VOLUME 41 OCTOBER 1, 1976 NUMBER 20 JOCEAH

THE JOURNAL OF Organic Chemistry

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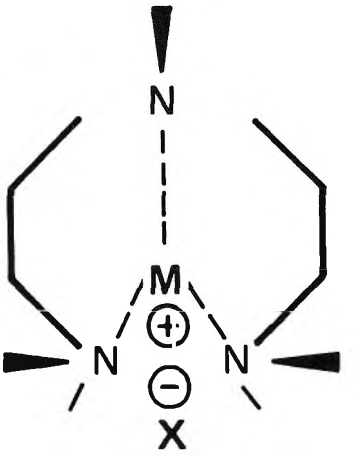

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NOTES

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OCTOBER 1, 1976

Stereochemistry and Mechanism of the Schmitz Diaziridine Synthesis Leading to 2,4,6-Trisubstituted 1,3,5-Triazabicyclo[3.1.0]hexanes[1]

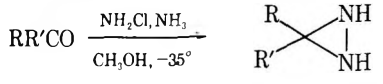
Arnold T. Nielsen,* Donald W. Moore, Ronald L. Atkins,[2] Daniel Mallory, John DiPol, and Jeanne Marie LaBerge

Organic Chemistry Branch, Chemistry Division, Code 3856, Michelson Laboratory, Naval Weapons Center, China Lake, California 93555

Received April 20, 1976

The Schmitz reaction of aldehydes with chloramine and methanolic ammonia leads to a mixture of two epimeric 2,4,6-trisubstituted 1,3,5-triazabicyclo[3.1.0]hexanes, each with exocyclic C-6 substituent; the major product (**3a**) and minor one (**3b**) have substituents at C-2, C-4 with trans and at C-2, C-4 with cis exocyclic stereochemistry, respectively. Isolation of Schmitz products under alkaline (kinetic) conditions yields a mixture of **3a,b** and a small amount of an epimer (**3c**) with endocyclic C-6 substituent and C-2, C-4 cis exocyclic substituent stereochemistry. The acid-catalyzed equilibration of **3a–c** generally yields a ca. 1:1 mixture of **3a** and **3b** (12 examples with alkyl, phenyl, and benzyl substituents); the equilibration mechanism is discussed. ^1H and ^{13}C NMR spectroscopy were employed in determination of product assay and stereochemistry. Oxidation of all equatorial 2,4,6-trialkyl-1,3,5-hexahydrotriazines (**17**) with *tert*-butyl hypochlorite in alkaline medium leads to a mixture of **3a** (predominantly) and **3b,c**; the reaction mechanism of this oxidation is discussed. It is concluded that a diaziridine intermediate, not a 2,4,6-trisubstituted 1,3,5-hexahydrotriazine, is involved in the Schmitz synthesis of **3**.

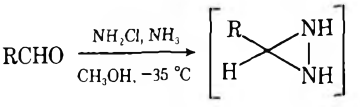
The Schmitz diaziridine synthesis involves reaction of a ketone or aldehyde and ammonia with a chloramine or hydroxylamine *O*-sulfonic acid.[3] For example, to prepare 3,3-disubstituted diaziridines (**1**) a ketone is added to cold



1 (R, R′ = alkyl, aryl)

methanolic ammonia containing chloramine (conveniently generated from *tert*-butyl hypochlorite[4]). The reaction was discovered independently by Abendroth and Henrich[5] and by Paulsen.[6] Many substituted diaziridines have been synthesized from imines including 1,3-disubstituted and 1,2,3- and 1,3,3-trisubstituted types.[7–10] Diaziridine formation is described as an intramolecular displacement of chloride ion from an *N*-chloroaminal intermediate.[3]

The Schmitz reaction of aldehydes with ammonia and chloramine leads to 2,4,6-trisubstituted 1,3,5-triazabicyclo[3.1.0]hexanes (**3**), rather than monocyclic diaziridines as the isolated products (eq 1).[7e,g,11] 3-Substituted diaziridines (**2**) are proposed to be intermediates which give **3** by further reaction with ammonia and aldehyde;[11] this suggestion has been confirmed in the present work. It has not been possible to prepare **2** directly by use of an excess of ammonia over aldehyde, nor from **3** by direct fractional hydrolysis.[7c] Indirect methods are required to prepare **2**.[7e,g] The present work is concerned principally with the stereochemistry and mechanism of formation of **3**.



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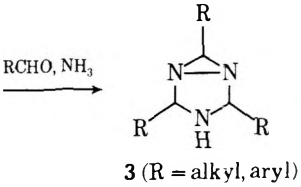


(1)

3 (R = alkyl, aryl)

Synthesis. 2,4,6-Trisubstituted 1,3,5-triazabicyclo[3.1.0]-hexanes (**3**) were synthesized by two methods. The principal procedure, that of Schmitz, was employed with slight modifications.[7g,11,12] *tert*-Butyl hypochlorite was added to 10 M methanolic ammonia followed by addition of the aldehyde; reaction proceeded at ca. −35 °C for 1 h followed by warming to ambient temperature. Workup gave mixtures of epimers in high yields (60–90%) from which the less soluble, predominant isomer (trans) could be readily isolated in pure form by crystallization from hexane (25–50% yield). Thirteen of these compounds (**4a–16a**) were prepared (Table I). Pure cis epimers were isolated with difficulty from the mother liquors by fractional crystallization.

In a second route to the title compounds, 2,4,6-trialkyl-1,3,5-triazacyclohexanes (**17**) were oxidized with *tert*-butyl hypochlorite in methanol containing 1 molar equiv of sodium carbonate (−35 °C), eq 2. The reactant monocyclic hexahydrotriazines (**17**) were prepared by reaction of aldehydes with ammonia at 0 °C.[12,13] Yields of **3** by this alternate procedure are poor (2–20%). Mixtures of epimers are produced despite the steric homogeneity of the reactant, **17**.[12,13]

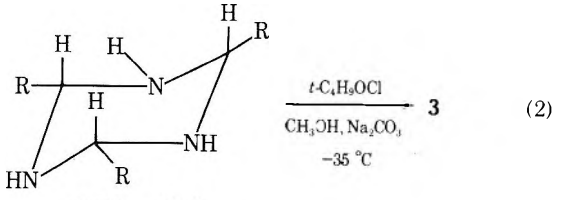
The bicyclic triazines (Table I) are stable, white, crystalline

Table I. 2,4,6-Trialkyl-1,3,5-triazabicyclo[3.1.0]hexanes

Compd	R	Prepn method[a]	Yield %[b]	Mp, °C[c]	Molecular formula[d]
4a	CH_3	A	75	113–114[e]	$C_6H_{13}N_3$
4c	CH_3	B	(6)	133–134	$C_6H_{13}N_3$
5a	C_2H_5	A (B)	90 (9)	98–100[f]	$C_9H_{19}N_3$
6a	n-C_3H_7	A (B)	90 (20)	82–84[g]	$C_{12}H_{25}N_3$
7a	i-C_3H_7	A (B)	58 (16)	140–143	$C_{12}H_{25}N_3$
8a	n-C_4H_9	A (B)	82 (6)	68–69	$C_{15}H_{31}N_3$
9a	i-C_4H_9	A (B)	89 (6)	134–139	$C_{15}H_{31}N_3$
10a	t-C_4H_9	A	27	93–95[h]	$C_{15}H_{31}N_3$
11a	n-C_5H_{11}	A (B)	90 (6)	51–55	$C_{18}H_{37}N_3$
11b	n-C_5H_{11}	A	10[i]	50–54	$C_{18}H_{37}N_3$
12a	$(C_2H_5)_2CH$	A	65	145–147	$C_{18}H_{37}N_3$
13a	C_6H_5	A	42	162–164[j]	$C_{21}H_{19}N_3$
14a	n-C_6H_{13}	A (B)	86 (8)	65–67	$C_{21}H_{43}N_3$
15a	$C_6H_5CH_2$	A (B)	94 (4)	172–175[k,l]	$C_{24}H_{25}N_3$
16a	$C_6H_5(CH_3)$-CH	A (B)	3 (2)	161–165[k]	$C_{27}H_{31}N_3$

[a] Method A: from alkanal and chloramine in methanolic ammonia. Method B: from 2,4,6-trialkyl-1,3,5-hexahydrotriazines by *tert*-butyl hypochlorite oxidation. [b] Yields of crystalline product mixtures by method A. Values in parentheses are yields of recrystallized products prepared by method B. [c] Capillary metling point of analytically pure sample crystallized from hexane, heptane, or ether; recovery yields are 30–50%. [d] Satisfactory analytical data (±0.3% for C, H, and N) and molecular weight data (±4%, by vapor osmometry in chloroform) for all compounds were submitted for review. [e] Lit.[11] mp 114–115 °C. [f] Lit.[11] mp 104–104.5 °C. [g] Lit. mp 84–86 °C. [h] Lit.[7g] mp 92–93 °C. [i] Prepared by fractional crystallization of product mixture. [j] Lit.[11] mp 160–162 °C. [k] Data reported in ref 12. [l] A material, mp 133–145 °C, isolated by fractional crystallization of the Schmitz reaction product was found to contain 73% of cis isomer **15b** (^{13}C NMR assay).

solids which may be stored indefinitely in air at ambient temperature, in contrast to the derived 3-substituted diaziridines (2) which decompose rapidly under such conditions.



