, MeOH; j, *p*-TsCl, C_5H_5N; k, C_5H_5N.

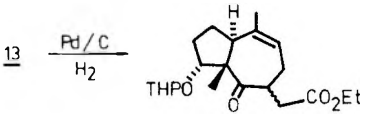
the steric influence of the 8α ether group it was decided to perform the catalytic hydrogenation at this stage and not earlier; indeed, the anticipated faster reduction of the enone system would provide us with a trans-fused hydroazulene possessing an almost inaccessible β face. The catalytic hydrogenation on 5% platinum on carbon gave as sole reduction products the alcohol **18** and the isomeric product at C-2 **18a** (85:15, respectively), with concomitant cleavage of the protective ether group.[14] Isomer **18a** was not separated at this



18a **19a**, R = H; **22a**, R = CH_2OH **1a**

stage, but was taken through the remaining reaction sequence. Jones oxidation led to the cyclopentanones **19** and **19a**. The former lactone has already been synthesized and transformed into (±)-damsin[6] (**1**). Our present synthesis was completed using the same six-step reaction sequence, yielding (±)-damsin (**1**) and its C-2 epimer[15] (**1a**); both compounds were easily separated on silica gel. The spectral properties and TLC behavior of the synthetic material were identical with naturally occurring damsin[16] (**1**).

We are currently investigating the further potentiality of products **6**, **11**, and **12** for the synthesis of other pseudoguaianolides. In this context we also want to report the accidental formation of the trisubstituted olefin **23** in high yield



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during an attempted catalytic hydrogenation of ester **13** using 5% palladium on carbon; this ester looks promising for the functionalization of the 4 position, which is often encountered in pseudoguaianolides.

Experimental Section[17]

***c*-7-Methyl-*t*-8-(2′-tetrahydropyranyloxy)-*r*-1*H*-bicyclo[5.3.0]decane-2,6-dione (4).** A solution of 4.50 g (23 mmol) of hydroazulenol **3**, 9.5 mL (104 mmol) of dihydropyran, and 15 mg of *p*-toluenesulfonic acid in 100 mL of methylene chloride was stirred at room temperature for 15 min. The reaction solution was quenched with solid potassium carbonate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using 10% ethyl acetate–benzene, yielding 5.78 g (90%) of the dione **4** as a light yellow oil: R_f (2) 0.51; IR (film) 1700, 1220, 1210, 1130, 1030, 990 cm^{-1}; NMR δ_{Me_4Si} 4.20–4.05 (m, C-8 methine), 2.90–2.20 (m, C-1, C-3, and C-5 H), 1.35 and 1.33 (s, C-7 CH_3); MS *m/e* 196 (40), 179 (10), 152 (6), 151 (5), 85 (100). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.69; H, 8.71.

***t*-7-Methyl-*c*-8-(2′-tetrahydropyranyloxy)-*r*-1*H*-bicyclo[5.3.0]decane-2,6-dione (5).** A solution of 5.78 g (20.6 mmol) of cis-ring-fused diketone **4** in 100 mL of dry methanol containing 15 mg of powdered sodium hydroxide was stirred at room temperature for 70 h. After evaporation of the solvent, workup yielded 5.70 g of a semisolid product (85% **5**; 15% **4**). White crystalline diketone **5** (yield 80%; conversion 100%) was obtained by recrystallization from isooctane: R_f (2) 0.51; IR (KBr) 1700, 1130, 1030, 1025, 990 cm^{-1}; NMR δ_{Me_4Si} 4.30–4.10 (m, C-8 methine), ~3.9 (m, C-1 methine), 0.93 and 0.87 (s, C-7 CH_3); MS *m/e* 280 (M^+, 2), 262 (1), 196 (100), 179 (92), 161 (65), 152 (61), 85 (100), 67 (96), 41 (100). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.72; H, 8.72.

***t*-7-Methyl-2-methylene-*c*-8-(2′-tetrahydropyranyloxy)-*r*-1*H*-bicyclo[5.3.0]decan-6-one (6).** To a suspension of methylene triphenylphosphorane (from 8.93 g, 25 mmol of methyltriphenylphosphonium bromide and 12.5 mL of 2.0 M butyllithium–hexane solution) in 30 mL of tetrahydrofuran was added a solution of 1.44

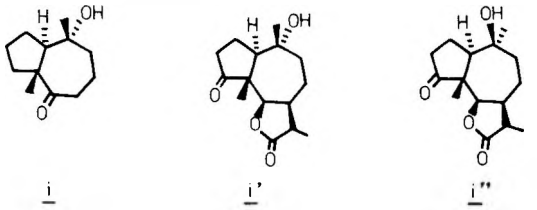
g (5.13 mmol) of dione **5** in 5 mL of tetrahydrofuran at room temperature. After 15 min the reaction mixture was poured into a saturated ammonium chloride solution. Workup and purification by column chromatography on silica gel using 6% ethyl acetate–benzene yielded 1.13 g (80%) of a colorless oil: R_f (2) 0.66; IR (film) 3100, 1700, 1650, 1125, 1115, 1060, 1020, 985 cm^{-1}; NMR δ_{Me_4Si} 5.03 and 4.86 (s, *exo*-CH_2 vinyl H's), 4.27 and 4.13 (m, C-8 methine), 2.6–2.3 (m, C-5 CH_2), 3.3 (t, J = 8.4 Hz, C-1 methine), 0.93 and 0.87 (s, C-7 CH_3); MS *m/e* 194 (30), 85 (100). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.51; H, 9.43.

The ^1H NMR spectrum of the reaction mixture from the same reaction using dimethyl sulfoxide as solvent showed the presence of the isomeric ketone **8**: NMR δ_{Me_4Si} 4.83 (s, *exo*-CH_2 vinyl H's) and 1.23 (s, C-7 CH_3).

The stereohomogeneous acetate **7** was isolated accidentally upon treatment of **6** with acetic anhydride and a trace of perchloric acid (70%) in carbon tetrachloride: R_f (1) 0.43; IR (KBr) 1750, 1700, 1240 cm^{-1}; NMR δ_{Me_4Si} 5.20 (m, C-8 methine), 5.10 and 4.92 (s, *exo*-CH_2 vinyl H's), 3.36 (t, J = 9.0 Hz, C-1 methine), 2.0 (s, $OCOCH_3$), 1.00 (s, C-7 CH_3); MS *m/e* 236 (M^+, 2), 194 (36), 176 (70), 161 (22), 150 (29), 137 (57), 43 (100).

***c*-2,*t*-7-Dimethyl-*t*-2-hydroxy-*c*-8-(2′-tetrahydropyranyloxy)-*r*-1*H*-bicyclo[5.3.0]decan-6-one (9).** To a solution of 2.10 g (7.5 mmol) of diketone **5** in 6 mL of tetrahydrofuran was added 3.5 mL of a 2.12 M methyllithium–ether solution at room temperature. Stirring was continued for 2 h, the reaction mixture poured on ice, and the product isolated with ether. Purification by column chromatography on silica gel with 20% ethyl acetate–benzene yielded 0.356 g (83% conversion) of starting material and 0.694 g (38%) of alcohol **9** as a colorless oil: R_f (1) 0.50; IR (film) 3500, 1695, 1125, 1025, 990 cm^{-1}; NMR δ_{Me_4Si} 1.33 (s, C-2 CH_3) and 1.17, 1.14 (s, C-7 CH_3); MS *m/e* 296 (M^+, 0.4), 212 (20), 195 (20), 168 (98), 85 (100).

2,*t*-7-Dimethyl-*r*-8-(2′-tetrahydropyranyloxy)bicyclo[5.3.0]-dec-1,2-en-6-one (11). A solution of 0.225 g (0.76 mmol) of alcohol **9** and 0.25 g (0.154 mL) of thionyl chloride in 2 mL of pyridine was stirred at room temperature for 12 h. The reaction mixture was poured into ice water and isolated with pentane, yielding 0.168 g (79%) of tetrasubstituted olefin **11** as a pale yellow oil: R_f (1) 0.56; IR (film)



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1700, 1125, 1110, 1020, 980 cm^{-1}; NMR δ_{Me_4Si} 1.80 (s, C-2 CH_3) and 1.19, 1.15 (s, C-7 CH_3); MS *m/e* 278 (M^+, 1), 194 (28), 85 (100). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.54; H, 9.45.

***t*-2-Hydroxy-*t*-7-methyl-*c*-8-(2′-tetrahydropyranyloxy)-*r*-1*H*-bicyclo[5.3.0]decan-6-one (10).** To a suspension of 29 mg (7.6 mmol) of lithium aluminum hydride in tetrahydrofuran was added 0.28 mL of *tert*-butyl alcohol at 0 °C. Stirring was continued for 30 min and a solution of 105 mg (0.38 mmol) of the diketone **5** in tetrahydrofuran was added dropwise over 2 min at 0 °C. After 30 min the reaction mixture was poured into a saturated ammonium chloride solution and the product isolated with ether, yielding 100 mg (93%) of a colorless oil: R_f (1) 0.26; IR (film) 3500, 1700, 1030, 990 cm^{-1}; NMR δ_{Me_4Si} 1.22 and 1.18 (s, C-7 CH_3); MS *m/e* 198 (18), 154 (52), 85 (100). Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.08; H, 9.22. Found: C, 68.26; H, 9.25.

***t*-7-Methyl-*r*-8-(2′-tetrahydropyranyloxy)bicyclo[5.3.0]-dec-1,2-en-6-one (12).** The above mentioned procedure with thionyl chloride–pyridine on 100 mg (0.35 mmol) of the alcohol **10** yielded crude trisubstituted olefin **12** as a pale yellow oil: R_f (1) 0.54; IR (film) 1705, 1125, 1110, 1030, 1020, 980 cm^{-1}; NMR δ_{Me_4Si} 5.7 (m, vinyl H), 1.20 (s, C-7 CH_3); MS *m/e* 264 (M^+, 1), 246 (2), 216 (2), 85 (100).

Ethyl [2-Methylene-6-oxo-*t*-7-methyl-*c*-8-(2′-tetrahydropyranyloxy)-*r*-1*H*-bicyclo[5.3.0]dec-5-yl]acetate (13). The procedure described by Marshall[4] was slightly modified. To a solution of 0.924 mL (6.6 mmol) of *N,N*-diisopropylamine in 10 mL of tetrahydrofuran was added at −78 °C 3.3 mL (6.6 mmol) of 2.0 M *n*-butyllithium–hexane solution dropwise over 2.0 min. The temperature was raised to 0 °C over 30 min. A solution of 0.911 g (3.3 mmol) of ketone **6** in 2 mL of tetrahydrofuran was added at −78 °C and stirring was continued for 3 h at room temperature. Finally, a solution of 0.8 mL (7.2 mmol) of ethyl bromoacetate and 1.26 mL (7.2 mmol) of hexamethylphosphoric triamide in 4 mL of tetrahydrofuran was added (−78 °C). Stirring was continued for 30 min and the reaction mixture poured into a saturated ammonium chloride solution. Workup and purification by column chromatography on silica gel using 25% ethyl acetate–isooctane yielded 0.964 g (80%) of **13** (light yellow oil): R_f (2) 0.67; IR (film) 3100, 1740, 1700, 1640, 1195, 1170, 1125, 1110, 1075, 1030, 1020, 985, 830 cm^{-1}; δ_{Me_4Si} 5.13 and 4.96 (s, *exo*-CH_2 vinyl H's), 4.16 (q, J = 7.3 Hz, $COOCH_2CH_3$), 1.26 (t, J = 7.3 Hz, $COOCH_2CH_3$). 0.92 and 0.88 (s, C-7 CH_3); MS *m/e* 280 (10), 251 (10), 217 (18), 213 (40), 185 (55), 85 (100).

[2-Methylene-*t*-7-methyl-*c*-8-(2′-tetrahydropyranyloxy)-6-oxo-*r*-1*H*-bicyclo[5.3.0]dec-5-yl]acetic Acid (14). A solution of 0.70 g (1.92 mmol) of ester **13** and 0.40 g (7.1 mmol) of potassium hydroxide in 10 mL of dry methanol was heated at reflux for 2 h. The solution was cooled and concentrated in vacuo. Water was added to the residue and the solution was acidified to pH 4 with 1.2 M hydrochloric acid. Workup yielded 0.61 g (90%) of **14** as semisolid oil: R_f (2) 0.55; R_f (1) 0.39; IR (melt) 3200–2500 (br), 1750–1700, 1650 cm^{-1}; NMR δ_{Me_4Si} 5.03 and 4.86 (s, *exo*-CH_2 vinyl H's), 2.55 (m, CH_2COOH), 0.9 (s, C-7 CH_3), 9.5 (COOH); MS (*m/e* 250 (40), 217 (20), 195 (8), 177 (10), 85 (100). Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.89; H, 8.41.

[2-Methylene-*t*-6-hydroxy-*t*-7-methyl-*c*-8-(2′-tetrahydropyranyloxy)-*r*-1*H*-bicyclo[5.3.0]dec-5-ylidene]acetic Acid γ-Lactone (15). A mixture of 0.60 g (1.78 mmol) of acid **14** and 2.16 g (26.3 mmol) of sodium acetate in 18 mL of acetic anhydride was heated at reflux for 1 h. The mixture was cooled to 0 °C and 20 mL of methanol was added. The solution was stirred for 2 h at 0 °C and then poured into water and the product extracted with ether. The product was freed from acetic acid by azeotropic distillation in vacuo with toluene. Purification by column chromatography on silica gel using 30% ethyl acetate–isooctane yielded 0.36 g (64%) of butenolide **15** as a white crystalline product: R_f (2) 0.54; IR (KBr) 3100, 1770, 1640 cm^{-1}; δ_{Me_4Si} 5.86 (m, vinyl H), 5.63 and 5.43 (s, C-6 methine), 5.03 and 4.90 (s, *exo*-CH_2 vinyl H's), 0.46 and 0.43 (s, C-7, CH_3), MS *m/e* 318 (M^+, 0.8), 234 (30), 217 (44), 216 (50), 85 (100).

Prolonged reaction times and careless (temperature!) workup lowered the yield and led in preliminary experiments to considerable amounts of the corresponding acetate **16** (mp 125–126 °C): IR (KBr) 3100, 1760, 1740, 1650, 1640, 1250 cm^{-1}; NMR δ_{Me_4Si} 5.88 (q, J = 1.8 Hz, vinyl H), 5.40 (s, C-6 methine), 5.08 and 4.93 (s, *exo*-CH_2 vinyl H's), 5.02 (m, C-8 methine), 2.10 (s, $OCOCH_3$), 0.50 (s, C-7 CH_3); MS *m/e* 276 (M^+, 2), 234 (20), 216 (70), 43 (100).

The corresponding hydroxy derivative **17** showed δ_{Me_4Si} 5.85 (q, J = 1.8 Hz, vinyl H), 5.43 (s, C-6 methine), 5.03 and 4.90 (s, *exo*-CH_2 vinyl H's), 4.16 (m, C-8 methine) and 0.41 (s, C-7 CH_3).

(*t*-2,*t*-7-Dimethyl-*t*-6,*c*-8-dihydroxy-*r*-1*H*-bicyclo[5.3.0]-dec-5-yl)acetic Acid γ-Lactone (18). A suspension of 0.36 g (1.13 mmol) of butenolide **15** and 120 mg of 5% platinum on carbon in 6 mL of absolute ethanol was hydrogenated at room temperature under a pressure of 4 bar. After 70 h the reaction mixture was filtered and concentrated in vacuo, yielding 0.233 g (87%) of lactone (**18** and **18a**) as a white crystalline solid: R_f (2) 0.39; IR (KBr) 3500, 1780, 1180, 1040, 1010, 990 cm^{-1}; NMR δ_{Me_4Si} 4.96 (d, J = 9.3 Hz, C-6 methine), 3.86 (m, C-8 methine), 1.05 (d, J, 7.2 Hz, C-2 CH_3), 0.93 (s, C-7 CH_3); MS *m/e* 238 (M^+, 4), 236 (2), 220 (52), 205 (83), 179 (60), 41 (100). The contaminating isomer **18a** showed δ_{Me_4Si} 3.96 (m, C-8 methine) and 0.85 (s, C-7 CH_3).