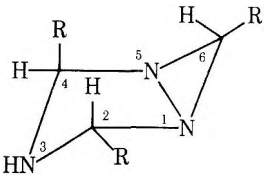
(2)

17 (R = alkyl)

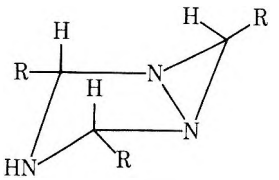
Results and Discussion

Stereochemistry of the Schmitz Reaction. The stereochemistry of 2,4,6-trisubstituted 1,3,5-triazabicyclo[3.1.0]-hexanes has not been studied by others.[1] Schmitz assumed that the ethyl groups in **5a**, obtained from propanal by his procedure, were all pseudoequatorial.[7f] No evidence was offered for this assignment, however. It has now been established that the predominant isomer formed (and isolated) in the Schmitz reaction is **3a**, with trans C-2 and C-4 substituents and an exocyclic C-6 substituent.[14] Previously reported bicyclotriazines have now been shown to exist in this configuration. A second isomer formed in smaller amounts is the cis-exo form (**3b**), having all pseudoequatorial substituents. Virtually none of the cis-endo isomer (**3c**) is produced under the reported conditions of the Schmitz reaction.

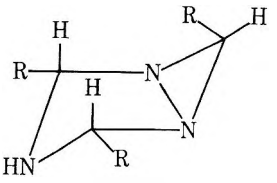
Although spectroscopic evidence suggests that the parent hydrocarbon, bicyclo[3.1.0]hexane,[15] and its diaziridine analogue, 1,5-diazabicyclo[3.1.0]hexane,[16] exist in boat or



3a (trans-exo)



3b (cis-exo)



3c (cis-endo)

twist-boat forms, the actual departure from planarity of the five-membered ring is not great and would doubtless be strongly influenced by the orientation of substituents. We have, accordingly, treated the five-membered ring in 1,3,5-triazabicyclo[3.1.0]hexane as nearly planar.

The assignment of stereochemistry in the title compounds rests on ^1H and ^{13}C NMR spectral data as well as equilibration studies. ^1H NMR data are summarized in Table II and ^{13}C data in Table III. The trans compounds (**3a**) are each characterized by separate ^{13}C signals for the C-2 and C-4 ring carbons. In trans compounds having simple ring methine proton spectra (e.g., **4a, 7a, 10a, 13a**) separate signals are readily observed for the C-2 and C-4 ring methine protons. In the cis compounds (**3b,c**) only one signal is seen for the C-2, C-4 carbons and ring methine protons. The differentiation of cis-exo (**3b**) and cis-endo (**3c**) forms rests on ^{13}C NMR, kinetic, and equilibration data.

The most striking chemical shift differences in the carbon-13 spectra of the three epimers are seen at C-6, the diaziridine carbon (Table III). For typical alkyl substituents the shielding is greatest for the cis-exo form, 5 ppm less for the trans-exo, and 12 ppm less for the cis-endo. A possible explanation is the change in dihedral angle between the two rings caused by steric repulsion between endo substituents. Thus, in the cis-exo epimer with no endo substituents, the angle should approach the value of 116 ± 5° found for the parent hydrocarbon.[15] The trans-exo epimer with the endocyclic C-4 substituent would show some steric repulsion and an increased angle. The cis-endo epimer with the C-6 substituent in the position of greatest steric interaction would have the largest dihedral angle. Apparently, as the molecule becomes more planar due to steric repulsion, the change in bond character at C-6 results in progressively greater deshielding. This effect is even more noticeable with bulky substituents. In the trans-exo epimer of the *tert*-butyl derivative (**10b**) the shielding at C-6 is reduced 8.5 ppm; little or no cis-endo form is found to be present. In the diethylmethyl derivative (**12b**) trans-exo substitution leads to a 6.5 ppm deshielding, and cis-endo substitution (**12c**) gives a 15.8 ppm reduction of the shielding value, the largest change observed.

The kinetic composition of epimer mixtures produced in the Schmitz reaction has been established (Table IV). A kinetic preference for the trans isomer is observed. Substantial amounts of the cis-exo and cis-endo forms are also present. Products were obtained by adding excess sodium hydroxide to the ammoniacal reaction mixture prior to workup; ammonium chloride, an equilibration catalyst, was thereby removed from the isolated products.

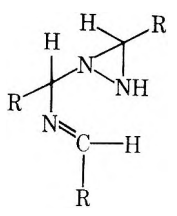
The transition state leading to the bicyclic triazine favors a repulsion of bulky groups in a monocyclic precursor at or removed from the bond-forming site (e.g., **18a** favored over **18b**). Aldol cyclization stereochemistry (formation of a C–C bond) exhibits a similar transition state.[17] The presence of an

Table II. ^{1}H NMR Spectra of 2,4,6-Trisubstituted 1,3,5-Triazabicyclo[3.1.0]hexanes [a]

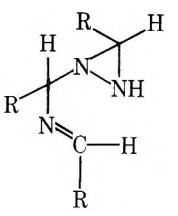
Compd	R	Chemical shift, δ, ppm: Ring CH at C-2; C-4	Ring CH at C-6	R-Substituted protons [b]
4a	CH_3	4.25 (q, 6.0); 4.14 (q, 6.0) [c]	2.20 (q, 4.8)	1.38 (d, 5.9, CH_3 at C-2); 1.27 (d, 4.9, CH_3 at C-6); 1.26 (d, 6.5, CH_3 at C-4)
4b	CH_3	4.39 (q, 6.0)	2.31 (q, 5.0)	1.36 (d, 5.8, CH_3 at C-2,4); 1.27 (d, 4.9, CH_3 at C-6)
4c	CH_3	4.42 (q, 6.5)	2.13 (q, 5.0)	1.26 (d, 6.4, CH_3 at C-2,4); 1.15 (d, 5.0, CH_3 at C-6)
5a	C_2H_5	4.07 (t, 5.5); 3.99 (t, 5.0) [c]	2.09 (dd, 4.5, 6.5)	1.3–1.9 (m, CH_2); 1.15 (t, 6.5, CH_3); 0.98 (t, 6.5, CH_3)
5b	C_2H_5	4.05 (t, 7.0)	2.02 (t, 5.5)	1.2–1.8 (m, CH_2); 1.00 (t, 7.0, CH_3)
6a	n-C_3H_7	4.13 (t, 5.5); 4.06 (t, 5.5)	2.11 (t, 4.5)	1.2–1.8 (m, CH_2CH_2); 0.9–1.1 (m, CH_3)
7a	i-C_3H_7	3.75 (d, 7.0); 3.70 (d, 7.0) [c]	2.04 (d, 7.5)	1.2–1.7 (m, CH); 1.12 (d, 6.0, CH_3); 1.01 (d, 6.0, CH_3); 0.92 (d, 6.0, CH_3)
7b	i-C_3H_7	3.60 (d, 8.5)	1.90 (d, 7.5) [e]	1.2–1.7 (m, CH); 0.98 (d, 6.0, CH_3); 0.90 (d, 6.0, CH_3)
8a	n-C_4H_9	3.9–4.2 (m)	2.10 (m)	1.2–1.7 (m, CH_2); 0.8–1.2 (m, CH_3)
9a	i-C_4H_9	4.13 (t, 7.0) [c]	2.12 (t, 5.5)	1.2–1.8 (m, CH_2CH); 0.8–1.2 (m, CH_3)
10a	t-C_4H_9	3.92 (s); 3.60 (s) [c]	1.93 (s)	1.07 (s, CH_3); 0.96 (s, CH_3); 0.94 (s, CH_3)
10b	t-C_4H_9	3.70 (s) [d]	2.34 (s)	1.09 (s, CH_3); 0.95 (s, CH_3)
10c	t-C_4H_9	3.52 (s)	2.32 (s)	1.03 (s, CH_3); 0.85 (s, CH_3)
11a	n-C_5H_{11}	3.9–4.2 (m)	1.9–2.1 (m)	1.2–1.8 (m, CH_2); 0.9–1.2 (m, CH_3)
11b	n-C_5H_{11}	3.9–4.2 (m)	1.9–2.1 (m)	1.2–1.8 (m, CH_2); 0.9–1.2 (m, CH_3)
12a	$(C_2H_5)_2CH$	3.92 (dd, 7.2, 5.5 [d]); 3.84 (dd, 8.5, 9.5 [d])	1.92 (d, 6.7) [e]	1.2–1.8 (m, CH, CH_2); 0.7–1.2 (m, CH_3)
12b	$(C_2H_5)_2CH$	3.86 (d, 8.5)	2.12 (d, 7.0)	1.2–1.8 (m, CH, CH_2); 0.7–1.2 (m, CH_3)
13a	C_6H_5	5.60 (d, 6.0 [d]); 5.22 (d, 9.5 [d])	3.20 (s)	7.2–7.9 (m, C_6H_5); 3.05 (broad t, NH)
13b	C_6H_5	5.51 (d, 10.5 [d])	3.17 (s)	7.2–7.9 (m, C_6H_5)
14a	n-C_6H_{13}	4.0–4.3 (m)	2.1–2.3 (m)	1.2–1.8 (m, CH_2); 0.8–1.2 (m, CH_3)
15a	$C_6H_5CH_2$	4.26 (t, 4.2); 4.18 (t, 5.5)	2.20 (t, 5.5)	7.0–7.5 (m, C_6H_5); 2.6–3.2 (m, CH_2)
15b	$C_6H_5CH_2$	4.27 (t, 5.5)	2.08 (t, 6.0)	7.0–7.5 (m, C_6H_5); 2.5–3.1 (m, CH_2)
16a	$C_6H_5(CH_3)$-CH	4.20 (d, ~8); 4.10 (d, ~8)	2.30 (d, ~8)	7.3 (m, C_6H_5); 2.0–3.0 (m, CH); 1.0–1.6 (m, CH_3)

[a] All measurements at 60 or 100 MHz, $CDCl_3$ solvent (+1% Me_4Si) ca. 27 °C. Multiplicity of signal and coupling constant (Hz) in parentheses. [b] A broad NH signal (~20 Hz) appears near δ 2.0–2.5 in all spectra except where noted otherwise. [c] Broadened signal (~2 Hz) which sharpens on addition of D_2O, apparently due to unresolved NH proton coupling. [d] Indicated splitting due to NH proton, collapses on addition of D_2O.

acyclic imine precursor related to **18** [i.e., i-$C_3H_7CH{=}N$-$CH(i$-$C_3H_7)NHCH(i$-$C_3H_7)NH_2$], derived from the very labile monocyclic triazine **17d** (R = i-C_3H_7), is seen in the ^{13}C NMR spectrum (Table V, footnote *b*).[13]



18a



18b

Equilibration of the bicyclic triazines is observed in methanolic ammonium chloride or hydrogen chloride at ambient temperature; recovery of epimerized products is quantitative. No observed epimerization occurs in basic media. In neutral protic solvents such as methanol a slow epimerization is sometimes observed. At equilibrium the cis-endo isomer virtually disappears leaving trans-exo and cis-exo epimers (**3a,b**) in a nearly 1:1 ratio (Table IV). A preference for the trans-exo form at equilibrium is observed for compounds with substituents methyl, *tert*-butyl, and phenyl.

The rate of acid-catalyzed equilibration of the bicyclic triazines depends on reaction conditions, structure, and stereochemistry of reactants. In 1% methanolic ammonium chloride solution at 25 °C equilibration is complete within 2–6 h in all cases examined except the cis- and trans-exo methyl and phenyl compounds **4** and **13**, which were unaffected after 48 h. However, these substances and all others are equilibrated in methanolic hydrogen chloride (pH 1–2, 25 °C) very rapidly (less than 10 min). Prolonged exposure of the bicyclic triazines to such strongly acidic conditions causes degradation (formation of aldehydes, hydrazine, and diaziridines).[7]

The rate of acid-catalyzed epimerization of cis-endo epimers (**3c**) is much more rapid than that of the exo isomers **3a,b.** For example, although methanolic ammonium chloride will not equilibrate trans- or cis-exo methyl isomers (**4a,b,** R = CH_3) the cis-endo form (**4c**) is converted quantitatively into the trans-exo form in this medium within 10 min. Similar results are observed with other cis-endo isomers. Mixtures containing three isomers (**3a–c**) in methanolic ammonium chloride are converted into mixtures containing only two isomers (**3a,b**) within 10 min. In each instance during this short reaction period the cis-endo form (**3c**) is converted exclusively into the trans-exo form; the amount of cis-exo form (**3b**) remains unchanged. Only on more extended exposure (2–6 h) is equilibrium attained involved interconversion of cis-exo and trans-exo forms. In methanol a slow, uncatalyzed cis-endo → trans-exo conversion is observed. This epimerization is most rapid with the methyl compound (1–2 days), but very slow with others (several weeks).

Epimerization of bicyclic triazines was found to involve no incorporation of deuterium at the C-2 or C-4 positions when the reaction was conducted in methanol-*O-d* containing ammonium chloride (**3,** R = C_2H_5, i-C_3H_7) or hydrogen chloride (**3,** R = CH_3).

A mechanism for the acid-catalyzed equilibrations and epimerizations is suggested by the above observations (Scheme I). Acid-catalyzed ring opening of cis-endo **3c** at N-1,C-2 would lead to iminium ion **19a.** Diaziridine nitrogen inversion would provide invertomer **19b;** ring closure would then give trans-exo **3a** only. The other possible epimer derived by ring closure of **19b** would be an unobserved, disfavored cis isomer (**3d**), having two endocyclic substituents (at C-2, C-4).

Table III. ^{13}C NMR Spectra of 2,4,6-Trisubstituted 1,3,5-Triazabicyclo[3.1.0]hexanes [a]

		Chemical shift, ppm					
		Ring carbons[b]			Substituent α carbon[b]		
R	Compd	C-2	C-4	C-6	C-2	C-4	C-6
CH_3	**4a**	75.3	72.4	46.2	15.2	17.0	21.4
	4b	74.9		41.0	15.3		17.1
	4c	75.7		53.2	24.9		23.0
C_2H_5	**5a**	81.1	78.2	52.1	24.1	24.3	28.1
	5b	80.2		47.0	24.1		24.2
	5c	81.9		59.2	31.2		24.6
n-C_3H_7	**6a**	79.5	76.8	50.9	33.4	33.6	37.4
	6b	78.8		45.8	33.4		33.4
	6c	80.4		58.2	40.6		33.6
i-C_3H_7	**7a**	84.2	86.1	58.2	32.0	33.1	30.4
	7b	84.9		52.3	31.5		30.1
	7c	87.7		66.4	35.0		30.8
n-C_4H_9	**8a**	79.6	77.0	50.9	30.8	31.0	34.8
	8b	78.8		45.9	30.9		31.0
	8c	80.3		57.9	38.0		31.2
i-C_4H_9	**9a**	78.0	75.4	49.7	40.4	40.4	44.0
	9b	77.5		44.5	40.4		40.4
	9c	78.8		57.1	47.2		40.4
t-C_4H_9	**10a**	87.4	89.9	62.7	32.8	31.3	36.5
	10b	86.2		54.2	32.8		32.8
n-C_5H_{11}	**11a**	79.7	77.0	50.9	31.5	31.2	35.2
	11b	78.9		45.8	32.0		31.7
	11c	80.4		58.1	38.3		30.9
$(C_2H_5)_2CH$	**12a**	82.4	80.4	55.5	43.3	42.7	44.4
	12b	81.4		49.0	43.2		42.0
	12c	83.5		64.8	46.1		44.0
C_6H_5	**13a**	81.4	80.5	51.9	136.2	136.1	140.4
	13b	82.3		48.1	136.2		140.4
n-C_6H_{13}	**14a**	79.9	77.2	51.3	31.7	31.5	35.4
	14b	79.1		46.1	31.8		31.8
	14c	80.6		58.4	38.4		32.0
$C_6H_5CH_2$	**15a**	81.1	72.1	53.0	36.5	38.3	41.6
	15b	78.8		48.3	36.5		41.4
$C_6H_5(CH_3)CH$	**16a**[c]	84.7	81.4	58.3	44.4	42.9	41.0
	16a'	85.3	82.8	58.6	45.1	43.4	41.6

[a] Fourier transform mode (proton decoupled) 25.14 MHz, $CDCl_3$ solvent with tetramethylsilane internal reference. [b] Substituent at C-2 is assumed to be exocyclic in the trans compounds. [c] Mixture of four diastereoisomers. Spectrum of recrystallized sample consists of the two sets of relatively strong lines shown and two sets of weaker lines that have not been assigned.