(*t*-2,*t*-7-Dimethyl-8-oxo-*t*-6-hydroxy-*r*-1*H*-bicyclo[5.3.0]-dec-5-yl)acetic Acid γ-Lactone (19). To a solution of 0.233 g (0.96 mmol) of alcohol **18** in 10 mL of acetone was added at −15 °C Jones reagent till the red color persisted. The mixture was quenched with isopropyl alcohol, solid sodium hydrogen carbonate added, and the mixture filtered and concentrated in vacuo. Usual workup yielded 0.230 g of ketone (100%) as a colorless oil which solidified on standing. Recrystallization from diisopropyl ether gave analytically pure material (mp 133–134 °C): R_f (2) 0.29; IR (melt) 1750, 1765 cm^{-1}; δ_{Me_4Si} 4.6 (d, J = 7.2 Hz, C-6 methine), 1.16 (s, C-7 CH_3), 1.10 (d, J = 7.2 Hz, C-2 CH_3); MS *m/e* 236 (M^+, 3), 220 (100), 97 (41). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.32; H, 8.61. The isomeric ketone **19a** showed: R_f (2) 0.33; δ_{Me_4Si} 4.6 (d, 6.0 Hz, C-6 methine), 1.13 (s, C-7 CH_3), and 0.96 (d, 5.7 Hz, C-2 CH_3).

Ethylene Ketal of (t-2,*t*-7-Dimethyl-*t*-6-hydroxy-8-oxo-*r*-1*H*-bicyclo[5.3.0]dec-5-yl)acetic Acid γ-Lactone (20). A solution of 0.150 g (0.63 mmol) of ketone **19**, 1 mg of *p*-toluenesulfonic acid, and 0.5 mL of ethylene glycol in 10 mL of benzene was heated at reflux for 6 h using a Dean–Stark water separator. The solution was cooled, solid potassium carbonate was added, and the mixture was filtered and concentrated in vacuo. Purification by column chromatography on silica gel using 45% ethyl acetate–isooctane yielded 0.15 g (84%) of lactone **20** (and its C-2 epimer) as a white crystalline solid: R_f (2)

0.50; mp 92–98 °C (from isooctane); IR (KBr) 1770 cm^{-1}; NMR δ_{Me_4Si} 4.96 (d, J = 6.0 Hz, C-6 methine), ~4.0 (m, ketal), 1.12 (s, C-7 CH_3), 1.03 (d, J = 7.2 Hz, C-2 CH_3); MS m/e 280 (M^+), 265, 235, 219, 100, 99, 86. The contaminating C-2 α-CH_3 isomer showed δ_{Me_4Si} 4.96 (d, J = 8.4 Hz), 1.07 (s, C-7 CH_3) and 0.9 (d, J = 5.4 Hz, C-2 CH_3).

Ethylene Ketal of (*t*-2,7-Dimethyl-*t*-6-hydroxy-8-oxo-*r*-1*H*-bicyclo[5.3.0]dec-5-yl)β-hydroxypropionic Acid γ-Lactone (21). The procedure of Minato and Horibe[18] was employed. To a suspension of 76 mg of 55% sodium hydride suspension in 4 mL of ether was added at 0 °C a solution of 0.323 g (1.15 mmol) of lactone **20** and 0.17 mL (2 mmol) of ethyl formate in 4 mL of ether dropwise over 2 min. The suspension was stirred for 1 h at 0 °C and for an additional 7 h at room temperature. The reaction mixture was poured into a saturated ammonium chloride solution and extracted with ether. Workup yielded 0.342 g (97%) of crude product; no purification of this product was attempted.

To a solution of 50 mg (1.31 mmol) of sodium borohydride in 3 mL of absolute methanol was added at −18 °C a solution of 0.342 g (1.11 mmol) of the above α-formyl-γ-butyrolactone in 2 mL of absolute methanol. The solution was stirred at −18 °C for 1 h, slowly brought to room temperature, and poured into a saturated ammonium chloride solution. The product was isolated with ether and purified by column chromatography on silica gel using 50% ethyl acetate–isooctane, yielding 0.206 g (60%) of a white crystalline solid: R_f (2) 0.34; NMR δ_{Me_4Si} 4.93 (d, J = 9.3 Hz, C-6 methine), ~3.9 (m, ethylene ketal), ~3.8 (m, CH_2OH), 1.10 (s, C-7 CH_3), 1.06 (d, J > 6.6 Hz, C-2 CH_3). The contaminating C-2 α-CH_3 isomer showed δ_{Me_4Si} 1.06 (s, C-7 CH_3) and 0.90 (d, J = 5.4 Hz, C-2 CH_3).

(*t*-2,7-Dimethyl-8-oxo-*t*-6-hydroxy-*r*-1*H*-bicyclo[5.3.0]-dec-5-yl)-β-hydroxypropionic Acid γ-Lactone (22). A solution of 0.206 g (0.66 mmol) of ethylene ketal **21** in 5 mL of 40% 3 M hydrochloric acid–methanol was stirred at 0 °C for 15 min. Methanol was evaporated in vacuo, water was added, and the product extracted with ether. Isolation and purification by column chromatography on solica gel using 25% isooctane–ethyl acetate yielded 0.144 g (81%) of **22** as a colorless oil: R_f (2) 0.13; NMR δ_{Me_4Si} 4.56 (d, J = 8.7 Hz, C-6 methine), 4.1 (m, $CHCH_2OH$), 3.9 (m, CH_2OH), 2.9 (m, C-5 methine), 1.13 (s, C-7 CH_3), 1.07 (d, C-2 CH_3); MS m/e 266 (M^+, 2), 251 (100), 233 (25), 97 (50). The isomeric ketone **22a** showed: R_f (2) 0.17; δ_{Me_4Si} 4.66 (d, J > 7.2 Hz, C-6 methine), 1.09 (s, C-7 CH_3), 1.00 (d, J = 5.4 Hz, C-2 CH_3).

(±)-Damsin (1). A solution of 0.144 g (0.54 mmol) of the above β′-hydroxy-γ-butyrolactone **22** and 126 mg of *p*-toluenesulfonyl chloride in 1.6 mL of freshly distilled pyridine was stirred for 24 h at 0 °C. The solution was poured into water and the product isolated with chloroform, yielding 0.227 g (100%) of a yellow oil. A solution of the above crude tosylate in 2 mL of pyridine was heated at reflux for 4 h. The solution was cooled and poured into water; extraction with ether and evaporation of the solvent gave 0.134 g (100%) of yellow oil. Purification by column chromatography on silica gel using 50% ethyl acetate–isooctane yielded 73 mg (51%) of white crystalline product, whose spectra and TLC behavior were identical with those of naturally occurring damsin (**1**): R_f (2) 0.35; mp 122–124 °C; IR (KBr) 2950, 2875, 1760, 1735, 1655, 1280, 1165, 1155, 1130, 1060, 1000, 985, 970, 955, 820 cm^{-1}; NMR δ_{Me_4Si} 6.27 and 5.53 (d, J = 3.1 and 2.75 Hz, respectively, vinyl H's), 4.53 (d, J = 8.5 Hz, C-6 methine), 3.30 (m, C-7 methine), 1.08 (d, J = 7.5 Hz, C-2 CH_3), 1.08 (s, C-7 CH_3); MS m/e 248 (M^+, 5), 2.33 (100), 123 (36), 97 (42), 95 (30), 55 (50). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.61; H, 8.14.

(±)-2-*epi*-Damsin (1a), contaminated with (±)-damsin (a fraction of the above mentioned column chromatography), was purified by preparative TLC using 50% ethyl acetate–isooctane, affording 2 mg of white crystalline compound: R_f (2) 0.41; NMR δ_{Me_4Si} 6.26 and 5.57 (d, J = 2.5 and 2.0 Hz, respectively, vinyl H's), 4.53 (d, J = 7.75 Hz, C-6 methine), 3.11 (m, C-7 methine), 1.00 (d, J = 6.5 Hz, C-2 CH_3), 1.11 (s, C-7 CH_3).

Ethyl [2,*t*-7-Dimethyl-*c*-8-(2′-tetrahydropyranyloxy)-6-oxo-*r*-1*H*-bicyclo[5.3.0]dec-2-en-5-yl]acetate (23). A suspension of 0.364 g (1.0 mmol) of olefin **13** and 10 mg of 5% palladium on carbon in 1 mL of absolute ethanol was hydrogenated at room temperature and atmospheric pressure. After 6 h the suspension was filtered and concentrated in vacuo, yielding 0.362 g (100%) of trisubstituted olefin **23**: R_f (1) 0.49; IR (film) 1740, 1700, 1195, 1175, 1160, 1130, 1115, 1025, 985 cm^{-1}; NMR δ_{Me_4Si} 5.83 (m, vinyl H), 4.20 (q, J = 7.2 Hz, $COOCH_2CH_3$), 1.26 (t, J = 7.2 Hz, $COOCH_2CH_3$), 0.95 (s, C-7 CH_3).

Acknowledgment. We thank the "Nationaal Fonds voor Wetenschappelijk Onderzoek" for financial support to the laboratory.

Registry No.—**1**, 60133-11-1; **1a**, 63039-02-1; **3**, 62990-77-6; **4**, 62990-78-7; **5**, 62990-79-8; **6**, 62990-80-1; **7**, 62990-81-2; **8**, 62990-82-3; **9**, 62990-83-4; **10**, 62990-84-5; **11**, 62990-85-6; **12**, 62990-86-7; **13**, 62990-87-8; **14**, 62990-88-9; **15**, 62990-89-0; **16**, 62990-90-3; **17**, 62990-91-4; **18**, 62990-92-5; **18a**, 62990-93-6; **19**, 60090-71-3; **19a**, 62990-94-7; **20**, 60090-72-4; **21**, 62990-95-8; **22**, 62990-96-9; **23**, 62990-97-0; **20** C_2 isomer, 63039-03-2.

References and Notes

(1) Aangesteld navorser N.F.W.O.
(2) (a) H. Yoshioka, T. J. Mabry, and B. N. Timmerman, "Sesquiterpene Lactones", University of Tokyo Press, Tokyo, Japan, 1973; (b) J. Romo, and A. R. de Vivar, *Prog. Chem. Org. Nat. Prod.*, **25**, 90 (1967).
(3) For a review see J. A. Marshall, *Synthesis*, 517 (1972); R. A. Kretchmer and W. M. Schafter, *J. Org. Chem.*, **38**, 95 (1973); H. Z. Lin, *Synth. Commun.*, **4**, 237 (1974); J. P. Marino and T. Kaneko, *J. Org. Chem.*, **39**, 3175 (1974).
(4) J. A. Marshall and W. R. Snyder, *J. Org. Chem.*, **40**, 1656 (1975).
(5) D. Termont, P. De Clercq, D. De Keukeleire, and M. Vandewalle, *Synthesis* 46 (1977).
(6) R. Kretchmer and W. J. Thompson, *J. Am. Chem. Soc.*, **98**, 3379 (1976).
(7) J. A. Marshall and R. H. Ellison, *J. Am. Chem. Soc.*, **98**, 4312 (1976).
(8) Dione **3** is now available in 60% overall yield from 2-methyl-2-cyclopentenone using slight modifications of procedures in ref 5: unpublished results of the laboratory.
(9) W. Hückel and L. Schnitzspahn, *Justus Leibigs Ann. Chem.*, **505**, 274 (1933); J. A. Marshall and W. F. Huffman, *J. Am. Chem. Soc.*, **92**, 6358 (1970).
(10) This feature could be used to reverse the stereochemistry expected from control by the angular methyl group: this laboratory, work in progress.
(11) C. V. Wilson, *Org. React.*, **9**, 332 (1957).
(12) The alcohol i (with epimeric C-2), synthesized by Marshall,[4] yielded under the same circumstances a mixture of three double bond isomers (25% exo, 60% trisubstituted, and 15% tetrasubstituted). Consideration of this and our own results tend to assign the still unknown configuration of franserin at C-2 as depicted in i′, since dehydration with thionyl chloride–pyridine leads to a trisubstituted olefin and not a tetrasubstituted one as would be expected from dehydratation of i″; J. Romo, A. Romo de Vivar, A. Vélez, and E. Urbina, *Can. J. Chem.*, **46**, 1535 (1968).
(13) H. Minato and T. Nagasaki, *Chem. Commun.*, 377 (1965).
(14) To the best of our knowledge this cleavage of a 2-tetrahydropyranyl ether under neutral but rather drastic (70 h, 4 bar) conditions is unprecedented and could prove to be useful in certain circumstances.
(15) For the sake of consistency we have retained the same numbering for this compound as has been used throughout the paper; the generally accepted numbering for pseudoguaianolides (ref 2a) would indicate this product as (±)-10-*epi*-damsin. The α configuration was assigned to the C-2 CH_3 group of the **a** isomers (**1a**, **18a**–**22a**), the only marked difference between the NMR data of the natural products and their **a** isomers being the chemical shifts and vicinal exocyclic J values of the C-2 CH_3 groups. Especially significant is the larger value of the exo coupling constant in the natural products compared to the corresponding **a** isomers, in accordance with the higher strain present in the former compounds; M. Anteunis, *Bull. Soc. Chim. Belg.*, **80**, 3 (1971); Z. Samek, *Tetrahedron Lett.*, 1709 (1971).
(16) We thank Dr. J. Romo for kindly sending a sample of natural damsin.
(17) Reaction products were isolated by the addition of water and extracted with the specified solvent. The combined extracts were washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was removed from the filtered solutions on a rotary evaporator. R_f values are quoted for Merck silica gel 60 GF_{254} TLC plates of thickness 0.25 mm; R_f (1) refers to the solvent system acetic acid–ethyl acetate–isooctane = 2:15:20; R_f (2) to acetic acid–ethyl acetate–isooctane = 2:15:10. IR spectra were recorded on a Perkin-Elmer 337 spectrometer, ^1H NMR spectra on a Varian EM-390 spectrometer ($CDCl_3$), and mass spectra on an AEI MS-50 mass spectrometer. Melting points are uncorrected. Stereochemical designations of substituents in bicyclic compounds are indicated by *c* (cis) and *t* (trans) relative to a reference substituent *r*.
(18) H. Minato and I. Horibe, *J. Chem. Soc. C*, 1575 (1967).

Thermal Decomposition of Phenylmethyldiazirine. Effect of Solvent on Product Distribution

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Received May 17, 1977

The thermal decomposition of phenyl-*n*-butyldiazirine[1] in Me_2SO at 100 °C resulted in a quantitative evolution of nitrogen and the formation of *cis*- and *trans*-1-phenyl-1-pentenes plus less than 5% of valerophenone. In addition, 1-phenyldiazopentane has been isolated as an intermediate

Table I. Product Distribution in the Thermal Decomposition of Phenylmethyldiazirine

Reaction conditions	Azine	Products, % Acetophenone	Styrene	Cyclopropyl derivatives
Neat 16 h at 130 °C	65	3–4	Trace	30
5% Solution in Me_2SO, 16 h at 65 °C and 6 h at 110 °C	40	50	Trace	8–10
10% Solution in nitrobenzene, 16 h at 130 °C	95	0	Trace	5
5% Solution in hexane, 72 h at 68 °C	45	17–19	Trace	35
5% Solution in isooctane, 16 h at 99 °C	40	3–4	Trace	56
0.6% Solution in nitrobenzene 16 h at 130 °C	32	32	Trace	35
0.6% Solution in chlorobenzene, 16 h at 130 °C	40	10	Trace	48–50
0.01 Torr at 120 °C	—	—	98	Trace

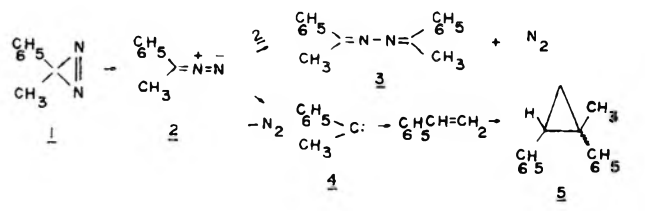
during this decomposition. In the light of the above observation, it is then reasonable to assume the intermediacy of 1-phenyldiazoethane **2** in the thermal decomposition of phenylmethyldiazirine **1**.