Table IV. Composition of Epimeric Mixtures of 2,4,6-Trisubstituted 1,3,5-Triazabicyclo[3.1.0]hexanes (±2%) ^{13}C NMR Assay

		Kinetic mixture (base catalysis)			Equilibrium mixture (acid catalysis)			Schmitz reaction product mixture	
Compd	R	Trans-exo **a**	Cis-exo **b**	Cis-endo **c**	Trans-exo **a**	Cis-exo[a] **b**	Catalyst[b]	Trans-exo **a**	Cis-exo[a] **b**
4	CH_3	53	38	9	65	35[c]	B	61	38[c]
5	C_2H_5	61	31	8	55	45	A	69	31
6	*n*-C_3H_7	57	32	12	55	45	A	69	32
7	*i*-C_3H_7	71	20	9	45	55[c]	A	80	20[c]
8	*n*-C_4H_9	55	33	12	45	55	A	67	33
9	*i*-C_4H_9	49	35	16	47	53	A	65	35
10	*t*-C_4H_9	85	15	*a,c*	80	20	A, B	85	15
11	*n*-C_5H_{11}	56	31	13	50	50	A, B	69	31
12	$(C_2H_5)_2CH$	81	13	6	53	47	A	87	13
13	C_6H_5	70	30	*a,c*	70	30[c]	B	70	30[c]
14	*n*-C_6H_{13}	61	29	10	55	45	A	71	29
15	$C_6H_5CH_2$	43	47	10	50	50	A	53	47

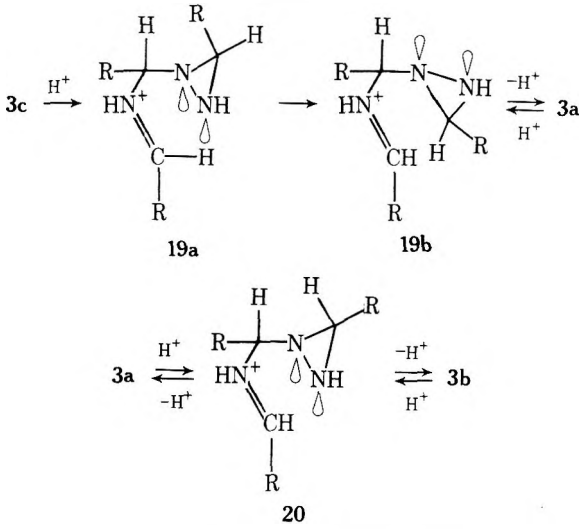
[a] Cis-endo (**c**) concentration <3%. [b] Catalyst: (A) ammonium chloride, (B) hydrogen chloride. [c] Assay by ^1H NMR gave the same results, ±2%.

Table V. ^{13}C NMR Spectra of 2,4,6-Trisubstituted 1,3,5-Triazacyclohexanes [a]

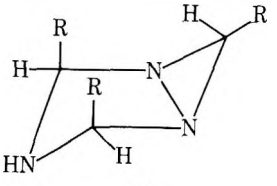
Compd	R	Chemical shift, ppm: Ring carbons	Chemical shift, ppm: Substituent carbons
17a	CH_3	66.2	22.8 (CH_3)
17b	CH_2CH_3	71.6	29.8 (CH_2); 9.3 (CH_3)
17c	$CH_2CH_2CH_3$	75.4	43.2, 21.3 (CH_2); 16.8 (CH_3)
17d	$CH(CH_3)_2$ [b]	75.9	33.7 (CH); 18.2 (CH_3)
17e	$C_6H_5CH_2$	73.2	139.1, 131.8, 130.8, 128.9 (C_6H_5); 45.1 (CH_2)
17f	$C_6H_5(CH_3)CH$ [c]	77.8, 77.6, 76.9	144.9, 130.6, 130.3, 129.9, 129.8, 128.8, (C_6H_5); 47.8, 47.7, 47.2 (CH); 19.6, 19.0, 18.7 (CH_3)

[a] Fourier transform mode, 25.14 MHz, $CDCl_3$ solvent with internal tetramethylsilane reference. [b] On standing in $CDCl_3$ solution at 25 °C for 12 h, peaks appear which are attributed to the acyclic dissociation product, i-$C_3H_7CH{=}NCH(i\text{-}C_3H_7)NHCH(i\text{-}C_3H_7)NH_2$: 168.4 (C=N); 96.8, 91.8 (NCHN); 34.1, 33.5 [$(CH_3)_2CH$]; 19.5, 17.4 (CH_3). [c] A statistical 1:3 mixture of two diastereoisomers. One component shows a single line of unit intensity. The other shows two lines with intensities in the ratio 1:2.

Scheme I



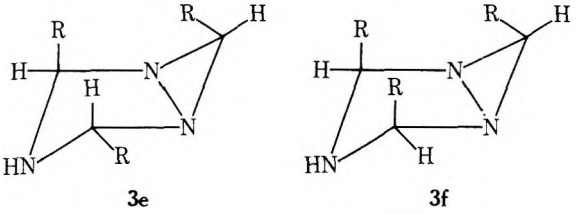
To achieve the slower cis-exo, trans-exo (**3a,b**) equilibration would involve iminium ion intermediate **20.**



3d

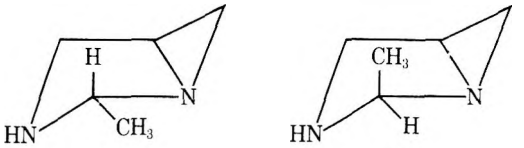
The epimer composition of reaction products obtained under normal Schmitz reaction conditions is different from that observed under kinetic conditions (alkaline workup) or at equilibrium (Table IV). Schmitz reaction products contain a higher percentage of trans isomer (**3a**) than either kinetic or equilibrium conditions, and very little cis-endo isomer (**3c**). The results are understandable in light of the equilibration and stereochemical studies. The normal workup procedure involves removal of excess ammonia and methanol by concentration of the reaction mixture to dryness at temperatures near 25 °C. During the final stages of concentration the methanolic solution changes from basic (excess ammonia) to weakly acidic (excess ammonium chloride). Under these conditions the cis-endo isomer (**3c**) is rapidly epimerized to the trans-exo form **3a.** The product contact time with ammonia-free methanolic ammonium chloride during workup is sufficiently short so that the relatively slower cis-exo to trans-exo (**3b,a**) equilibration occurs only slightly. These conclusions were confirmed by ^{13}C NMR assay of Schmitz reaction product mixtures. Also treatment of kinetic product mixtures (containing large amounts of cis-endo isomer) with ammonium chloride in 10 M methanolic ammonia followed by concentration to dryness (simulated Schmitz workup) gave reaction mixtures having compositions corresponding closely to those of Schmitz reaction products obtained by normal workup procedures.

Alternate structures with two or three endocyclic substituents could be written for the bicyclic triazines (e.g., **3d–f**).



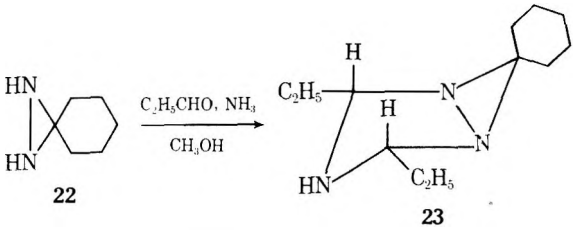
3e **3f**

There is evidence against such sterically unfavorable configurations, however. For example, in the related simple monosubstituted 2-methyl-1,3-diazabicyclo[3.1.0]hexane the exo methyl structure (**21a**) is favored 3:1 over the endo (**21b**).[18]



21a **21b**

2,4-Diethyl-6,6-pentamethylene-1,3,5-triazabicyclo-[3.1.0]hexane (**23**) was prepared by reaction of 6,6-pentamethylenediaziridine (**22**) with propanal under Schmitz reaction conditions. The crude reaction product contained only one isomer with cis stereochemistry of the C-2, C-4 substituents. The structure is supported by ^1H and ^{13}C NMR spectra. The ^1H NMR spectrum of **23** reveals a single triplet at δ 4.12 for the triazolidine ring protons. The ^{13}C NMR spectrum reveals the expected cis isomer signals. The ring C-6 signal appears in the region corresponding to those found for other cis-endo compounds (Table III). A line at δ 38.0 is assigned to the endocylic α-methylene carbon of the pentamethylene



22 **23**

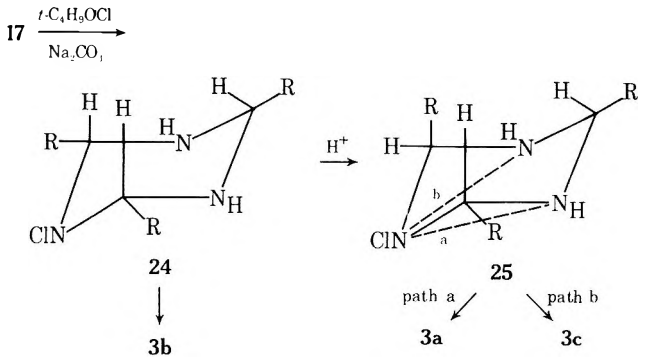
group owing to its position 13 ppm downfield from the other carbons of this ring. A similar deshielded α-carbon signal is observed in the methyl cis-endo compound **4c**, presumably arising from interaction with the triazolidine ring hydrogens. Such an interaction of the endocyclic methylene at C-6 disfavors a trans diethyl C-2, C-4 **23** epimer with two endocyclic substituents.

Stereochemistry of 2,4,6-Trialkyl-1,3,5-hexahydrotriazine Oxidations. Despite the steric homogeneity of reactant 2,4,6-trialkyl-1,3,5-hexahydrotriazines (**17**) their oxidation with *tert*-butyl hypochlorite in basic medium leads to epimeric mixtures of 2,4,6-trialkyl-1,3,5-triazabicyclo-[3.1.0]hexanes (**3**, eq 2). No equilibration of products occurs under the reaction conditions. The all equatorial stereochemistry of the parent 2,4,6-trialkyl-1,3,5-hexahydrotriazines (**17**) is indicated by their simple NMR spectra. The proton spectra of these materials have been discussed.[12,13] Their ^{13}C NMR spectra have now been determined and support the structure assignments. For example, the spectrum of 2,4,6-trimethyl-1,3,5-hexahydrotriazine (**17a**) reveals two lines, one each for the three ring carbons and three methyl substituents (Table V).

The stereochemistry and mechanism of 2,4,6-trialkyl-1,3,5-hexahydrotriazine oxidation was examined with the aid of ^{13}C NMR spectroscopy. Oxidation of anhydrous 2,4,6-trimethyl-1,3,5-hexahydrotriazine (**17a**) in methanol containing 1 equiv of sodium carbonate with 1 molar equiv of *tert*-butyl hypochlorite at −35 °C gave a crude reaction product containing only trans-exo and cis-endo bicyclic triazines (**4a** and **4c**, respectively). The reaction mixture is alkaline throughout; no epimerization occurs during the reaction period. The pure cis-endo form (**4c**) is readily isolated from the reaction mixture by extraction with hexane.

When the crude original product mixture was dissolved in deuteriochloroform the cis-exo compound **4b**, which was absent initially, was observed to appear slowly on standing (^{13}C NMR). After 3 days a nearly 1:1 equilibrium mixture of trans and cis-exo forms (**4a,b**) appeared; the cis-endo form (**4c**) had disappeared. The equilibration catalyst is believed to be hydrogen chloride formed from *N*-chloro-2,4,6-trimethyl-1,3,5-hexahydrotriazine (**24a**, R = CH_3, Scheme II) present

Scheme II



in the crude reaction mixture. This *N*-chloro compound is characterized by ^{13}C lines at δ 90.1 and 145.3. After 3 days these lines had disappeared and a spectrum appeared corresponding only to trans-exo and cis-exo bicyclotriazines (**4a,b**). Oxidation of 2,4,6-trimethyl-1,3,5-hexahydrotriazine-*2,4,6-d*$_3$ in methanol-*O-d* gave no CH deuterium incorporation into the bicyclic triazine products.

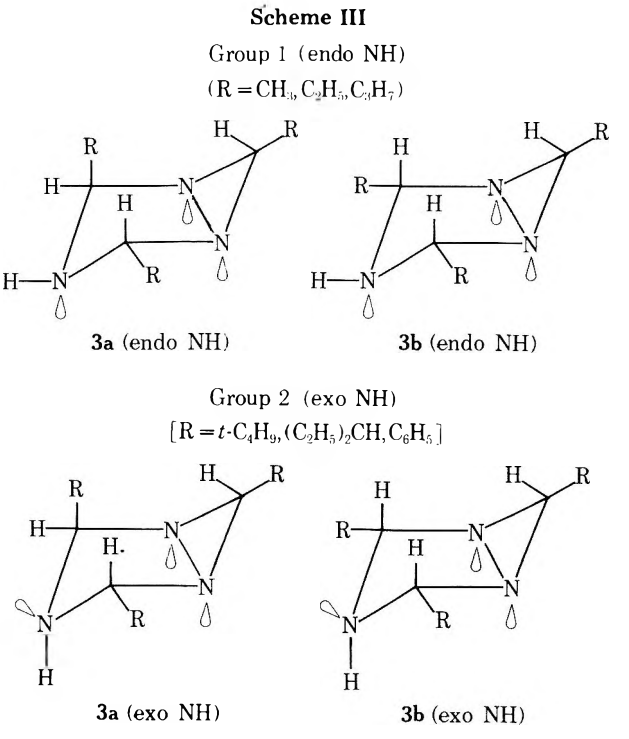
The above observations may be explained by the steps shown in Scheme II. The initially formed all-equatorial *N*-chloro compound **24a** (R = CH_3) rapidly epimerizes to yield a sterically favored 2-axial methyl isomer **25a** (R = CH_3) via an acyclic iminium intermediate formed by acid-catalyzed ring opening. The rate-limiting ring closure reactions in **25** lead to **3a** and **3c** by intramolecular chloride ion displacements (paths a and b, respectively); path a predominates.

With other triazines (**17**, R = alkyl) similar results are observed: the predominant reaction products are the trans-exo isomers (**3a**). However, in addition to the cis-endo form (**3c**), cis-exo form (**3b**) is also observed. The latter isomer could form by ring closure in **24** which may be favored to some extent over **25** when R is larger than methyl. Thus, depending on structure and method of workup, bicyclic triazines derived by oxidation of monocyclic triazines could have various epimer compositions. However, the predominant product isomer obtained is trans (**3a**). Our original report[1] describing the hexahydrotriazine oxidation products as only cis-exo (**3b**) and trans-exo (**3a**) was incorrect. The present findings permit a distinction between cis-endo and cis-exo products, and the rather surprising conclusion that despite the all-equatorial configuration of reactant **17**, the oxidation initially yields products having little or none of this stereochemistry.

NH Stereochemistry. The ^1H NMR data of Table II provide evidence of two different orientations of the NH proton in rigid bicyclic triazines ($CDCl_3$ solvent). Line broadening of one of the ring proton signals (H-2,4) which is observed in some trans-exo compounds (group 1—**4a, 5a, 7a**; R = CH_3, C_2H_5, *i*-C_3H_7, respectively) is absent in the corresponding cis-exo and/or cis-endo epimers. This broadening, presumably arising from a weak unresolved spin coupling to the NH proton, disappears on addition of deuterium oxide. In a second group of compounds (group 2) characterized by bulky substituents, line broadening or an observable strong NH spin coupling is observed for H-2 or H-4 of the trans-exo compounds [**10a, 12a, 13a**; R = *t*-C_4H_9, $(C_2H_5)_2CH$, and C_6H_5, respectively] *and* for both H-2 and H-4 in the cis-exo forms. In the phenyl-substituted trans compound **13a**, –NH spin-coupling values of 6.0 and 9.5 Hz were observed for H-2 and H-4, while the cis compound **13b** showed only one splitting of 10.5 Hz for the two ring protons. In the remaining compounds studied the NMR spectra were not sufficiently resolved to reveal NH coupling information.

The above observations suggest an endocyclic NH in the group 1 compounds (**4, 5, 6**) and an exocyclic NH in group 2 compounds (**10, 12, 13**) (Scheme III).

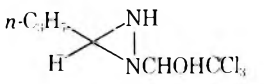
Scheme III



In group 1 the endocyclic NH proton of **3a** nearly eclipses H-2 and a weak coupling would be predicted, while it is almost trans to H-4 and should couple strongly with it. In **3b** both H-2 and H-4 eclipse the endocyclic NH proton and only weak coupling is expected. In group 2 the spectra of **3a** and **3b** both show at least one strong coupling of H-2 and H-4 to the NH proton. Since the R groups should be exocyclic because of their bulk, it follows that the NH proton must also be exocyclic to permit the observed spin coupling. In the trans compounds of group 1 the ring proton signal at highest field represents exocyclic H-4, while in the group 2 compounds it is the endocyclic H-2. In flexible heterocycles with 1,3-heteroatom substitution there is a preference for an axial NH.[19,20] However, configurations in these and other heterocycles are known to depend on substituent bulk.[21,22]

Mechanism of the Schmitz Reaction. Two mechanisms may be considered for formation of 2,4,6-trisubstituted 1,3,5-triazabicyclo[3.1.0]hexanes: (1) the Schmitz mechanism[11] involving reaction of a 3-substituted diaziridine (**2**) with aldehyde and ammonia to yield **3** (eq 1), and (2) oxidation of initially formed 2,4,6-trisubstituted 1,3,5-hexahydrotriazine (**17**) to yield **3** (eq 2).