Overberger and Anselme[3] could not duplicate the synthesis of **1** as reported by Schmitz and Ohme.[3] However, in the decomposition of **2**, Overberger and Anselme[3] reported acetophenone azine **3** as the only product. No styrene was detected although Schmitz and Ohme[2] reported it as the sole decomposition product of **1** in nitrobenzene. Due to this apparent difference, we have reinvestigated the thermal decomposition of **1** with a view to resolve these inconsistencies.

1 is a colorless liquid and is stable at 0 °C for several weeks. When **1** was heated neat or in solvents listed in Table I, the solution turned red. The red material has a strong IR absorption at 2040 cm^{-1} and was isolated and identified as **2**.[4] The red color of the solution persisted even after heating a solution of **1** or **2** in hexane at 68 °C for over 48 h. **2** begins to decompose significantly at temperatures greater than 100 °C.

Thermal decomposition of **1** carried out in different solvents under varying conditions results in the formation of a mixture of products as given in Table I. A decrease in the amount of **3** and a corresponding increase in cyclopropyl derivatives was observed with decreasing solvent polarity. The same effect was observed for a decrease in concentration of **1** in the decomposition mixture. Only trace amounts of styrene could be detected, a fact which contradicts the results obtained by Schmitz and Ohme,[2] who reported styrene as the only product in the decomposition. However, the gas phase (0.01 Torr) decomposition of **1** gave styrene as the major product with trace amount of **5**.

The following scheme shows the two probable pathways for the decomposition of **1**. Polar solvents stabilize better the



transition state for dimerization of **2** and thus the formation of **3** is favored over further fragmentation to the carbene **4**, but in nonpolar solvents, due to the lack of such stabilization, further decomposition to **4** is favored. **4** is a precursor to styrene and cyclopropyl derivatives. An alternative possibility involved the attack of carbene **4** on either **1** or **2** to produce the azine **3**.[5,6] However, we consider this only as a minor possibility as it has to compete with the intramolecular rearrangement of **4** to styrene. The formation of cyclopropyl derivatives is presumably the result of the 1,3-dipolar reaction of **2** with styrene followed by elimination of N_2. It is to be noted that in nonpolar solvents, the formation of **3** is still considerable. However, only traces of styrene are detected as most of it gets converted to the cyclopropyl derivatives. Also in dilute solutions, the probability for dimerization to **3** is less and hence the formation of **4** is favored. The presence of fairly large amounts of acetophenone in Me_2SO is due to solvent participation in the oxidation of **2** whereas its presence in small quantities in other solvents is presumably due to aerial oxidation of **2**. The absence of azine in the decomposition of phenyl-*n*-butyldiazirine[1] could well be explained in terms of a steric effect.

In the photolysis of 1-phenyldiazoethane **2** at 5 °C, the formation of acetophenone azine **3** was reported.[7] However, in recent studies by Moss and Joyce[8] on the photolysis of **2** in isobutene matrices, **3** was not detected.

Experimental Section

General. NMR spectra were recorded from a Varian T-60 instrument using $CDCl_3$ as solvent and Me_4Si as internal standard. IR spectra were obtained from a Perkin-Elmer 137 spectrophotometer asd mass spectra with VG Micromass MM601 spectrometer. A Perkin-Elmer Model F11 gas chromatograph was used for VPC analysis (20% Carbowax column). All the solvents used were of Analar grade.

3-Phenyl-3-methyldiazirine (1). This compound was prepared by the procedure of Schmitz and Ohme[2] with minor modification. *N*-Benzyl-methylphenylketimine (20.9 g, 100 mmol) in methanol (200 mL) was added dropwise to liquid ammonia (100 mL) and stirred at −60 °C for 3 h. A solution of hydroxylamine-*O*-sulfonic acid (14.0 g, 150 mmol) in methanol (100 mL) was added and stirred for 2 h. The reaction mixture was allowed to warm up to room temperature and the excess ammonia was allowed to evaporate; the residue was extracted with ether and concentrated to a yellow oil. This oil was oxidized with freshly prepared silver oxide (from silver nitrate (25.5 g, 150 mmol) and sodium hydroxide (6.5 g, 160 mmol)) in a solution of 1:1 MeOH + H_2O (600 mL) at room temperature for 3 h. The silver salts were filtered out and the product was extracted with ether, dried, and concentrated to a pale yellow oil. Chromatography over silica gel afforded 5.28 g of **1** (40%): IR 1600 cm^{-1} (N=N); NMR τ 2.8 (m, 3, meta and para aromatics), 3.2 (m, 2, ortho), 8.52 (s, 3, methyl); UV_{max} (methanol) 368 nm (ϵ 187).

Thermal Decomposition of 1. The same general procedure was employed for the decomposition of **1** in all the solvents mentioned in Table I. A solution of **1** of desired concentration was taken in a round-bottomed flask equipped with a reflux condenser and drying tube. The flask was immersed in an oil bath and heated at temperature and period indicated in Table I. In all cases the solution turned red in a few minutes and this red material, IR 2040 cm^{-1}, was identified as phenyldiazoethane.[4] When the red color had completely disappeared, the solvent was removed under vacuum and the residue was analyzed by recording its NMR spectra. The residue was then chromatographed over silica gel and the products were separated. The products were identified as acetophenone azine, *m/e* 236, mp 120 °C (lit.[3] mp 119–120 °C), acetophenone (>C=O, 1695 cm^{-1}), and a mixture of cyclopropanes *m/e* 208, NMR τ 2.70–3.45 (m, 10H); 7.50–8.00 (m, 1H); 8.50 and 8.90 (2s, 3H); and 8.50–8.90 (m, 2H).[9] No styrene was isolated but VPC analysis indicates its presence in trace amounts. In the case of decomposition in Me_2SO, the solvent was first removed by repeated washing with water.

Acknowledgment. Grateful acknowledgment is made by M.T.H.L. for a grant-in-aid of research from National Research Council of Canada and from the Senate Research Committee of U.P.E.I.

Registry No.—**1**, 63269-86-3; **2**, 22293-10-3; **3**, 729-43-1; *cis*-**5**,

14161-72-9; *trans*-**5**, 1416173-0; acetophenone, 98-86-2; *N*-benzylmethylphenylketimine, 14428-98-9; hychoxylamine-*O*-sulfonic acid, 2950-43-8.

References and Notes

(1) B. M. Jennings and M. T. H. Liu, *J. Am. Chem. Soc.*, **98**, 6416 (1976).
(2) E. Schmitz and R. Ohme, *Chem. Ber.*, **94**, 2166 (1961).
(3) C. G. Overberger and J.-P. Anselme, *J. Org. Chem.*, **29**, 1188 (1964).
(4) 1-Phenyldiazoethane was synthesized independently according to the procedure of D. G. Farnum, *J. Org. Chem.*, **28**, 870 (1963).
(5) D. M. Gale, W. J. Middleton, and C. G. Krespan, *J. Am. Chem. Soc.*, **88**, 3617 (1966).
(6) N. W. Grayston and D. M. Lemal, *J. Am. Chem. Soc.*, **98**, 1278 (1976).
(7) Y. Yamamoto, S.-I. Murahashi, and I. Moritani, *Tetrahedron*, **31**, 2663 (1975).
(8) R. A. Moss and M. A. Joyce, *J. Am. Chem. Soc.*, **99**, 1262 (1977).
(9) J. A. Landgrebe and A. G. Kirk, *J. Org. Chem.*, **32**, 3499 (1967).

Aromatic Electrophilic Substitution by Pummerer Rearrangement Intermediates

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Received April 1, 1977

Sulfoxides have been developed extensively as synthetic reagents. The most common reactions are β elimination for the introduction of double bonds[1] and [2,3] sigmatropic rearrangement for allylic transposition of alcohols.[2] Sulfoxides have also been ingeniously used for benzo[*b*]thiophene synthesis, i.e., the Thyagarajan rearrangement.[3] Replacement of the sulfoxide moiety with an *N*-oxide resulted in a new general synthesis of indoles.[4]

The present study was initiated in the hope that replacement of the acetylenic moiety with a cyano group might result in a general 4,5-benzoisothiazole synthesis via a pathway analogous to the Thyagarajan process. In the event, however, a very different sequence intervened leading to a novel electrophilic aromatic substitution reaction, the first example of intermolecular attack of Pummerer rearrangement intermediates on an aromatic ring.

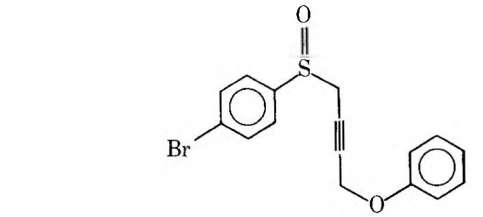
Compound **1** was found to be inert under conditions which converted **2** into the benzo[*b*]thiophene skeleton[3] (refluxing chloroform). Indeed, **1** proved to be quite thermally stable, being recovered unchanged after prolonged reflux in benzene, carbon tetrachloride, ethanol, 1-butanol, and toluene. However, **1** in refluxing xylene formed two products, *p*-bromophenyl disulfide and a crystalline solid, α-(4-bromophenylthio)-2,5-xylylacetonitrile (**3**), corresponding to a condensation of **1** with *p*-xylene and loss of a water molecule. This structure was deduced from spectral data. The IR showed a nitrile absorption and lacked a sulfoxide band. The NMR showed two nonidentical methyl groups (δ 2.32 and 2.42), a methine singlet (δ 4.97), and seven aromatic hydrogens, and the mass spectrum showed a molecular ion at *m/e* 333/331.

A similar reaction took place when **1** was refluxed in anisole, yielding *p*-bromophenyl disulfide, the ortho and para condensation products **5** and **6**, and bis(4-methoxyphenyl)acetonitrile (**4**).[12]

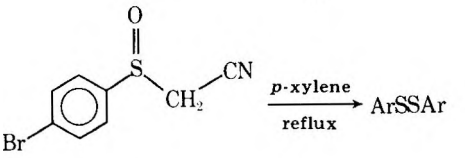
In view of the unexpected nature of the reaction of **1**, several analogous compounds (**7**–**10**) were synthesized and refluxed in anisole to delineate the scope and mechanism of this transformation.

Compound **7** gave the corresponding condensation product **11**, and **8** led to **12**. Compounds **9** and **10** do not provide condensation products in refluxing anisole or xylene.[5]

The reactions are reminiscent of the Pummerer rearrangement,[6] an acid-catalyzed reaction of sulfoxides in which sulfur becomes reduced with concomitant functionalization of the α-carbon. The catalysts normally used are HCl or *p*-toluenesulfonic acid. The present examples are rare cases of "uncatalyzed"[7] Pummerer rearrangements and are the first examples of reaction with such weakly nucleophilic species as xylene and anisole.[8]



(2)



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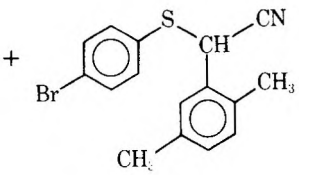

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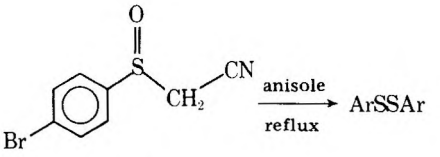

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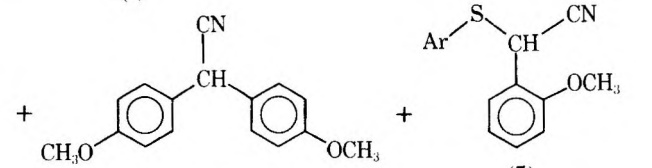
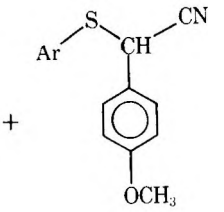


(4) (5)



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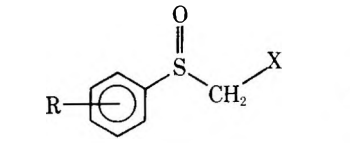
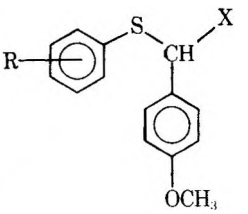


(7) R = 4-Br, X = CO_2CH_3

(8) R = H, X = CO–C$_6$H$_4$–Cl

(9) R = 2-CN, X = Ph

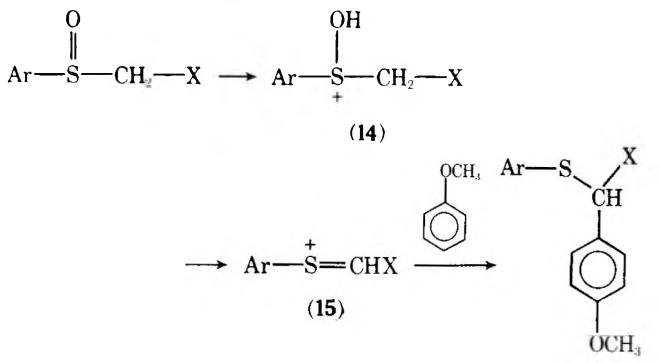
(10) R = H, X = Ph



(11) R = 4-Br, X = CO_2CH_3

(12) R = H, X = CO–C$_6$H$_4$–Cl

Scheme I



The present result is presumed to be due to the very acidic nature of the methylene hydrogens in **1**, **7**, and **8**. These acid hydrogens apparently act as the proton source for initiation of the rearrangement (Scheme I). This hypothesis is supported by the lack of reactivity of **9** and **10** in the thermal Pummerer process. However, heat plays an important role in these "uncatalyzed" reactions as the sulfoxides were inert below 140 °C when heated with xylene or anisole. When refluxed in toluene or benzene, all sulfoxides were recovered unchanged. Additionally, benzene and toluene solutions of **7** in sealed tubes at 150–160 °C underwent no reaction (although in some instances decomposition to 4-bromophenyl disulfide and methyl 4-bromophenylthioacetate occurred). On no occasion was reaction with toluene or benzene observed.

The addition of *p*-toluenesulfonic acid to solutions of **8** in acetonitrile, benzene, and toluene at their respective boiling points gave *p*-chlorobenzoic acid[13] and diphenyl disulfide as the only isolable products. It thus appears that, although intermediate **15** of Scheme I may form, benzene and toluene are not sufficiently nucleophilic to capture it and another reaction mode intervenes.

Application of this process to oxindole and benzofuran-2(3*H*)-one synthesis is currently under investigation.

Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Spectal data was collected as follows: ir, crystallized melts unless otherwise specified, Perkin Elmer 621 or 435B; NMR, $CDCl_3$, Me_4Si reference (δ 0.00), Varian T-60; mass spectra, Hitachi-Perkin Elmer RMU-6E. Microanalyses were performed by Mr. Mike Gilles in the Michigan Technological University microanalytical laboratory. The sulfoxides utilized in this study were prepared by oxidation of the corresponding sulfides with *m*-chloroperbenzoic acid (vide post). The sulfides were prepared by halide displacement from the corresponding alkyl halide with the appropriate thiol in ethanolic KOH. The following data was collected for the sulfoxides.

4-Bromophenylsulfinylacetonitrile (1): mp 105.5–106.5 °C (from ethylene dichloride/hexane; MS (70 eV) M^+· 243, 203 (100%); NMR δ 7.90–7.45 (4 H, m), 3.86 (1 H, d, J = 14.5 Hz), 3.54 (1 H, d, J = 14.5 Hz). Anal. Calcd for C_8H_6BrNOS: C, 39.3; H, 2.5. Found: C, 39.0; H, 2.5.

Methyl 4-Bromophenylsulfinylacetate (7): mp 84.5–85 °C (from benzene); NMR δ 7.80–7.40 (4 H, m), 3.90 (2 H, d, J = 13 Hz), 3.64 (2 H, d, J = 13 Hz), 3.73 (3 H, s); MS (70 eV) *m/e* 276 (M^+·), 203 (100%). Anal. Calcd for $C_9H_9BrO_3S$: C, 39.0; H, 3.3. Found: C, 39.3; H, 3.3.