Evidence obtained previously favoring the Schmitz mechanism includes trapping of a 3-substituted diaziridine intermediate with chloral to form 1-(2-trichloromethyl-1-hydroxyethyl)-3-propyldiaziridine (**26**) in low yield (8%).[7e] The possibility that **26** had formed by cleavage of the bicyclic triazine **6** has been discounted. In the present study treatment



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of bicyclic triazine **6a** (trans-exo, R = n-C_3H_7) in methanol with chloral at 25 °C gave quantitative recovery of reactants after 20 h.

Other evidence favors the Schmitz mechanism. Certain bicyclic triazines are formed in the Schmitz reaction which form no monocyclic triazines (**17**) under the reaction conditions [e.g., **10a**, R = t-C_4H_9, **12a**, R = $CH(C_2H_5)_2$, **13a**, R = C_6H_5].[13] Also, the rate of bicyclic triazine formation in the Schmitz reaction (1–2 h) is more rapid than formation of comparable yields of most monocyclic triazines (**17**) under the same conditions (several days except for those derived from acetaldehyde and propanal).[13]

Finally, the stereochemistry of the Schmitz reaction leading to **3** is somewhat different from that found for 2,4,6-trialkyl-1,3,5-hexahydrotriazine oxidation under comparable conditions (basic medium, −35 °C). The Schmitz reaction gives a mixture of three epimers (**3a–c**) under kinetic conditions (Table IV). The oxidation of 2,4,6-trimethyl-1,3,5-hexahydrotriazine, on the other hand, can yield trans-exo and cis-endo isomers (**4a,c**) only. All evidence of this study favors the originally proposed Schmitz mechanism involving a diaziridine intermediate (eq 1).

Experimental Section[23]

Aldehydes. All aldehydes were commercial samples, reagent grade, distilled immediately before use.

2,4,6-Trimethyl-1,3,5-hexahydrotriazine-*1,3,5-d*$_3$ was prepared by dissolving a 2.5-g sample of the anhydrous protiotriazine[13] in 25 ml of deuterium oxide and concentrating the solution to dryness under reduced pressure at 25 °C; the process was repeated. Final drying in a vacuum desiccator over calcium chloride gave 2.25 g of trideuteriotriazine showing no NH or H_2O in its ^1H NMR spectrum.

Preparation of 2,4,6-Trialkyl-1,3,5-triazabicyclo[3.1.0]hexanes. A. General Schmitz Procedure. The procedure of Schmitz was employed with slight modifications and is illustrated with preparation of ***cis*- and *trans*-2,4,6-tris(*n*-pentyl)-1,3,5-triazabicyclo[3.1.0]hexanes** (**11b** and **11a**, respectively). A solution of *tert*-butyl hypochlorite (2.71 g, 0.026 mol) in 3 ml of *tert*-butyl alcohol was added dropwise, stirring magnetically during 5 min, to 25 ml of 10 M methanolic ammonia contained in a 125-ml Erlenmeyer flask (reaction temperature maintained at ca. −35 °C by immersing the flask in an ethylene dichloride/dry ice bath). Hexanal (5.0 g, 0.05 mol) was added dropwise with stirring during 5 min and stirring continued (calcium chloride tube attached) for 1 h, maintaining the reaction temperature near −35 °C. The flask was removed from the cold bath and allowed to stand at ambient temperature (no stirring) for 2.5 h. The mixture was concentrated to dryness under reduced pressure and the residue extracted thoroughly with boiling hexane; concentration of the extracts gave 4.26 g (87%) of a mixture of cis-exo and trans-exo triazines **11b** (33%) and **11a** (67%), respectively; assay by ^{13}C NMR. Fractional crystallization from heptane gave pure samples of the less soluble trans-exo **11a**, 0.67 g, mp 51–55 °C, and more soluble cis-exo **11b**, mp 50–54 °C.

The above procedure was employed to prepare the trans triazines listed in Table I, procedure A. Pure trans products were obtained by recrystallization from hexane, ethanol, or ether to constant melting point (assay by ^1H and ^{13}C NMR). Fractional crystallization of mother liquors gave material enriched in the cis-exo isomers. NMR data of these products are summarized in Tables II (^1H) and III (^{13}C).

To a 0.10-g (0.50 mmol) sample of *trans-exo*-2,4,6-tri-*n*-propyl-1,3,5-triazabicyclo[3.1.0]hexane (**6a**) dissolved in 1.0 ml of methanol was added 0.080 g (0.50 mmol) of chloral hydrate. After standing at 25 °C for 20 h the solution was concentrated to dryness and the residue fractionally crystallized from hexane to yield 0.095 g (95%) of unreacted **6a** in successive crops, mp 79–84 °C; chloral was also recovered.

B. The general kinetic procedure is illustrated by preparation of 2,4,6-triisobutyl-1,3,5-triazabicyclo[3.1.0]hexane isomer mixture (**9a–c**). The general Schmitz procedure above was followed (using 0.05 mol of isovaleraldehyde and 0.025 mol of *tert*-butyl hypochlorite) except that prior to concentration of the reaction mixture excess aqueous sodium hydroxide solution was added (2.5 mol of 50% solution, 1.9 g, 0.047 mol, of sodium hydroxide) to assure conversion of the ammonium chloride to sodium chloride. The alkaline reaction mixture was concentrated to dryness at 25 °C and the residue extracted thoroughly with methylene chloride. Concentration of the extracts gave 3.75 g (89%) of crude product: small prisms, mp 124–131 °C [mixture of 48% trans-exo (**9a**), 35% cis-exo (**9b**), and 16% cis-endo (**9c**) by ^{13}C NMR assay]. Total yields of crude triazine mixtures by the above procedure were essentially the same as obtained by the general Schmitz procedure (A). Data are summarized in Table IV.

2,4,6-Trimethyl-1,3,5-triazabicyclo[3.1.0]hexane (4c, Cis-Endo). Oxidation of 2,4,6-Trimethyl-1,3,5-hexahydrotriazine (17a). A solution of anhydrous 2,4,6-trimethyl-1,3,5-hexahydrotriazine (**17a**, 2.58 g, 0.02 mol)[13] in methanol (100 ml) mixed with sodium carbonate (1.06 g, 0.01 mol) was chilled to −35 °C (ethylene dichloride/dry ice bath). While stirring, *tert*-butyl hypochlorite (2.2 g, 0.02 mol) was added dropwise during 2 min. A calcium chloride tube was attached and stirring continued at ca. −35 °C for 1 h. The cold bath was removed and the mixture allowed to warm to 25 °C during 1 h and then filtered. The filtrate was concentrated to dryness at 25 °C and the residue extracted several times with hot hexane. The extracts were immediately concentrated under reduced pressure to ca. 20 ml and chilled at −15 °C to deposit a solid which was fractionally crystallized from hexane to yield 0.15 g (6%) of **4c** as long needles, mp 133–134 °C. A solution of **4c** dissolved in methanol was concentrated after standing at 25 °C for 48 h to yield trans-exo **4a**, mp 111–114 °C.