ω-Phenylsulfinyl-4-chloroacetophenone (8): mp 124–125 °C (from cyclohexane/chloroform); NMR δ 8.00–7.75 (2 H, d, J = 8 Hz), 7.70–7.30 (7 H, m), 4.61 (2 H, d, J = 14 Hz), 4.19 (2 H, d, J = 14 Hz); IR 1665, 1090, 1050 cm^{-1}; MS (70 eV): *m/e* 278 (M^+·), 125 (100%). Anal. Calcd for $C_{14}H_{11}ClO_2S$: C, 60.3; H, 4.0. Found: C, 60.4; H, 3.9.

Preparation of 2-Cyanophenyl Benzyl Sulfide. The corresponding amide[9] (mp 150.5–152 °C, lit. 150–151 °C; 5.9 g, 0.024 mol) was refluxed 5 h with thionyl chloride (5 mL, d = 1.66 g/ml, 0.070 mol) in dry benzene (4 mL). Evaporation of volatiles in vacuo followed by filtration through neutral alumina gave 2-cyanophenyl benzyl sulfide (4.0 g, 74%): mp 57–58 °C (C_2H_5OH); IR (KBr) 2210 cm^{-1}; NMR δ 7.67–7.03 (9 H, m), 4.18 (2 H, s); MS (70 eV) *m/e* 225 (M^+·), 91 (100%). Anal. Calcd for $C_{14}H_{11}NS$: C, 74.6; H, 4.9; N, 6.2. Found: C, 74.6; H, 4.9; N, 6.0.

Table I

Chrom fraction	% yield	Composition
1 in *p*-xylene:		
1–2	17	4-Bromophenyl disulfide[a]
5–6	32	(3)[b]
1 in anisole:		
2–3	14	4-Bromophenyl disulfide[a]
8–9	17	(5)[c]
10–12	39	(6)[d]
14–17	11	(4)[e]

[a] Identical with an authentic sample. [b] mp 101–102 °C (hexane); NMR δ 7.65–6.78 (7 H, m), 4.97 (1 H, s), 2.42 (3 H, s), 2.32 (3 H, s); IR 2245 cm^{-1}; MS (20 eV) *m/e* 331 (M^+·), *m/e* 144 (100%). Anal. Calcd for $C_{16}H_{14}BrNS$: C, 57.8; H, 4.2. Found: C, 57.9; H, 4.2. [c] mp 58–59 °C (hexane); NMR δ 7.60 (8 H, m), 5.33 (1 H, s), 3.80 (3 H, s); IR 2250 cm^{-1}; MS (70 eV) *m/e* 333 (M^+·), 146 (100%). Anal. Calcd for $C_{15}H_{12}BrNOS$: C, 53.9; H, 3.6, N, 4.2. Found: C, 54.1; H, 3.6, N, 4.0. [d] mp 121.5–122 °C (hexane); NMR δ 7.63–6.73 (8 H, m), 4.90 (1 H, s), 3.75 (3 H, s); IR 2255 cm^{-1}; MS (70 eV) *m/e* 333 (M^+·) *m/e* 146 (100%). Anal. Calcd for $C_{15}H_{12}BrNOS$: C, 53.9; H, 3.6; N, 4.2. Found: C, 54.1; H, 3.6; N, 4.2. [e] mp 155 °C (petroleum ether) [lit.[11] mp 154–155 °C]; NMR δ 7.42–6.78 (8 H, m), 5.03 (1 H, s), 3.75 (6 H, s); MS (70 eV) *m/e* 253 (M^+·).

Preparation of 2-Cyanophenyl Benzyl Sulfoxide (9). The sulfide (2.25 g, 0.01 mol) in methylene chloride (50 mL) was cooled to 0 °C in an ice bath and *m*-chloroperbenzoic acid (85%, 2.02 g, 0.01 mol) in methylene chloride (50 mL) was added dropwise. The cold solution was stored overnight at 0 °C. The mixture was then filtered and the filtrate washed with K_2CO_3 solution (5%, 100 mL). Drying ($MgSO_4$) and solvent evaporation in vacuo gave the sulfoxide (2.21 g, 92%): mp 114–116 °C (C_2H_5OH); IR 2250, 1085 cm^{-1}; NMR δ 7.63–7.43 (4 H, m), 7.33–6.83 (5 H, m), 4.34 (2 H, d, J = 14 Hz), 4.08 (2 H, d, J = 14 Hz); MS (70 eV) *m/e* 241 (M^+·), 91 (100%). Anal. Calcd for $C_{14}H_{11}NOS$: C, 69.7; H, 4.6; N, 5.8. Found: C, 69.7; H, 4.5; N, 5.7.

Thermolysis of 4-Bromophenylsulfinylacetonitrile (1) in *p*-Xylene. The title compound (1.5 g) in *p*-xylene (50 mL) was refluxed 15 h at which time the solvent was evaporated in vacuo. The resultant oil was chromatographed on silica gel (hexane slurry, 2.5 × 26 cm) The column was eluted with gradually increasing amounts of ether in hexane (4–50%), 125-mL fractions being collected. Data for these fractions are summarized in Table I.

Thermolysis of 1 in Anisole. The title compound (3.0 g) in anisole (75 mL) was refluxed 12.5 h under nitrogen at which time the anisole was evaporated in vacuo. The residue was chromatographed on silica gel (hexane slurry, 5 × 30 cm) as described above. Data for these fractions are summarized in Table I.

Thermolysis of Methyl 4-Bromophenylsulfinylacetate (7) in Anisole. The sulfoxide (2.02 g) in anisole (20 mL) was refluxed 18 h at which time the solvent was evaporated in vacuo. Chromatography of the residue on silica gel [5 × 40 cm column eluted with hexane (1.6 L) and 10% CH_2Cl_2 in hexane (4 L), 250-mL fractions being collected] gave *p*-bromophenyl disulfide (fractions 3–12, 0.25 g, identical with an authentic sample prepared by Me_2SO oxidation of *p*-bromophenylthiophenol[10]) and 1.3 g of an oil (fractions 15–18) from which 0.7 g of pure **11** could be obtained by crystallization from hexane: mp 85–88 °C (constant melting point); IR 1740 cm^{-1}; NMR δ 7.60–7.20 (6 H, m), 7.10–6.80 (2 H, d, J = 9 Hz), 4.93 (1 H, s), 3.83 (3 H, s), 3.73 (3 H, s); MS (70 eV) *m/e* 366 (M^+·), *m/e* 179 (100%), Anal. Calcd for $C_{16}H_{15}BrO_3S$: C, 52.3; H, 4.1. Found: C, 52.2; H, 4.0.

The mother liquor could not be crystallized nor could the components be separated chromatographically. The NMR indicated the presence of **11** and another substance, presumably the ortho isomer [NMR δ 5.23 (s)] of **11**. The integral ratio of the δ 4.93 peak of the methine hydrogen in **11** and the δ 5.23 peak was 1/1 in the mother liquor.

Thermolysis of 7 in Toluene. Compound **7** (0.50 g) was dissolved in toluene (10 mL) and the resulting solution was sealed at atmospheric pressure in a soft glass tube (1.6 × 8 cm). The sealed tube was heated at 160 °C (oven temperature) for 24 h. Solvent evaporation and preparative layer chromatography (SiO_2, benzene) gave 4-bro-

mophenyl disulfide (147 mg), methyl 4-bromophenylthioacetate (95 mg), and recovered starting material (90 mg). No evidence of reaction with toluene was found even in the NMR of the crude product.

Thermolysis of 8 in Anisole. A solution of 8 (1 g, 0.0038 mol) in anisole (20 mL) was refluxed for 4 h. The residue remaining after evaporation of excess anisole in vacuo was chromatographed on SiO_2 (3 × 18 cm) and eluted with hexane (3 L), and then with 5% $CHCl_3$ in hexane (10 L). Collection of 250-mL fractions gave diphenyl disulfide (0.2 g, fractions 3–29) and **13** (0.4 g, 28%, fractions 40–45): mp 71.5–72.5 °C (C_2H_5OH); IR 1680 1585, 1260 cm^{-1}; NMR δ 8.00–7.75 (2 H, d, J = 8 Hz), 7.45–7.15 (9 H, m), 6.95–6.70 (2 H, d, J = 8 Hz), 5.75 (1 H, s), 3.72 (3 H, s); MS (70 eV), m/e 368 ($M^{+\cdot}$), 229 (100%). Anal. Calcd for $C_{21}H_{17}ClO_2S$: C, 68.4; H, 4.7. Found: C, 68.8; H, 4.5.

Acknowledgments. The author thanks Sigma Xi for partial support of this work and Dr. V. Sandel for reviewing the manuscript.

Registry No.—**1**, 63215-96-3; **3**, 63215-97-4; **4**, 6275-26-9; **5**, 63215-98-5; **6**, 63215-99-6; **7**, 63216-00-2; **8**, 58936-71-3; **9**, 63216-01-3; **11**, 63216-02-4; **12**, 63216-03-5; 4-bromophenylthioacetonitrile, 50837-23-5; methyl 4-bromophenylthioacetate, 50397-69-8; ω-phenylthio-4-chloroacetophenone, 33192-00-6; 2-carboxamidophenyl benzyl sulfide, 54705-18-9; 2-cyanophenyl benzyl sulfide, 63216-04-6; **11** ortho isomer, 63216-05-7; 4-bromophenyl disulfide, 5335-84-2; 4-bromobenzenethiol, 106-53-6; benzenethiol, 108-98-5.

References and Notes

(1) B. M. Trost and T. N. Salzmann, *J. Am. Chem. Soc.*, **95**, 6840 (1973); B. M. Trost and K. K. Leung, *Tetrahedron Lett.*, **48**, 4197 (1975); P. A. Grieco, D. Boxler, and C. S. Pogonowski, *Chem. Commun.*, 497 (1974); P. A. Grieco and C. S. Pogonowski, *Chem. Commun.*, 72 (1975); D. K. Bates and B. S. Thyagarajan, *Int. J. Sulfur Chem.*, **8**, 419 (1973)

(2) D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974).

(3) K. C. Majumdar and B. S. Thyagarajan, *Chem. Commun.*, **83** (1972); K. C. Majumdar and B. S. Thyagarajan, *Int. J. Sulfur Chem., Part A*, **2**, 93 (1972); B. El-Osta, K. C. Majumdar and B. S. Thyagarajan, *J. Heterocycl. Chem.*, **10**, 107 (1972).

(4) B. S. Thyagarajan, J. B. Hilliard, K. V. Reddy, and K. C. Majumdar, *Tetrahedran Lett.*, **23**, 1999 (1974).

(5) Compound **10** is recovered unchanged; **9** decomposes in anisole to give at least four products, none of which contain anisole. The reaction of **9** is under further investigation.

(6) G. A. Russell and G. Mikol, "Mechanisms of Molecular Migrations", Vol. 1, B. S. Thyagarajan, Ed., Wiley, New York, N.Y. (1968).

(7) Some "activated" sulfoxides have been observed to undergo rearrangement in protic solvents such as water and ethanol to give sulfides in which solvent has attacked the α-carbon; cf. E. F. Schroeder and R. M. Dodson, *J. Am. Chem. Soc.*, **84**, 1004 (1962); H. D. Becker and G. A. Russell, *J. Org. Chem.*, **28**, 1896 (1963).

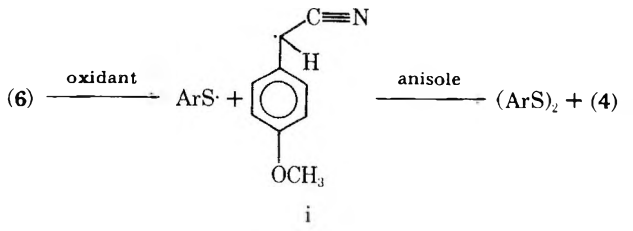
(8) Recently, the *p*-toluenesulfonic acid catalyzed *intramolecular* counterpart of this reaction was reported: Y. Oikawa and O. Yonemitsu, *J. Org. Chem.*, **41**, 1118 (1976).

(9) S. Oae and T. Numata, *Tetrahedron*, **30**, 2641 (1974).

(10) W. W. Epstein and F. W. Sweat, *Chem. Rev.*, **67**, 247 (1967).

(11) T. Kametani *et al.*, *Chem. Pharm. Bull.*, **16**, 1584 (1968).

(12) Compounds **5** and **6** are quantitatively recovered after prolonged (24 h) reflux in anisole alone or anisole containing a molar excess of *p*-toluenesulfonic acid. The formation of **4** via a sequence of sulfur protonation in **6** followed by loss of *p*-bromobenzenethiol and electrophilic attack on anisole by the resultant carbocation is therefore untenable. An alternative process involves conversion of **6** into **I** followed by free radical attack on anisole. Due to the scale of the reaction, other isomers of **4**, though



i

probably formed, were present in quantities too small to detect. The oxidant in this reaction would be unreacted **1**; sulfoxides are known oxidants (ref 10). Using *m*-chloroperbenzoic acid (CH_2Cl_2) as the oxidant, the sulfoxide of **6** and 2,3-di(4-methoxyphenyl)succinonitrile, the coupling product of **I**, were isolated. Formation of **I** appears to be quite facile; in the presence of anisole **4** forms, but in the absence of a reactive solvent **I** dimerizes.

(13) The mode of formation of *p*-chlorobenzoic acid is unknown. In the presence of moisture a retro-Claisen condensation could convert **8** into *p*-chlorobenzoic acid and methyl phenyl sulfoxide. The latter product was not observed however. One could speculate that *p*-chlorobenzoic acid arises from decomposition of the hemihydrate of *p*-chlorophenylglyoxal, the expected Pummerer rearrangement product from **8** in acid solution in the presence of fortuitous water (ref 14).

(14) G. A. Russell and G. J. Mikol, *J. Am. Chem. Soc.*, **88**, 5498 (1966); H. D Becker and G. A. Russell, *J. Org. Chem.*, **28**, 1895 (1963).

Determination of the Rate of Reduction of Benzophenone-*1*-^{14}C by Lithium Benzhydrolate

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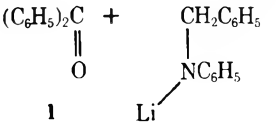
Received April 5, 1977

In previous work concerning the properties of N-metalated secondary amines as hydride donors, Wittig and co-workers[2,3] found that lithium *N*-benzylanilide (**2**) effected a reduction of ketones [e.g., benzophenone (**1**)] to yield corresponding lithium alcoholates and Schiff bases. On the basis of kinetic studies, the authors proposed that a rapid equilibrium was established between starting materials and a 1:1 "ate complex"[4] (**3**), and that hydride transfer occurred in a subsequent



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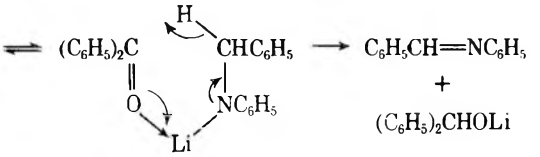

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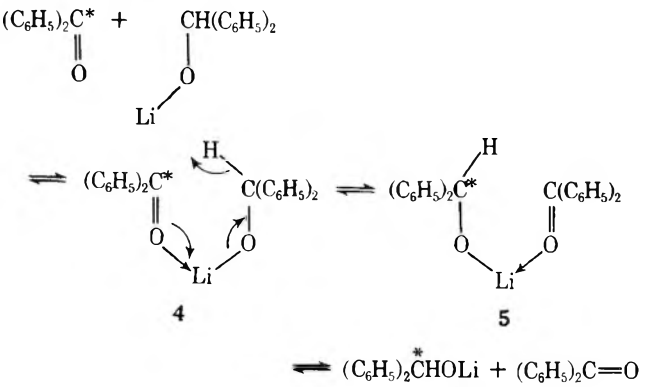
irreversible rate-determining step. The reaction was found to be second order, being first order with respect to each reactant.

In view of these results, it was of interest to investigate the nature of the reduction between an analogous O-metalated alcohol, benzhydrol, and benzophenone. Of special interest was the determination of the rate of the carbinol–carbonyl equilibrium for comparison to that of the N-metalated amine/benzophenone system. It was thought that the reaction would proceed via rapid formation of an ate complex (**4**), slow transfer of hydride to form a new ate complex (**5**), and, finally, rapid equilibration to form products. Similar mechanisms involving cyclic intermediates such as **4** and **5** have been



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generally adopted for both Grignard[5] and Meerwein–Ponndorf–Verley (MPV)[6] reductions. Further, it has been established that hydrogen transfer takes place directly from metalated component to ketone in these reactions.[5,7]

In this study, radioactive benzophenone-*1*-^{14}C was allowed to react with inactive benzhydrol in tetrahydrofuran (THF) at 90 °C. At various time intervals, the reaction was quenched

Table I. Increase in Radioactivity of Benzhydrol with Time

Run	Time, s, $\times 10^{-3}$	Benzhydrol-*1*-^{14}C, mg, per 50-mg sample[a]
1	5.4	5.50
	12	7.50
2	12	7.38
	24	12.75
	48	19.38
3	9	6.12
	12	7.28
	15	8.62
	18	10.25
	24	12.38
	36	15.50
	42	17.12

[a] The infinity value for benzhydrol-*1*-^{14}C per 50-mg sample was taken to be 25.28 mg (50 mmol).

by hydrolysis and the products were separated by column chromatography. Both the decrease of radioactivity in benzophenone and the increase of radioactivity in benzhydrol were determined by liquid scintillation counting methods.

Systematic monitoring of the products by thin-layer chromatography indicated the absence of by-product formation during the reaction. Thus, for example, formation of benzpinacol, which occurs in photolysis reactions between ketone and benzhydrol,[8] was not observed. It is known that condensation and enolization reactions do not occur with benzophenone.[5]

The intermediacy of free radicals or of radical anions was not expected on the basis of previous findings of Doering and Aschner[7] and of Russell et al.[9] In the former work, an alcoholate-catalyzed MPV reduction was unaffected when carried out in the presence of radical inhibitors. In the latter work, only trace quantities of radicals were observed in a reaction between benzophenone and benzhydrol in 80% Me_2SO/20% *tert*-butyl alcohol with an excess of potassium *tert*-butoxide, conditions much more favorable to radical anion formation than those used in this study.

Data obtained for the increase of radioactivity in benzhydrol as a function of time are found in Table I. From the slope of the plot of log $[1 - (x/x_\infty)]$ vs. time (see Experimental Section), a rate of exchange, R, of 1.51×10^6 s^{-1} (9.06×10^{-5} min^{-1}) was determined for the reaction. Regardless of the actual kinetics of the exchange reaction, the rate of appearance of radioactivity in benzhydrol is first order with respect to radioactivity.[10] Although the data do not permit the conclusion that the reaction is second order, this molecularity is expected based on the similarity of the reaction to the lithium *N*-benzylanilide reduction. In contrast, an MPV reduction involving ketone and aluminum alcoholate is more complex, being first order in ketone but variable order in aluminum alcoholate.[11,12] Under the assumption that the benzophenone/lithium benzhydrolate reduction is indeed second order, a rate constant of 1.51×10^{-4} M^{-1} s^{-1} (9.06×10^{-3} M^{-1} min^{-1}) is obtained.

For the benzophenone/lithium *N*-benzylanilide system in ether at 20 °C, a second-order rate constant (K_2) of 1.67×10^{-2} M^{-1} min^{-1} has been reported.[2] This value of K_2, upon extrapolation of an Arrhenius plot, becomes ca. 5 M^{-1} min^{-1} at 90 °C in ether.[3] The reaction proceeds faster by a factor of 2 in THF.[3] Taking into consideration a statistical factor of 2 (lithium *N*-benzylanilide has two H's β with respect to Li vs. one for lithium benzhydrolate) leads to the result that benzophenone undergoes hydride reduction by lithium *N*-benzylanilide faster than by lithium benzhydrolate by a factor of ca. 500.

This difference in rate can be discussed in terms of the atoms occupying the α and β positions and their substituents. At the β position, the additional phenyl group of the alcoholate would be expected to accelerate release of hydride on the basis of its ability to stabilize incipient positive charge at the β carbon atom. At the α position, the greater electronegativity of the oxygen atom of the alcoholate would be expected to decrease hydride mobility. Apparently this latter effect dominates the former, thus slowing the hydride transfer by the factor observed.

It is also of interest to compare the K_2 value derived from this work with that found in previous investigations of the MPV reduction of deuterated acetone by tetrameric aluminum isopropoxide.[6e] In the MPV system, a K_2 value in benzene of 32.5×10^{-6} M^{-1} s^{-1} is obtained by Arrhenius extrapolation to 90 °C. Thus, only a factor of 5 separates the rate constants of these two reductions. It is possible that this difference can be accounted for on the basis of substituents (phenyls vs. methyls) and solvents (THF vs. benzene) for the two systems, thus suggesting that hydride transfer for a given ketone/alcoholate pair proceeds at similar rates regardless of the metal involved. Such a conclusion would be consistent with the present view that the first step, i.e., ketone–metal coordination, is a rapid and reversible step, followed by rate-determining hydride transfer.

Experimental Section

Solvents and Solutions. All solvents were dried and distilled. Ether was refluxed over sodium metal until the blue color of benzophenone ketyl was observed, then it was distilled and stored over sodium metal. Tetrahydrofuran was shaken with aqueous 50% potassium hydroxide and dried over solid potassium hydroxide, followed by anhydrous calcium chloride. The THF was then refluxed and distilled over sodium metal and stored over lithium aluminum hydride, from which it was freshly distilled prior to use. The scintillation solution was prepared by dissolving 0.4 g of 1,4-bis(2-methyl-5-phenyloxazolyl)benzene and 5.0 g of 2,5-diphenyloxazole in 1 L of dry toluene. For each activity determination, 50 mg of substance was dissolved in 15 mL of this solution.

Benzophenone-*1*-^{14}C. Benzoic acid-*1*-^{14}C (1.7 mg) having a specific activity of 21.3 μCi/mg was diluted with 4.99 g of inactive benzoic acid. This material was converted to benzophenone-*1*-^{14}C by the method described by Murray and Williams.[13] The product, obtained in 65% yield, was recrystallized from petroleum ether (80–90 °) to give pure benzophenone-*1*-^{14}C, mp 47–48 °C, having a specific activity of ca. 5 μCi/g. Dilution of this material (1.08 g) with inactive benzophenone (47 g) gave benzophenone-*1*-^{14}C with a specific activity of ca. 0.1 μCi/g.

Benzhydrol-*1*-^{14}C. This material was obtained from benzophenone-*1*-^{14}C as described by Murray and Williams.[14] Purification of the product was effected by column chromatography (Al_2O_3) and by recrystallization from petroleum ether (80–90 °C). A yield of 1.56 g (65%) of benzhydrol-*1*-^{14}C, mp 68–69 °C, specific activity ca. 0.1 μCi/g, was obtained.

Lithium Benzhydrolate. All operations described below were carried out under an atmosphere of dry nitrogen. In a typical run, benzhydrol (5.0 g, 27 mmol) was dissolved in dry ether (50 mL) and an equimolar amount of methyllithium was added. The solution was stirred for 2 h, during which time crystals of lithium benzhydrolate separated. The crystals were collected on a fritted glass filter, washed three times with dry ether, and dried under vacuum. The material was dissolved in dry THF (100 mL) and the concentration of the resulting solution was determined by removing an aliquot, hydrolyzing, and titrating with 0.1 N hydrochloric acid. In general, the solutions were about 0.14 M in lithium benzhydrolate.

Kinetics. Equimolar amounts of benzophenone-*1*-^{14}C and lithium benzhydrolate were added to dry THF at room temperature so that the solution was 0.1 M in each component. Aliquots (10-mL) of the solution were placed into sealed tubes under dry nitrogen and the tubes were placed into a thermostated bath kept at 90 ± 0.05 °C. At varying time periods, the tubes were removed, the contents quickly cooled, and the reaction quenched by addition of water. THF was removed in a stream of dry nitrogen and the aqueous solution was

extracted with ether. The ethereal extracts were combined, washed with water, and dried over sodium sulfate. A thin-layer chromatogram (Kieselgel G, benzene/CH_2Cl_2, 2/1) confirmed the presence of only two components, benzophenone and benzhydrol. These materials were separated by column chromatography (Al_2O_3) by eluting with cyclohexane (100 mL), carbon tetrachloride (250 mL), benzene (250 mL), and chloroform (300 mL). The appropriate fractions were combined, and the products were recrystallized twice from petroleum ether (80–90 °C). Samples (50-mg) of each of the materials were dissolved in the scintillation solution and the time required for 10^4 impulses was measured. From the time values obtained for each sample, the amount of active benzophenone and/or benzhydrol per 50-mg sample was determined by comparison to previously prepared calibration curves. In all cases, over 95% of the radioactivity could be accounted for. No exchange of carbon-14 was observed under the conditions of chromatographic separation. Three kinetic runs were made in which the reaction was followed through ca. 2 half-lives. These data are presented in Table I.

The rate of carbon-14 exchange, R, for a reaction of the type

$$BX^* + AX \rightleftharpoons AX^* + BX$$

is given by the general expression:[15]

$$R = -\frac{ab}{a+b}\left\{\frac{2.3}{t}\log\left[1 - (x/x_\infty)\right]\right\}$$

where a and b = total concentration of AX and BX*, respectively; X = concentration of active AX at time t; and $x_\infty = x$ at t_∞. Under the assumption that the reaction is second order, $K_2 = R/ab = -[2.3/a + b)t]\log[1 - (x/x_\infty)]$.[6e,16] A plot of log $[1 - (x/x_\infty)]$ vs. time was constructed and fitted by the method of least squares (correlation coefficient = 0.987). From the slope, R (and K_2) were evaluated.

Acknowledgment. R. D. H. gratefully acknowledges the support of an NSF Postdoctoral Fellowship, and the helpful discussions with Drs. A. Krebs, M. Rings, P. Suchanek, G. Steinhof, and H. Wulff during the course of this work.

Registry No.—Benzoic acid-*1*-^{14}C, 1589-66-8; benzophenone-*1*-^{14}C, 51594-23-1; benzyhydrol, 91-01-0; lithium benzhydrolate, 2036-66-0; benzhydrol-*1*-^{14}C, 55366-57-9.

References and Notes

(1) NSF Postdoctoral Fellowship Participant, Organisch Chemisches Institut, Heidelberg, W. Germany, 1964–1965.
(2) G. Wittig and H. D. Frommeld, *Chem. Ber.*, **97**, 3541 (1964).
(3) G. Wittig, H. F. Ebel, and G. Häusler, *Justus Liebigs Ann. Chem.*, **743**, 120 (1970).
(4) For a review of the role of ate complexes in organic chemistry, see W. Tochtermann, *Angew. Chem., Int. Ed. Engl.*, **5**, 351 (1966).
(5) G. E. Dunn and J. Warkentin, *Can. J. Chem.*, **34**, 75 (1956).
(6) (a) H. Meerwein, *J. Prakt. Chem.*, **147**, 211 (1936); (b) R. B. Woodward, N. L. Wendler, and F. J. Brutschy, *J. Am. Chem. Soc.*, **67**, 1425 (1945); (c) V. J. Shiner, Jr., and D. Whittaker, *ibid.*, **85**, 2337 (1963); (d) B. J. Yager and C. K. Hancock, *J. Org. Chem.*, **30**, 1174 (1965); (e) V. J. Shiner, Jr., and D. Whittaker, *J. Am. Chem. Soc.*, **91**, 394 (1969); (f) V. Hach, *J. Org. Chem.*, **38**, 293 (1973).
(7) W. v. E. Doering and T. C. Aschner, *J. Am. Chem. Soc.*, **75**, 393 (1953).
(8) A. Schonberg and A. Mustafa, *J. Chem. Soc.*, 276 (1943).
(9) G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Am. Chem. Soc.*, **84**, 4155 (1962); **86**, 1807 (1964).
(10) R. B. Duffield and M. Calvin, *J. Am. Chem. Soc.*, **68**, 557 (1946).
(11) W. N. Moulton, R. E. Van Atta, and R. R. Ruch, *J. Org. Chem.*, **26**, 290 (1961).
(12) M. S. Bains and D. C. Bradley, *Chem. Ind. (London)*, 1032 (1961).
(13) A. Murray and D. I. Williams, "Organic Synthesis with Isotopes", Part I, Interscience, New York, N.Y., 1958, p 662.
(14) A. Murray and D. I. Williams, ref 13, p 524.
(15) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", 2nd ed, Wiley, New York, N.Y., 1961, p 192.
(16) A. A. Frost and R. G. Pearson, ref 15, p 187.

A Simple and Practical Synthesis of Olivetol

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Received March 7, 1977

The complete structural elucidation[1,2] of some psychotomimetically active components of marihuana and the extensive biological activity[3] of these components have stimulated interest in the synthesis of cannabinoids.[4–7] The synthesis of these compounds depends largely on the availability of the key intermediate olivetol, 1-*n*-pentyl-3,5-dihydroxybenzene, and homologs. A practical and efficient synthesis which makes these compounds readily available in quantity will considerably facilitate and stimulate further investigation of the synthetic and biological aspects of the cannabinoids.

While several papers on the synthesis of olivetol have appeared recently,[8–10] they did not differ much from the earlier investigations[11,12] in that 3,5-dimethoxybenzoic acid was used as the starting material. This substance is, in fact, expensive and not readily available. In the case where trimethoxy derivatives have been employed,[13] the in situ 4-demethoxylation, as Birch and Slabbe[9] pointed out, results in a poorer quality product. Finally, a recently described synthesis starting from an α,β-unsaturated ester[14] involves complicated steps and has severe steric limitations.

We would like to report a three-step total synthesis[15] of olivetol (**3**) from readily available aliphatic precursors. The α,β-unsaturated ketone[16] **1** was reacted with dimethyl malonate enolate to give the cyclic Michael adduct **2** which was aromatized and subsequently decarbomethoxylated when treated with bromine in DMF, initially at 0 °C[17] and then at refluxing temperature, to yield olivetol in 62% overall yield.

Alternatively, **2** was decarbomethoxylated by successive treatment with alkali and acid to afford the enol **4** which was etherified with methanolic hydrogen bromide to furnish the keto enol ether **5**. Aromatization with etherification[18] of **5** with cupric bromide in methanol gave 1-*n*-pentyl-3,5-dimethoxybenzene (**6**) in an overall yield of 37%. Compound **6** was then demethylated with pyridine hydrochloride to provide 82% of **3**.

Olivetol (**3**) prepared directly by route **1** → **2** → **3** (see Scheme I) is practical and inexpensive. This synthesis is general and suitable for the preparation of homologues of olivetol containing lower or higher or branched alkyl groups (see Table I). This sequence has also been used to incorporate a labeled carbon atom in the aromatic ring.[19]

The alternative route leads to a variety of intermediates which per se could be of synthetic interest. The keto-enol **4**, used originally by adams[20] and co-workers in the synthesis of cannabinol, was laboriously prepared by partial reduction of olivetol.

Experimental Section

All melting points (uncorrected) were taken in open capillary tubes in a Thomas–Hoover melting point apparatus. Vapor phase chromatographs were determined with an F & M Model 810 instrument, using a 4 ft × 1/4 in. S.S. column of 3% silicon rubber on Diatoport 5 at 160 °C under helium gas flow of 90 mL/min. Infrared spectra were determined with a Beckman IR-5 infrared spectrophotometer and ultraviolet spectra were measured with a Cary Model 14 M spectro-

Scheme I

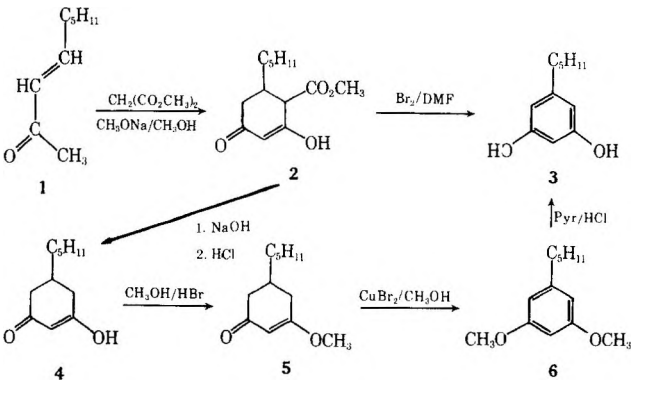


Table I. Other 1-Alkyl-3,5-dihydroxybenzene Prepared by the Direct Route

1 Substituent	Registry no.	Yield, %	Mp or bp, °C
Propyl	500-49-2	80.4	48–50 (lit.[21] mp 51)
Heptyl	500-67-4	74.7	55–56 (lit.[12] mp 55–55.5)
1-Methylheptyl	27871-95-0	86.4	Bp 129–130 (0.04 mm) (lit.[11] bp 179–184 (4 mm)

photometer. Nuclear magnetic resonance spectra were obtained with a Varian A-60A or HA-100 spectrometer.