In a parallel run employing 6.36 g (0.05 mol) of anhydrous 2,4,6-trimethyl-1,3,5-hexahydrotriazine the resulting hexane extracts were concentrated to dryness to yield 3.9 g of a solid mixture of products. The ^{13}C NMR spectrum (in $CDCl_3$) of this material showed the bicyclic triazine component to be a mixture of 66% trans-exo **4a** and 34% cis-endo **4c**. Additional strong peaks were observed in the ^{13}C spectrum at δ 90.1 and 58.1 (intensity ratio 2:1) attributed to C-2, C-4, and C-6 ring carbons, respectively, of all-equatorial 1-chloro-2,4,6-trimethyl-1,3,5-hexahydrotriazine (**24a**, R = CH_3); peaks for the corresponding C-2, C-4, and C-6 methyl carbons appeared at δ 23.5 and 15.3, respectively, also in a 2:1 intensity ratio. On standing in deuteriochloroform the intensities of these *N*-chloro peaks diminished and after 72 h had completely disappeared. After 14 h the bicyclic triazine composition had changed to 80% **4a**, 15% **4b**, and 5% **4c**; after 72 h there was present 53% **4a**, 47% **4b**, and 0% **4c**. The *N*-chlorotriazine **24a** (R = CH_3) was also prepared in deuteriochloroform (3.5 ml) by reaction of anhydrous triazine **17a** (R = CH_3) (0.42 g) with *tert*-butyl hypochlorite (0.37 g) at −35 °C; examination of the ^{13}C NMR spectrum of the solution at 30 °C revealed the presence of all-equatorial *N*-chlorotriazine; no bicyclic triazine formation was ob-

served in 1 h, and only the trans form (**4a**) was evident after 16 h. The reaction of triazine **17a** (R = CH_3) (0.42 g) and sodium carbonate (0.18 g) in methanol (3 ml) with *tert*-butyl hypochlorite (0.37 g) at −35 °C was followed by ^{13}C NMR; no *N*-chlorotriazine peaks were evident and after 1 h only the trans bicyclotriazine (**4a**) spectrum appeared.

2,4,6-Trimethyl-1,3,5-hexahydrotriazine-*1,3,5-d*$_3$ (1.30 g, 0.01 mol) was oxidized in the same manner as the protio compound **17a** in methanol-*O-d* to yield a crude product (0.62 g) showing a ratio of CH_3/CH of 3:1 by ^1H NMR. Crystallization from hexane gave crude cis-endo triazine **4c**-*N-d*, 0.05 g, mp 90–106 °C, showing no deuterium incorporation at ring CH positions.

Oxidation of 2,4,6-Trialkyl-1,3,5-hexahydrotriazines. The procedure employed with the trimethyltriazine **17a** (R = CH_3) was used with other anhydrous triazines, prepared as described previously.[13] 2,4,6-Triisopropyl-1,3,5-hexahydrotriazine (**17d**, *i*-C_3H_7) gave a crude product, mp 131–134 °C (16% yield), of a mixture containing 77% **7a**, 16% **7b**, and 6% **7c** by ^{13}C NMR; recrystallization from hexane gave trans-exo **7a**, mp 140–143 °C.

The crude product obtained from 2,4,6-triethyl-1,3,5-hexahydrotriazine (**17b**, R = C_2H_5) contained 70% **5a**, 30% **5b**, and only traces of **5c**; recrystallization from ether gave a 9% yield of crystalline trans **5a**, mp 99–102 °C. The crude product from the anhydrous tri-*n*-propyl compound (**17c**, R = *n*-C_3H_7) contained 90% trans **6a** and 10% **6b**; one recrystallization from hexane gave trans **6a**, mp 78–82 °C. Other 2,4,6-trialkyl-1,3,5-hexahydrotriazines were oxidized to yield trans bicyclotriazines after recrystallization from hexane. Yields are listed in Table I.

Epimerization Experiments. Procedure A. Methanolic Ammonium Chloride. A sample of 2,4,6-tri-*n*-propyl-1,3,5-triazabicyclo[3.1.0]hexane (**6a**, 0.30 g) was added to a solution of ammonium chloride (300 mg) in 30 ml of methanol. After standing at ambient temperature (25 °C) for 30 h the solution was concentrated to dryness and the mixture extracted with methylene chloride. Concentration of the extracts gave 0.30 g of recovered triazine which was assayed by ^{13}C NMR revealing a mixture of 51% trans **6a** and 49% **6b**, and only trace amounts of **6c**. The same procedure was employed with other triazines (pure cis or trans or mixtures of two or three epimers; reaction times 6–74 h). No epimerization was observed with the pure trans phenyl compound **13a** during 68 h nor with the trans methyl compound **4a** during 16 h (reactants recovered). Data are summarized in Table IV.

The rate of epimerization of the tri-*n*-pentylbicyclotriazine **11a** was evaluated using the same procedure. Starting with a mixture of 70% trans-exo **11a** and 30% cis-exo **11b**, samples were removed at intervals, quenched with excess sodium hydroxide, and assayed by ^{13}C NMR; observed time in hours followed by percent trans-exo **11a** in parentheses were as follows: 0 (70), 0.1 (68), 0.35 (60), 2.5 (54), 6 (50), 30 (50).

The ammonium chloride catalyzed epimerization of mixtures containing appreciable amounts of cis-endo isomer was examined using short reaction times. The equilibration reaction was stopped by addition of 50% aqueous sodium hydroxide to adjust the pH to ca. 10. A tri-*n*-propylbicyclotriazine mixture (57% **6a**, 32% **6b**, 12% **6c**) gave after 5 min 64% **6a**, 32% **6b**, 4% **6c**. A tris-isobutylbicyclotriazine mixture (49% **9a**, 35% **9b**, 16% **9c**) gave after 5 min 67% **9a**, 33% **9b**, and 0% **9c**.

Pure cis-endo trimethylbicyclotriazine (**4c**, mp 133–134 °C) in 1% methanolic ammonium chloride for 30 min gave the trans epimer only (**4a**, mp 111–114 °C, ^{13}C NMR assay).

A modified ammonium chloride catalyzed epimerization procedure was employed which approximates the workup procedure employed in the Schmitz reaction. A mixture of 0.36 g of *n*-pentylbicyclotriazine (containing 56% **11a**, 31% **11b**, and 13% **11c**), 0.36 g of ammonium chloride, and 36 ml of 10 M methanolic ammonium chloride was concentrated to dryness under reduced pressure during ca. 12 min. The residue was extracted with methylene chloride and the extracts concentrated to dryness to yield a product (0.36 g) containing 64% **11a**, 31% **11b**, and 5% **11c** (the crude product isolated from a 0.05-mol Schmitz reaction run requiring ca. 1 h concentration time during workup gave a mixture of 67% **11a**, 33% **11b**, and less than 2% **11c**). In a parallel experiment with a tri-*n*-propylbicyclotriazine sample containing 57% **6a**, 32% **6b**, and 12% **6c** there was obtained after ca. 12 min concentration time a mixture of 64% **6a**, 32% **6b**, and 4% **6c**.

Procedure B. Methanolic Hydrogen Chloride. A 0.30-g sample of 2,4,6-tri-*n*-pentyl-1,3,5-triazabicyclo[3.1.0]hexane (70% trans-exo, **11a**, and 30% cis exo, **11b**) was dissolved in methanol (30 ml). Hydrochloric acid (12 N) was added dropwise (5 drops) to adjust to pH ca. 2. After 10 min aqueous sodium hydroxide solution (50%) was added dropwise to adjust the pH to ca. 9. The solution was concentrated to dryness and the residue extracted with methylene chloride. Concentration of the extracts gave 0.30 g of epimerized product (48% trans, **11a**; 49%; cis-exo, **11b**; and 3% cis-endo, **11c**). Samples of certain other triazines were epimerized using the same conditions for 10 min. Product equilibrium mixture compositions agreed (±2%) with values obtained using methanolic ammonium chloride (procedure A). Data are summarized in Table IV.

Procedure C. Epimerizations in Methanol-*O-d*. A 0.20-g sample of trimethylbicyclotriazine (67% trans **4a**, 33% cis **4b**) was dissolved in 20 ml of methanol-*O-d*. Hydrochloric acid was added dropwise to adjust to pH 1. After standing for 2 h the solution was made alkaline (pH 8) by addition of 50% aqueous sodium hydroxide solution. The mixture was concentrated to dryness and the residue extracted with deuteriochloroform. The CH proton NMR spectrum was identical with that of the reactant mixture; the ratio of integrals for the C-2, C-4, C-6 ring CH and methyl protons remaining unchanged at 1:3.

A 0.10-g sample of triethylbicyclotriazine (55% trans **5a**, 45% cis **5b**) was exchanged with D_2O several times to prepare the *N*-deuterio compound. This material and deuterioammonium chloride (0.10 g) in 15 ml of methanol-*O-d* after standing at 25 °C for 16 h was concentrated to dryness and the residue extracted with deuteriochloroform. Except for the absence of an NH signal, the ^1H NMR spectrum of the product was identical with that of the reactant (no CH deuterium incorporation).