Methyl 6-*n*-Pentyl-2-hydroxy-4-oxo-cyclohex-2-ene-1-carboxylate (2).[22] To a solution of 32.4 g (0.60 mol) of sodium methoxide and 90 g (0.68 mol) of dimethyl malonate in 230 mL of anhydrous methanol was added portionwise with stirring 75 g (0.48 mol) of 90% pure 3-nonen-2-one[16] (1). The reaction mixture was then refluxed for 3 h under N_2 and allowed to cool to room temperature. The solvent was distilled under reduced pressure and the residue dissolved in 350 mL of water. The slurry of white crystals and the almost clear solution was extracted with 3 × 80 mL of $CHCl_3$, the aqueous acidified to pH 4 with concentrated HCl and the white precipitate allowed to stand overnight and filtered. The crystals were dried at 50 °C under high vacuum for 5 h to yield 106.5 g (92%) of **2**, mp 96–98 °C. An analytical sample prepared from heptane gave mp 98–100 °C; IR ($CHCl_3$): 3180, 3270–2500 (OH), 1740, 1710 (C=O ester), 1600 cm^{-1} (C=O and C=C); NMR ($CDCl_3$): δ 0.90 (CH_3), 1.33 ($4CH_2$), 5.50 (−CH=), 9.23 (OH).

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.01; H, 8.40.

1-*n*-Pentyl-3,5-dihydroxybenzene, Olivetol (3).[22] To an ice-cooled solution of 58.4 g (0.245 mol) of **2** dissolved in 115 mL of dimethylformamide was added dropwise with stirring a solution of 37.9 g (0.23 mol) of bromine dissolved in 60 mL of dimethylformamide. At the end of the addition (ca. 90 min) the reaction mixture was slowly heated to 80 °C during which time the evolution of carbon dioxide became quite vigorous. The reaction was maintained at this temperature until the gas evolution had ceased and was then heated to 160 °C and held at this temperature for 10 h. The DMF was removed under reduced pressure and the residue treated with 80 mL of water. The mixture was extracted with 2 × 250 mL of ether and the ether solution washed with water, 2 × 80 mL of a 10% solution of sodium bisulfite, 2 × 80 mL of a 10% solution of acetic acid, and then again with water. The ether solution was dried (Na_2SO_4) and the solvent removed under reduced pressure to give 46.8 g of a viscous oil. The oil was distilled through a 12 in. Vigreux column (¾ in. diameter) to give 30.3 g (69.3%) of **3**, 95% pure by VPC. An analytical sample recrystallized from ether gave: mp 85–86 °C; IR ($CHCl_3$) 3150 (OH), 1790, 1710 (C=O ester), 1600 cm^{-1} (C=O, C=C); NMR ($CDCl_3$): δ 0.90 (CH_3), 1.27 (6 CH_2), 5.55 (−CH=), 8.95 (OH).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.13; H, 9.02. Found: C, 67.28; H, 9.25.

3-Hydroxy-5-*n*-pentyl-2-cyclohexene-1-one (4). A solution of 50 g (0.20 mol) of **2** in 200 mL of 20% NaOH was heated on a steam bath for 2.5 h, cooled and extracted with two 100-mL portions of ether. The alkaline aqueous solution was acidified slowly with ca. 80 mL of concentrated hydrochloric acid. The resulting aqueous mixture was stirred and heated on a steam bath for 1 h longer, cooled, and extracted with three 200-mL portions of ether. The ether extracts were washed with water and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was treated twice with 50 mL of benzene, distilling the solvent each time, to leave 36.5 g (96%) of **4** as a viscous oil which solidified on standing. An anlytical sample prepared from heptane gave: mp 71–73 °C (lit.[20] mp 70–71 °C); IR ($CHCl_3$): 2700–2400 (OH), 1735, 1715 cm^{-1} (C=O); λ_{max}^{MeOH}: 258 (ε 17 000), 280 mμ (ε 13 200); NMR ($CDCl_3$): δ 0.88 (CH_3), 1.33 ($4CH_2$), 5.46 (−CH=).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.53; H, 9.70.

3-Methoxy-5-*n*-pentyl-2-cyclohexen-1-one (5). A solution of 91 g (0.50 mol) of **4** in 300 mL of 5% hydrogen bromide in methanol was stirred at room temperature for 24 h. The volatiles were removed under reduced pressure and the oily residue was dissolved in 700 mL of ether, extracted with four 150-mL portions of a saturated Na_2CO_3 solution, washed with 150 mL of water dried over anhydrous Na_2SO_4, and then distilled at 109 °C (0.06 mm) to give 50 g (51%) of **5**. An analytical sample crystallized from petroleum ether exhibited: mp 43–44 °C; IR ($CHCl_3$): 1650 (C=O), 1610 (enol ether), 1237 cm^{-1} (COC); NMR ($CDCl_3$): δ 0.89 (CH_3), 1.34 ($4CH_2$), 3.68 (OCH_3), 5.37 (−CH=).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.25; H, 10.14.

3,5-Dimethoxy-*n*-amylbenzene (6). A mixture of 3.6 g (0.18 mol) of **5** and 8.9 g (0.04 mol) of cupric bromide in 100 mL of methanol was stirred at room temperature for 24 h and filtered, and the filtrate evaporated under reduced pressure. The residual oil was partitioned between 100 mL of ether and 50 mL of water. The ether layer was separated, washed with two 50-mL portions of saturated Na_2CO_3 solution and 50 mL of water and dried (Na_2SO_4), and the solvent removed under reduced pressure. The dark oil was fractionally distilled to give 3.1 g (82%) of **6**, bp 110 °C (0.05 mm) (lit.[12] bp 199 °C (0.5 mm)); IR ($CHCl_3$): 1610, 1590, 1572 (aromatic), 1230, 1123 cm^{-1} (COC).

Acknowledgments. The authors are grateful to the following members of our Physical Chemistry Department (Director, Dr. R. P. W. Scott): Dr. T. Williams, Mr. S. Traiman, Dr. V. Toome, and Dr. C. G. Scott for the nuclear magnetic resonance, infrared, ultraviolet spectra, and vapor phase chromatographic data, respectively. We also thank Dr. F. Scheidl and his staff for the elemental analysis and we are particularly grateful to Mr. P. Heslin for his capable assistance.

Registry No.—1, 15309-570 **2**, 27871-89-2; **3**, 500-66-3; **4**, 58016-19-8; **5**, 58016-32-3; **6**, 22976-40-5; dimethyl malonate, 108-59-8; 3-hepten-1-one, 1119-44-4; methyl 6-*n*-propyl-2-hydroxy-4-oxocyclohex-2-ene-1-carboxylate, 2787-91-6; 3-undecen-2-one, 10522-37-9; methyl 6-*n*-heptyl-2-hydroxy-4-oxocyclohex-2-ene-1-carboxylate, 27871-93-3; 5-methyl-3-undecen-2-one, 58016-25-4; methyl 6-(1-methylheptyl)-2-hydroxy-4-oxocyclohex-2-ene-1-carboxylate, 27871-96-1; methyl 3-bromo-2-hydroxy-4-oxo-6-*n*-pentylcyclohex-2-ene-1-carboxylate, 27920-61-2; methyl 2,4-dihydroxy-6-*n*-pentylbenzoate, 58016-28-7.

References and Notes

(1) R. S. Cahn, *J. Chem. Soc.*, 1400 (1933).
(2) Y. Ganoi and R. Mechoulam, *J. Am. Chem. Soc.*, **86**, 1646 (1964).
(3) For a leading reference, see "Marijuana: Chemistry, Pharmacology and Patterns of Social Use", A. J. Singer, Ed., *Ann. N.Y. Acad. Sci.*, **191** (1971).
(4) R. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *J. Am. Chem. Soc.*, **89**, 5934 (1967).
(5) R. G. Razdan and G. R. Handrick, *J. Am. Chem. Soc.*, 92, 6061 (1970).
(6) R. Mechoulam, *Science*, **168**, 1159 (1970).
(7) L. Crombie and R. Ponsford, *J. Chem. Soc. C.*, 796 (1971).
(8) H. C. Krishnamurty and J. Siva Prasad, *Tetrahedron Lett.*, 29, 2511 (1975).
(9) A. J. Birch and J. Slabbe, *Tetrahedron Lett.*, **24**, 2079 (1976).
(10) J. R. Cannon, P. R. Cheong, C. J. Fallick, B. H. Hamilton, J. A. McDonald, and G. Vinciquerra, *Aust. J. Chem.*, **26**, 799 (1973).
(11) R. Adams, K. H. Chen, and S. Loewe, *J. Am. Chem. Soc.*, **67**, 1534 (1945).
(12) C. M. Suter and A. W. Weston, *J. Am. Chem. Soc.*, **61**, 232 (1939).
(13) R. Bailey, *Can. J. Chem.*, **52**, 2136 (1974).
(14) R. S. Marmor, *J. Org. Chem.*, **37**, 2901 (1972), and references cited therein.
(15) A. Brossi, A. Focella, and S. Teitel, U.S. Patent 3 919 322 (1975). During the preparation of our manuscript, we became aware of the recent publication by L. Cleaver, J. A. Croft, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.*, **29**, 1989 (1976), which uses a similar approach.
(16) I. G. Tishchenko and L. S. Stanishevskii, *J. Gen. Chem. (USSR)*, **33**, 141–145 (1963); Engl. Translation p 134. We are grateful to our colleague, Dr. H. Gurien, for his kind assistance in the preparation of this compound.
(17) When adduct **2** was treated with bromine at 0 °C the brominated intermediate methyl 3-bromo-2-hydroxy-4-oxo-6-*n*-pentylcyclohex-2-ene-1-carboxylate (mp 103–104 °C) was isolated. Heating of the latter gave the aromatized derivative methyl 2,4-dihydroxy-6-*n*-pentylbenzoate (mp 78–80 °C) which was refluxed with mineral acid to yield olivetol (**3**)
(18) A. W. Fort, *J. Org. Chem.*, **26**, 765 (1961).
(19) A. A. Liebman, D. H. Malarek, A. M. Dorsky, and H. H. Kaegi, *J. Labelled Compd.*, **7**, 241 (1971).
(20) R. Adams, B. R. Baker, and R. B. Wearn, *J. Am. Chem. Soc.*, **62**, 2204 (1940).
(21) Y. Asahina, *Ber.*, **69**, 1644 (1936).
(22) We are grateful to our colleagues, Dr. D. Andrews and Mr. R. Propper, for their contribution in refining this step.

Annelation of Phenols with Epoxides Derived from 2-Cycloalken-1-ones

Summary: The annelation of phenol to give tricyclic benzofuran **6** involves the intramolecular acylation–rearrangement of lactone **4**.

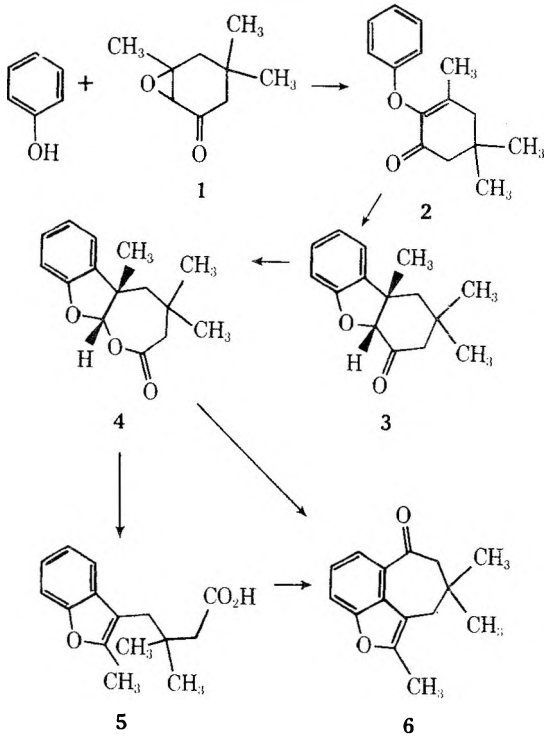
Sir: The annelation of an aromatic nucleus to form a multicyclic ring system is an important tactic in organic synthesis. Many annelation methods have been developed, but with most of these, electrophilic aromatic substitution (Friedel–Crafts acylation) is used in the formation of the initial bond in the annelation sequence; consequently, problems with regioselectivity are often encountered. In this communication, we report methodology for accomplishing aromatic ring annelation with high regiochemical control. The annelation reagents are epoxides derived from 2-cycloalken-1-ones containing n ring atoms, from which $n - 1$ atoms are incorporated into the new ring; only C(2) is excluded. The method is demonstrated here by annelation of phenol with isophorone epoxide ($n = 6$).

We have shown that potassium hydride initiated reaction of phenol with isophorone epoxide (**1**) gives 2-phenoxy-3,5,5-trimethyl-2-cyclohexen-1-one (**2**) in 91% yield; photochemical cyclization of **2** (heteroatom directed photoarylation) produces dihydrofuran **3** in 95% yield (Scheme I).[1] Thus, the initial carbon–carbon bond to the aromatic ring is formed in a completely regioselective manner.

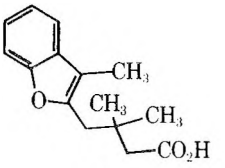
Baeyer–Villiger oxidation of **3** with *m*-chloroperbenzoic acid in methylene chloride solution at 25 °C gives lactone **4** in 97% isolated yield (mp 111 °C).[2,3] Generation of the lactone carbonyl in **4** provides a means for completion of the annelation via intramolecular acylation of the aromatic ring.

The acylation, accompanied by rearrangement to a benzofuran, is accomplished by refluxing a methylene chloride solution of lactone **4** with excess titanium tetrachloride. Partitioning the reaction components between ether and 1 N sodium hydroxide solution gives pure ketone **6** (mp 88–89 °C, 94% isolated yield) in the organic layer. Acidification of the sodium hydroxide layer gives, after ether extraction, carboxylic acid **7** in 1.4% yield.

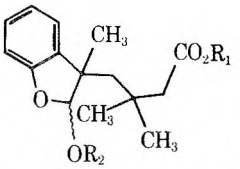
Scheme I



We have studied the Lewis acid induced rearrangement of ϵ-lactones (e.g., **4** and **9**) in some detail. Treatment of **4** with 1.5 equiv of $TiCl_4$ in CH_2Cl_2 at −78 °C for 2 h gives carboxylic acids **5** (98%) and **7** (trace). Although $SnCl_4$ may be used in the



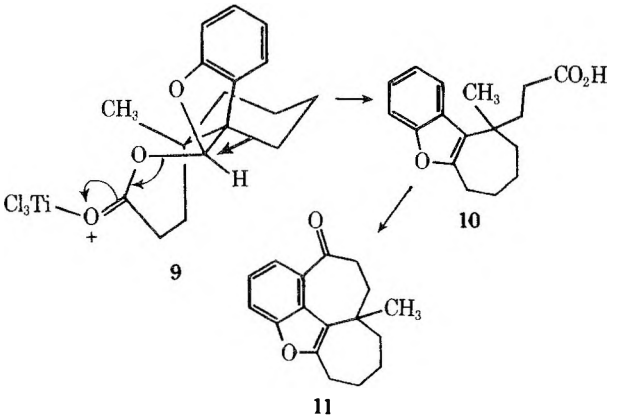
7



8a, $R_1 = CH(CH_3)_2$; $R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1 = CH_3$; $R_2 = CH_3$

rearrangement of **4** to **5**, substitution of titanium tetraisopropoxide results in lactone ring opening to give the isopropyl ester **8a**; similarly, sodium methoxide in methanol gives the methyl ester **8b**. Finally, methanolic hydrogen chloride gives the methyl ester acetal **8c**, but lactone **4** is recovered unchanged from its solution in refluxing methylene chloride saturated with hydrogen chloride.

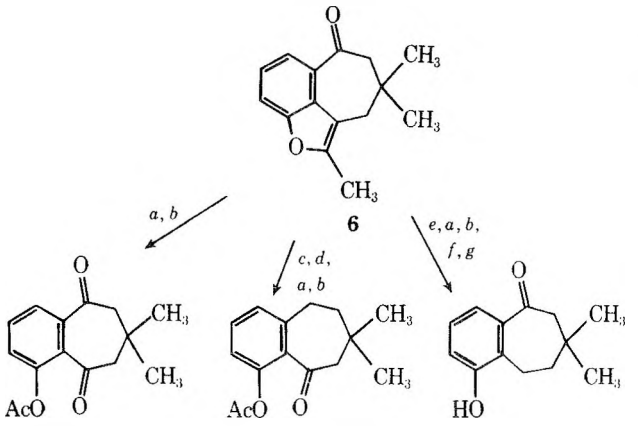
We note that the $TiCl_4$ induced rearrangement **4** → **5** is highly stereoselective; the carbon chain (here, the C(3) methyl group) in an anti orientation to the leaving carboxylate function undergoes preferential migration to C(2). In order to examine the generality of this rearrangement, lactone **9**[4] (mp 127–128 °C) was treated with 1.5 equiv of $TiCl_4$ in CH_2Cl_2 at 25 °C for 30 min, after which tricycle **10** was isolated as the major reaction product (94%). Polyphosphoric acid cyclodehydration of **10** at 110 °C for 1.5 h gave tetracyclic ketone **11** (mp 101–102 °C).[5]



The methyl-substituted furan carbon–carbon double bond in **6** represents a latent ketone carbonyl group, from which diketone **12** (Scheme II) can be liberated in 84% isolated yield (70% overall from phenol to diketone **12**). Furthermore, simple reactions coupled to the oxidative cleavage of **6** allow for preparation of monoketones **13** and **14** as well (Scheme II).[6]

Acknowledgment. This work was supported by the National Institutes of Health (Grant No. GM 21159-03 and DA01552-01). We thank undergraduate research participant

Scheme II



12 (84%; mp 122.5–123.5 °C) 13 (36%; mp 104–105 °C) 14 (41%; mp 176–177 °C)

[a] O_3/CH_2Cl_2 (−78 °C). [b] CH_3SCH_3 (25 °C). [c] $TsNHNH_2$/EtOH. [d] $NaCNBH_4$.[7] [e] $LiAlH_4$/THF. [f] H_2NNH_2, KOH/H_2O. [g] H_2CrO_4/CH_3COCH_3.

Cathy Stein for preparation of lactone **9** and early studies of the behavior of **9** with Lewis acids.

References and Notes

(1) A. G. Schultz and R. D. Lucci, *J. Org. Chem.*, **40**, 1371 (1975).
(2) For a related conversion of an α-alkoxycyclohexanone to a seven-membered lactone, see Y. Kishi, M. Aratani, T. Fukuyama, F. Nakatsubo, T. Goto, S. Inoue, H. Tanino, S. Sugiura, and H. Kakoi, *J. Am. Chem. Soc.*, **94**, 9217 (1972).
(3) The Baeyer–Villiger reaction has been demonstrated to occur with retention of configuration; see J. A. Berson and S. Suzuki, *J. Am. Chem. Soc.*, **81**, 4088 (1959), and H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968).
(4) A. G. Schultz and W. Y. Fu, *J. Org. Chem.*, **41**, 1483 (1976).
(5) Construction of the ring system in **11** represents an interesting potential approach to the alkaloid colchicine.
(6) Compounds **2–4, 6, 11, 12–14** give correct elemental analyses.
(7) R. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *J. Am. Chem. Soc.*, **95**, 3662 (1973).
(8) Undergraduate research participant, Cornell University, 1975–1976.

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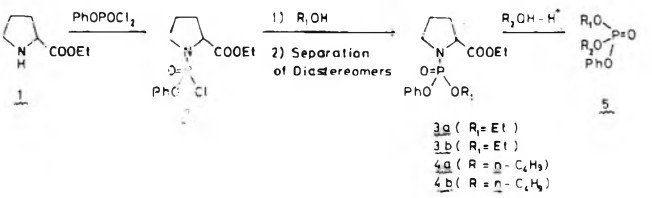
A Practical Method of Preparing Optically Active Dialkyl Phenyl Phosphates

Summary: A practical method for the preparation of optically active dialkyl phenyl phosphates using L-proline ethyl ester and requiring three overall steps is presented.

Scheme I



Sir: For the investigation of mechanistic aspects of chemical and enzymatic solvolysis of phosphotriesters, the use of chiral substrates offers an excellent approach.[1] However, to our knowledge, there have been only two methods for the preparation of optically active phosphotriesters. One[2] utilizes the enzymatic resolution of racemic phosphotriesters, and the other,[3] the first chemical method, employs the stereospecific alcoholysis of optically active tetrahydro-1,3,2-oxazaphosphorine or -oxazaphospholane derivatives. The latter method, however, requires more than five steps[4] to get trialkyl phosphates, and does not seem to be a practical method for obtaining chiral phosphotriesters in general.[5]

Herein we wish to report a new and simple method for the preparation of optically active dialkyl phenyl phosphates using easily available L-proline ethyl ester[6] as a chiral reagent. The reaction sequence of the present method, which is shown in Scheme I, consists of essentially three steps. A separation of diastereoisomeric phosphoramidates and their acid-catalyzed alcoholysis are the key steps.

The phosphoromonochloridate **2**, prepared in situ by the reaction[7] of L-proline ethyl ester (1.3 equiv mol) with phenyl phosphorodichloridate (1 equiv mol) in anhydrous pyridine, was reacted[8] with an excess of ethanol or with 1-butanol to afford a diastereoisomeric mixture of the corresponding alkyl phenyl phosphoramidate (**3** or **4**). The isomers were separated quite easily by column chromatography (silica gel, benzene–ethyl acetate) and isolated by distillation in fair yields: **3a**[9] (40%),[10] bp 173–180 °C (1.5 mm),[11] $[\alpha]^{17}_D$ −67° (c 1.7); **3b** (20%), bp 178–179 °C (1.7 mm), $[\alpha]^{16}_D$ −45° (c 3.0); **4a** (36%), bp 145 °C (0.015 mm), $[\alpha]^{23}_D$ −60° (c 2.6); **4b** (22%), bp 145 °C (0.015 mm), $[\alpha]^{24}_D$ −40° (c 3.0).

Acid-catalyzed alcoholysis[13] of each isomer at refluxing temperature gave the corresponding phosphotriester **5**[14] in a state of high optical purity.[15] The yields and physical data are listed in Table I.

Although the result is at present limited to the preparation of optically active dialkyl phenyl phosphates and the yields are not optimized,[16] the present method may well be applicable for the preparation of phosphotriesters in general, and also for other phosphoryl derivatives, such as phosphinates and phosphonates. Research along this line is now in progress in this laboratory and will be reported elsewhere.

Table I. Preparation of Optically Active Dialkyl Phenyl Phosphates by the Acid-Catalyzed Alcoholysis of Diastereomeric Phosphoramidates

Phosphoramidate	Dialkyl phenyl phosphate R_1	R_2	Yield, %	Bp, °C (mm)	$[\alpha]_D$, deg (c, °C)
3a	C_2H_5	CH_3	61	80 (0.02)	+3.4 (3.2, 25)
3b	C_2H_5	CH_3	63	76 (0.02)	−3.4 (3.6, 26)
4a	n-C_4H_9	CH_3	51	92 (0.03)	+5.5 (2.7, 21)
4b	n-C_4H_9	CH_3	54	90 (0.02)	−5.1 (2.9, 22)
4a	n-C_4H_9	C_2H_5	28[a]	85 (0.02)	+1.8 (1.5, 19)
4b	n-C_4H_9	C_2H_5	30[b]	85 (0.02)	−2.0 (1.7, 20)
4a	n-C_4H_9	n-C_3H_7	10	100 (0.01)	+0.9 (1.1, 24)
4b	n-C_4H_9	n-C_3H_7	11	100 (0.01)	−0.7 (1.5, 24)

[a] n-Butanolysis of **3b** gave the same compound [$[\alpha]_D$ +2.1° (1.4, 14)] in 19% yield. [b] n-Butanolysis of **3a** gave the same compound [$[\alpha]_D$ −2.0° (1.0, 19)] in 10% yield.

References and Notes

(1) It is established in the solvolysis of other phosphorus derivatives. (a) For general remarks, see: M. J. Gallagher and I. D. Jenkins, *Top. Stereochem.* **3**, Chapter 1 (1968). (b) For enzymatic solvolysis of cyclic phosphorothioates: W. Saenger, *Angew. Chem., Int. Ed. Engl.*, **12**, 591 (1973); D. A. Usher, D. I. Richardson, Jr., and F. Eckstein, *Nature (London)*, **228**, 663 (1970). (c) For nucleophilic substitution of chiral phosphorothioate: M. Mikolajczyk, J. Omelanczyk, and M. Para. *Tetrahedron*, **28**, 3855 (1972); J. Michalski and M. Mikolajczyk, *Chem. Ind. (London)*, 661 (1964). (d) For solvolysis of chiral phosphinamides: T. Koizumi, Y. Kobayashi, and E. Yoshii, *J. Chem. Soc., Chem. Commun.*, 678 (1974); *Chem. Pharm. Bull.*, **24**, 834 (1976).

(2) N. P. B. Dudman and B. Zerner, *J. Am. Chem. Soc.*, **95**, 3019 (1973).

(3) (a) C. R. Hall, T. D. Inch, G. J. Lewis, and R. A. Chittenden, *J. Chem. Soc., Chem. Commun.*, 720 (1975); (b) D. B. Cooper, C. R. Hall, and T. D. Inch, *ibid.*, 721 (1975); (c) D. B. Cooper, J. M. Harrison, and T. D. Inch, *Tetrahedron Lett.*, 2697 (1974); (d) J. M. Harrison, T. D. Inch, and G. J. Lewis, *J. Chem. Soc., Perkin Trans. 1*, 1892 (1975).

(4) In the case of ref 3a, several steps were required to secure the sugar moiety.

(5) It seems rather difficult to prepare dialkyl aryl phosphates by this method because the P–OAr bond is very labile to alkaline conditions.

(6) The use of L-proline derivatives for the asymmetric synthesis of chiral carbon compounds has been extensively studied by S.-I. Yamada and his collaborators: S.-I. Yamada, K. Hiroi, and K. Achiwa, *Tetrahedron Lett.*, 4233 (1969); S.-I. Yamada, and G. Otani, *ibid.*, 4237 (1969); 1133 (1971); K. Hiroi, K. Achiwa, and S.-I. Yamada, *Chem. Pharm. Bull.*, **20**, 246 (1972); K. Hiroi and S.-I. Yamada, *ibid.*, **23**, 1103 (1975); T. Sone, S. Terashima, and S.-I. Yamada, *ibid.*, **24**, 1273, 1288 (1976).

(7) The reaction was carried out at room temperature for 3–4 h.

(8) The reaction was carried out at room temperature for 8–12 h.

(9) All new compounds gave satisfactory elemental analyses and spectral data.

(10) Yields are based on phenyl phosphorodichloridate in the case of **3a, 3b, 4a,** and **4b.**

(11) All distillations were performed with a short-path distillation apparatus and bath temperatures are described.

(12) All $[\alpha]_D$ measurements were taken in carbon tetrachloride solution.

(13) The alcoholysis was performed with 0.4–1.0 mmol of the phosphoramidate in 4–10 mL of 1 M H_2SO_4–alcohol for 4 h.

(14) The reaction mixture was diluted with H_2O and extracted with Et_2O. After washings with dilute HCl, H_2O, dilute $NaHCO_3$, and H_2O there was obtained almost pure oily dialkyl phenyl phosphate, which was subjected to microdistillation.

(15) The enantiomeric purities of methyl ethyl phenyl phosphate and methyl *n*-butyl phenyl phosphate were determined as >97% according to Hall's method (ref 3a and 3b). When a twofold excess of $Eu(hfc)_3$ was added to a carbon tetrachloride solution of each enantiomer, only one P–OMe doublet was observed, whereas a pair of doublets was detected with a mixture (3:97) of enantiomers. Since the acid-catalyzed alcoholysis of phosphoramidate (**3** and **4**) should proceed through A-2 mechanism, other dialkyl phenyl phosphates are considered to possess a comparable degree of optical purity. The observed differences in $[\alpha]_D$ could be attributable to some experimental errors.

(16) Reaction conditions (temperature, acids, and acid concentration) and workup procedure for obtaining maximum yields are being investigated.

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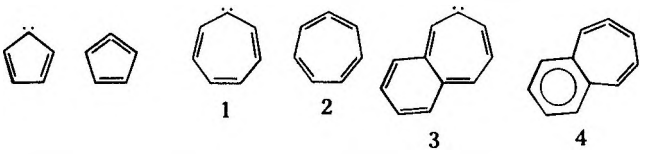
Received July 12, 1977

4,5-Benzo-1,2,4,6-cycloheptatetraene

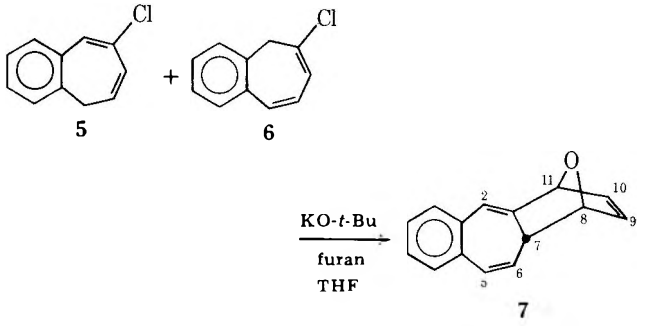
Summary: 4,5-Benzo-1,2,4,6-cycloheptatetraene and one of its methyl derivatives have been generated by the dehydrohalogenation of benzohalocycloheptatrienes.

Sir: Cyclic, fully conjugated carbenes have been the subject of considerable research interest.[1] In principle, valence isomeric allene structures can be postulated for each of the carbenes. While there has been no need to invoke an allenic isomer of cyclopentadienylidene, the situation has not been as clear with cycloheptatrienylidene.[2] The chemistry of the C_7H_6



intermediate generated from the photolysis or thermolysis of the sodium salt of tropone tosylhydrazone has been logically interpreted in terms of **1**.[3] The intermediate shows low reactivity with electron-rich alkenes[3a] and a positive ρ value in its addition to substituted styrenes.[3b] These properties are consistent with extended Hückel calculations which predict **1** to be a relatively nucleophilic carbene in its lowest energy singlet state.[4] Untch's report of the dehydrochlorination of 1-chloro-1,3,5-cycloheptatriene[5] generated interest in the cycloheptatetraene **2**, since the product, heptafulvalene, had previously been isolated from reactions where the intermediacy of **1** had been implicated.[3] The possibility that **2** might be involved in the reactions of **1** was increased when Jones, Sabin, and co-workers reported the results of INDO calculations which concluded that **2** (nonplanar) was more stable than **1** (planar) by 14 kcal/mol.[6,7] These calculations also indicated that the appropriate benzo annelation of the seven-membered ring would further stabilize the allene form (**4**) relative to its carbene analogue (**3**). In this paper, we wish to report the generation of **4** and one of its methyl derivatives.

When a mixture of **5** and **6**[8,9] was treated with potassium *tert*-butoxide (KO-*t*-Bu) in tetrahydrofuran (THF), a rapid, slightly exothermic reaction produced a golden polymer (81%).[10] When the reaction was carried out in the presence of excess furan, the adduct **7** was isolated (21%) along with some



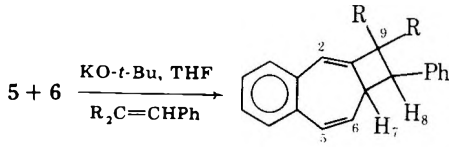
polymer. The use of $Eu(dpm)_3$ as a chemical shift reagent aided in the structure assignment of **7**.[11]

When the reaction was conducted in the presence of excess styrene, **8** was formed in 35% yield. The structure proof for **8** rests on its normal and decoupled NMR spectra and the analogous spectra for **9**, which was prepared by using β,β'-

Table I. NMR Data for 8 and 9 (CCl_4, Me_4Si, δ)

	H_2 and H_5	H_6	H_7	H_8	H_9, $H_{9'}$	H_{arom}
8	6.1–6.5 (m, 2 H)	5.62 (d of d, 11.8 and 2.0 Hz)	3.95 (br m, 1H)	3.2–3.8 (m, 1 H)	2.8–3.2 (m, 2 H)	7.2 and 7.4 (br s, 9 H)
9[a]	6.2–6.5 (m, 2 H)	5.62 (d of d, 11.8 and 2.0 Hz)	3.95 (d of m, 8.8 Hz)	3.49 (br d, 8.8 Hz)		7.2 and 7.4 (br s, 9 H total)

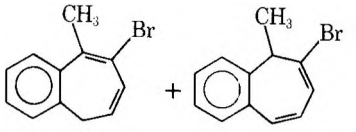
[a] When H_7 of **9** is irradiated in a decoupling experiment, H_5 collapses to a doublet (δ 6.32, $J_{5,6}$ = 11.8 Hz) and H_2 becomes a singlet (δ 6.26).



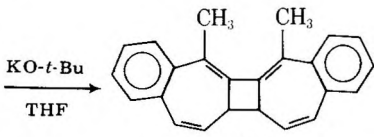
8, R = H
9, R = D

dideuteriostyrene as the trapping reagent.[13] Although the coupling constant between H_7 and H_8 (8.8 Hz) is of such a magnitude to be consistent with either a cis or a trans relationship,[14] a tentative trans arrangement is proposed on the basis of chemical shift evidence.[15]

Although the above intermediate readily underwent polymerization in the absence of trapping reagents, a methyl derivative gave excellent yields of a dimer. Thus, the reaction of KO-*t*-Bu with **10** and **11** at 0 °C gave the head-to-head



10 11



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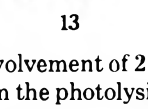
dimer **12**.[16] Other isomers were not detected by NMR spectroscopy.

The understanding of allene contributions to the chemistry of cyclic, fully conjugated carbenes is emerging.[17] Although mechanisms which involve carbene additions followed by rearrangements can be written for the above reactions, several points favor strained allene additions. First, the calculated relative energies favor **4** over **3** by 46 kcal/mol,[6] a very substantial difference. Secondly, in this base-promoted elimination method, a simple E2 elimination would result initially in either **4** or the doubly excited p^2 carbene state. The loss of halide ion from a delocalized anion would also give the p^2 carbene. Third, the cycloaddition of the intermediate to the electron-rich diene, furan, is not characteristic of nucleophilic, carbocyclic, aromatic carbenes. Finally, at higher temperatures (135–160 °C in diglyme) neither the intermediate derived from **5**–**6** nor the one from the **10**–**11** precursor system shows any tendency to undergo a carbene–carbene rearrangement as does **13**.[18] One of the remaining questions,



13

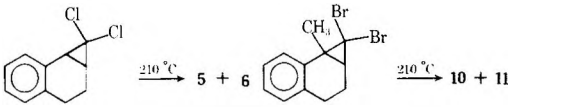
though, concerns the involvement of **2** itself in the chemistry of **1** when generated from the photolysis or thermolysis of the sodium salt of tropone tosylhydrazone.[19]

Acknowledgment. We wish to acknowledge the financial support of the Research Corporation and the Georgia College Faculty Research Fund. Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We would also like to thank Dr. W. M. Jones for many stimulating discussions. Finally, we thank Dr. R. W. King of the University of Florida for his assistance in obtaining mass spectra and 100-MHz ^1H NMR spectra and Mr. C. Pape of the University of Georgia for his running of a ^{13}C NMR spectrum.

References and Notes

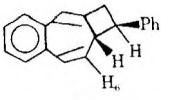
(1) For a review of this area, see H. Dürr, *Top. Curr. Chem.*, **40**, 103 (1973).
(2) Evidence for the intermediacy of cyclononapentaene has been presented: E. E. Waali and N. T. Allison, Southeast Regional American Chemical Society Meeting, Norfolk, Va., Oct 1974.

(3) (a) W. M. Jones and C. L. Ennis, *J. Am. Chem. Soc.*, **91**, 6391 (1969); (b) L. W. Christensen, E. E. Waali, and W. M. Jones, *ibid.*, **94**, 2118 (1972); (c) E. E. Waali and W. M. Jones, *ibid.*, **95**, 8114 (1973).
(4) R. Gleiter and R. Hoffmann, *J. Am. Chem. Soc.*, **90**, 5457 (1968).
(5) K. Untch, International Symposium on the Chemistry of Nonbenzenoid Aromatic Hydrocarbon Compounds, Sendai, Japan, August, 1970. We are indebted to Dr. Untch for his private communication of his work.
(6) R. L. Tyner, W. M. Jones, Y. Ohrn, and J. R. Sabin, *J. Am. Chem. Soc.*, **96**, 3765 (1974).
(7) As was pointed out,[6] the calculations do not take into account differences in solvation energies. Since the calculated dipole moment of **1** is significantly greater than that of **2**, the energy difference in solution may be much less than 14 kcal/mol.
(8) The starting halides were prepared by the thermolysis of the following dihalocyclopropanes.



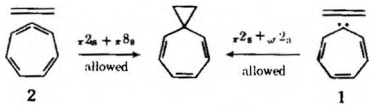
43% 57% (74% yield total) 64% 36% (73% yield total)

(9) IR and NMR spectra were consistent with the structures proposed for the new compounds. New compounds also gave satisfactory elemental analyses plus mass spectra or satisfactory high resolution mass spectra.
(10) Although the mass spectrum of this material showed a peak at *m/e* 560, appropriate for a tetramer of **4**, its ^{13}C NMR spectrum exhibited an absolute plethora of signals resulting in broad multiplets rather than the usual narrow band spectrum. All attempts to purify the material by column or thin-layer chromatography or by selective extraction failed.
(11) The structure proof for **7** was complex. Several Eu(dpm)$_3$ shifted 60-MHz NMR spectra provided the insight necessary to fully analyze the 100-MHz spectrum of **7**. The 100-MHz spectrum showed doublets of doublets at the following chemical shifts (CCl_4, Me_4Si, δ): 5.05 (10.5 and 3.0 Hz, H_8), 5.07 (1.8 and 1.0 Hz, H_{11}), 5.26 (4.9 and 1.0 Hz, H_8), 6.26 (10.5 and 2.4 Hz, H_5), 6.29 (5.7 and 1.0 Hz, H_9), 6.42 (2.0 and 1.0 Hz, H_2), and 6.74 (5.7 and 1.8 Hz, H_{10}). In addition, H_7 gave a six-line signal with some different spacings at δ 3.53. By using the measured values of $J_{7,8}$ (4.9 Hz), $J_{6,7}$ (3.0 Hz), $J_{5,7}$ (2.4 Hz), and $J_{2,7}$ (2.0 Hz), the H_7 pattern was calculated. The result was a six-line pattern which corresponded with the observed pattern. The aromatic resonances were found as a multiplet at δ 6.9–7.4.
The endo configuration was chosen for **7** on the basis of the agreement factors which were calculated[12] for the endo and exo isomers. Dreiding models were used for the manual measurement of angles and distances. Several 60-MHz spectra using various Eu(dpm)$_3$/**7** ratios were required to resolve each of the nonaromatic resonances in **7**. At Eu(dpm)$_3$/**7** ratios of 0.0725, 0.141, 0.170, and 0.478, agreement factors for the endo isomer (and exo isomer) were 0.095 (0.214), and 0.086 (0.170), 0.066 (0.105), and 0.079 (0.179), respectively.
(12) M. R. Willcott III, R. E. Lenkinski, and R. E. Davis, *J. Am. Chem. Soc.*, **94**, 1742 (1972).
(13) See Table I for NMR data for **8** and **9**.
(14) I. Fleming and D. H. Williams, *Tetrahedron*, **23**, 2747 (1967).
(15) A slight impurity (~5%) in the NMR spectrum of **8** is probably due to its geometric isomer. H_6 in the major isomer appears as a doublet of doublets (11.8 and 2.0 Hz) at δ 5.62. The impurity shows a similar doublet of doublets at δ 4.85. A Dreiding model shows that if the phenyl group is cis to C_6 it should suffer restricted rotation and H_6 would be held in the shielding region of the phenyl ring. Thus, the tentative assignment of **8a** as the predominant isomer.



8a

(16) NMR data for **12** (CCl_4): δ 2.36 (s, 6 H, methyl), 3.39 (broadened s, 2 H, methine), 5.84 (d, 11 Hz, 2 H, olefinic β to arom ring), 6.37 (d, 11 Hz, 2 H, olefinic α to arom ring), 7.0–7.6 (m, 8 H, arom). The configuration of the ring fusion is not known.
(17) In a methanoannulene series, Jones and co-workers have shown that the nature of the intermediate is controlled by the position of the carbene carbon (or the central allene carbon): R. A. LaBar and W. M. Jones, *J. Am. Chem. Soc.*, **96**, 3645 (1974); **95**, 2359 (1973); P. H. Gebert, R. W. King, R. A. La Bar, and W. M. Jones, *ibid.*, **95**, 2357 (1973).
(18) W. M. Jones, R. C. Joines, J. A. Meyers, T. Mitsuhashi, K. E. Krajca, E. E. Waali, T. L. Davis, and A. B. Turner, *J. Am. Chem. Soc.*, **95**, 826 (1973).
(19) Viewing the π system in **2** as a conjugated tetraene with both termini sharing



2 1

the same carbon (C_2), a thermally allowed $_{\pi}2_s + {}_{\pi}8_s$ cycloaddition giving cyclopropane products is conceivable.

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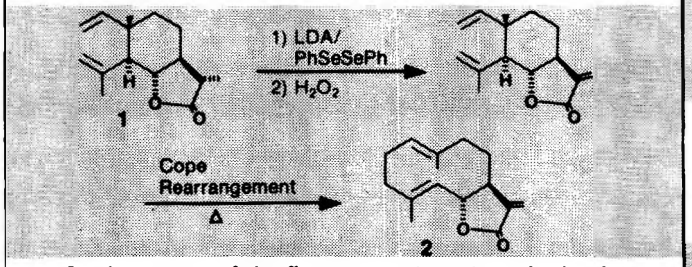
Received June 9, 1977

Organoselenium Reagents

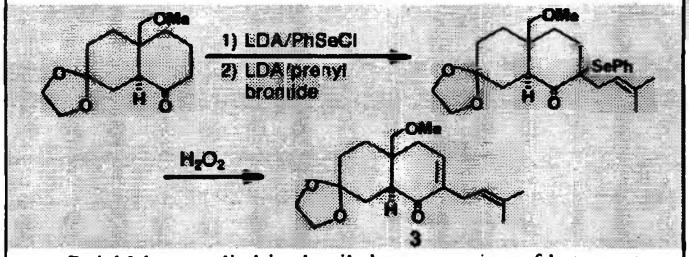
Olefination made easy!

Because of the ready decomposition of alkylphenyl selenoxides to form olefins,[1] organoselenium reagents are finding increasing use in organic synthesis. Lithium enolates of ketones, lactones, esters and aldehydes react with **diphenyl diselenide** or **phenylselenenyl chloride** to form α-phenylselenocarbonyl compounds, which can be oxidized easily to the corresponding selenoxides with concomitant *syn*-elimination[1,2] of benzeneseleninic acid to form the respective enones.

Grieco used this mild olefination procedure[3] for the total synthesis of several biologically active α-methylene lactones.[4] For example, selenenylation of saussurea lactone, **1**, led to (+)-costunolide, **2**.[5]

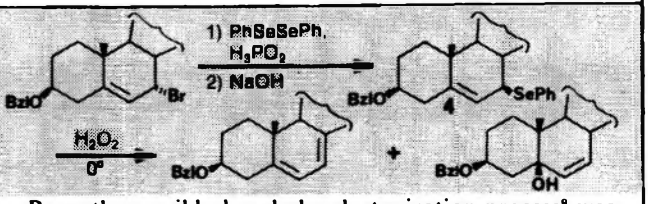


In the course of the first reported total synthesis of vernolepin and vernomenin, Grieco utilized oxidative elimination of phenyl selenoxide for the introduction of an *endocyclic* double bond in the intermediate **3**.[6]

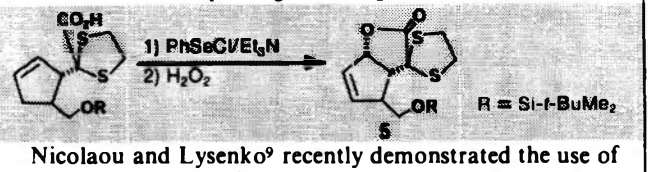


Reich[2] has studied in detail the conversion of ketones to enones by selenoxide elimination and has shown the utility of **diphenyl diselenide, phenylselenenyl chloride** and phenylselenenyl bromide (prepared from **PhSeSePh**) in the synthesis of α,β-unsaturated ketones and esters and α,β-dicarbonyl enones.

Allylic selenoxides yield allylic alcohols;[1] however, a competitive *syn*-elimination may occur as well. Salmond[7] used sodium phenylselenolate (from **PhSeSePh**) to prepare the selenide **4**, which yields both $\Delta^{5,7}$- and 5-β-hydroxy-Δ^{6}-steroids.

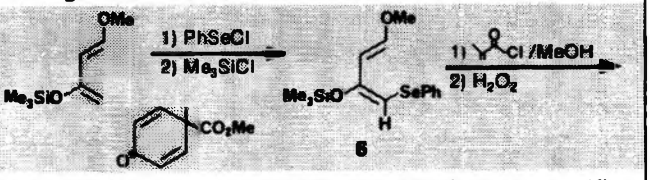


Recently, a mild phenylselenolactonization process[8] was developed for the synthesis of both saturated and unsaturated lactones from unsaturated acids. The highly functionalized lactone **5**,[8a] synthesized by this process, may be elaborated to form prostaglandin A_2 and brefeldin A.



Nicolaou and Lysenko[9] recently demonstrated the use of **PhSeCl** in the synthesis of cyclic ethers.

Danishefsky[10] used **PhSeCl** to prepare the synthetically useful diene **6**, in the course of preparing cyclohexadienones through a Diels-Alder route.



Clive used **triphenylphosphine selenide**[11] for stereospecific conversion of epoxides to olefins, retaining the same relative stereochemistry about the C-C bond of the epoxide.

References:

1) K.B. Sharpless, M.W. Young, and R.F. Lauer, *Tetrahedron Lett.*, 1979 (1973); K.B. Sharpless, R.F. Lauer, and A.Y. Teramish, *J. Am. Chem. Soc.*, **95**, 6137 (1973).
2) H.J. Reich, J.M. Renga, and I.L. Reich, *ibid.*, **97**, 5434 (1975).
3) P.A. Grieco and M. Miyashita, *J. Org. Chem.*, **39**, 120 (1974).
4) For a review, see S.S. Newaz, *Aldrichimica Acta*, in preparation.
5) P.A. Grieco and M. Nishizawa, *J. Org. Chem.*, **42**, 1717 (1977).
6) P.A. Grieco *et al.*, *J. Am. Chem. Soc.*, **98**, 1612 (1976); *ibid.*, **99**, 5773 (1977).
7) W.G. Salmond, M.A. Barta, A.M. Cain, and M.C. Sobala, *Tetrahedron Lett.*, 1683 (1977).
8) a) K.C. Nicolaou and Z. Lysenko, *J. Am. Chem. Soc.*, **99**, 3185 (1977); b) D.L.J. Clive and G. Chittattu, *Chem. Commun.*, 484 (1977).
9) K.C. Nicolaou and Z. Lysenko, *Tetrahedron Lett.*, 1257 (1977).
10) S. Danishefsky, C.F. Yan, and P.M. McCurry, *J. Org. Chem.*, **42**, 1819 (1977).
11) D.L.J. Clive and C.V. Denyer, *Chem. Commun.*, 253 (1973).

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