2,4-Diethyl-6,6-pentamethylene-1,3,5-triazabicyclo[3.1.0]-hexane (23). 3,3-Pentamethylenediaziridine[4] (2.0 g, 0.018 mol) was dissolved in 100 ml of dry methanol and cooled to −35 °C. To the stirred solution was added methanolic ammonia (4.46 ml of 8 N solution, 0.036 mol) in one portion. Propanal (2.32 g, 0.040 mol) was added in one portion to the stirred solution. The solution was stirred for 1 h at −30 °C and an additional 1 h at 25 °C. Removal of solvent gave 3.55 g of clear mobile oil. The oil was taken up in 40 ml of isopentane and dried over Drierite; its ^{13}C NMR spectrum shows **23** in one configuration only. Filtration and concentration gave 3.1 g (82%) of white solid: mp 37–41 °C; ir 3320 cm^{-1} (NH); ^1H NMR ($CDCl_3$) δ 4.18 (t, 2 H, ring CH), 2.52 [s (broad), 1 H, NH], 1.87 [s (broad), 14 H, CH_2], 1.17 (t, J = 7.5 Hz, 6 H, CH_3); the ^1H NMR spectrum in pyridine-d_5 showed one exchangeable proton upon addition of D_2O; ^{13}C NMR ($CDCl_3$) δ 77.3 (ring C-2, C-4), 64.6 (ring C-6), 38.0 [endocyclic α-C of (CH_2)$_5$], 31.3 (CH_2CH_3), 25.9, 25.4, 24.8, 24.1 [(CH_2)$_5$ carbons except endocyclic α-C], 10.7 (CH_3).

Anal. Calcd for $C_{12}H_{23}N_3$: C, 68.85; H, 11.08; N, 20.08; mol wt, 209.33. Found: C, 68.66; H, 11.04; N, 19.95; mol wt, 212 (osmometry, $CHCl_3$).

Registry No.—**4a**, 41807-88-9; **4b**, 41807-89-0; **4c**, 59829-85-5; **4c**-*N-d* (R = CH_3), 59812-99-6; **5a**, 41807-90-3; **5b**, 41807-91-4; **5c**, 59829-86-6; **6a**, 41807-92-5; **6b**, 41807-93-6; **6c**, 59829-87-7; **7a**, 41807-94-7; **7b**, 41807-95-8; **7c**, 59829-88-8; **8a**, 41807-96-9; **8b**, 49829-89-9; **8c**, 59829-90-2; **9a**, 41807-97-0; **9b**, 59829-91-3; **9c**, 59829-92-4; **10a**, 41807-98-1; **10b**, 59829-93-5; **10c**, 59829-94-6; **11a**, 41807-99-2; **11b**, 59829-95-7; **11c**, 59829-96-8; **12a**, 41808-00-8; **12b**, 59829-97-9; **12c**, 59829-98-0; **13a**, 41808-01-9; **13b**, 59830-03-4; **13c**, 59830-04-5; **14a**, 41808-02-0; **14b**, 59829-99-1; **14c**, 59830-00-1; **15a**, 51003-11-3; **15b**, 59830-01-2; **15c**, 59830-02-3; **16a** [R = Ph(CH_3)CH], 51003-93-1; **17a**, 41808-03-1; **17b**, 41808-70-9; **17c**, 41808-04-2; **17d**, 41808-05-3; **17e**, 59830-05-6; **17f**, 51003-91-9; **23**, 59813-00-2; **24a** (R = Me), 59813-01-3; 2,4,6-trimethyl-1,3,5-hexahydrotriazine-*1,3,5-d*$_3$, 59813-02-4; 3,3-pentamethylenediaziridine, 185-79-5.

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(22) E. Breuer and D. Melumad, *J. Org. Chem.*, **38**, 1601 (1973).
(23) Infrared spectra were determined on a Perkin-Elmer Model 137, ^1H NMR spectra on a Varian A-60 or XL-100, and ^{13}C NMR spectra on a Varian XL-100 spectrometer with Transform Technology TT-100 pulsed Fourier transform system. ^1H and ^{13}C chemical shift measurements were determined at ca. 30 °C and are referenced to tetramethylsilane internal standard. Melting points were determined on a Kofler hot stage and are corrected. Elemental analyses and molecular weights (vapor osmometry) were determined by Galbraith Laboratories, Knoxville, Tenn.

Diaziridines. 5. Reaction of Some 1-Aroyl- and 1,2-Diacyldiaziridines

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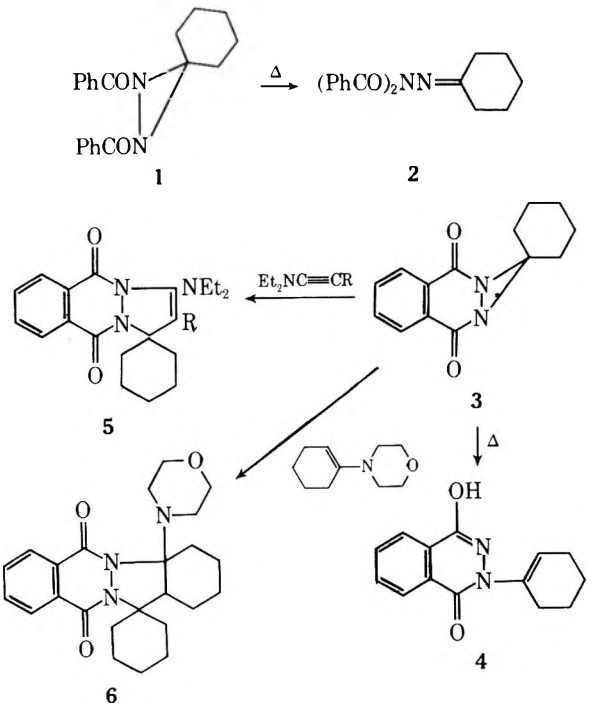
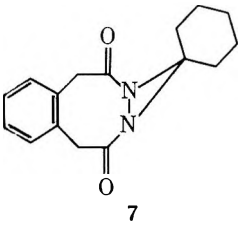
The diaziridine 4′,9′-dihydrospiro[cyclohexane-1,1′(1*H*)-diazirino[1,2-*c*][3,4]benzodiazocine]-3′,10′-dione (**7**) isomerizes in refluxing benzene into 3-(cyclohexylideneamino)-1*H*-3-benzazepine-2,4(3*H*,5*H*)-dione (**8**) and rearranges in refluxing benzene containing triethylamine hydrochloride into 3-(1-cyclohex-1-yl)-1,3,4,6-tetrahydro-3,4-benzodiazocine-2,5-dione (**9**). 1-*p*-Nitrobenzoyl-2,3,3-trialkyldiaziridines isomerize in chloroform or acetonitrile at ambient temperatures into labile 2-aryl-4,5,5-trialkyl-Δ^2-1,3,4-oxadiazolines (**11a–c**). The latter compounds react with both electrophiles and nucleophiles such as aromatic aldehydes and ynamines to give 2,5-diaryl-4-alkyl-Δ^2-1,3,4-oxadiazolines and pyrazoline derivatives, respectively.

Several studies on 1,2-diaroyldiaziridines have appeared recently. Schmitz and co-workers[1] reported the rearrangement of several 1,2-diaroyldiaziridines (**1**) to β,β-diaroylhydrazones (**2**) (Scheme I) and we[2,3] described the reactions of 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones (**3**). The latter compounds isomerize to 2-(1-alken-1-yl)-4-hydroxy-1(2*H*)-phthalazinones (**4**) in refluxing toluene and react with ynamines and enamines to give compounds **5** and **6**, respectively (Scheme I).

Scheme I



The difference in thermal behavior of **1** and **3** prompted us to undertake the preparation and thermolysis of a *N,N′*-diacyldiaziridine similar to **3** but less constrained, namely the benzodiazocine derivative **7**. For purposes of comparison with



7

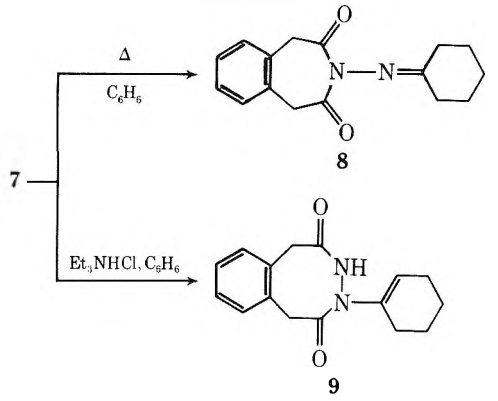
N,N′-diaroyldiaziridines we also prepared several 1-aroyl-2,3,3-trialkyldiaziridines. These substances isomerize in chloroform or acetonitrile to labile 2-aryl-4,5,5-trialkyl-Δ^2-1,3,4-oxadiazolines which react readily with both electrophilic and nucleophilic substrates such as aromatic aldehydes and ynamines.

Results

Compound **7** was synthesized in 41% yield by reacting *o*-phenylenediacetyl chloride with excess 3,3-pentamethylenediaziridine. The NMR spectrum of **7** is consistent with the structure proposed (see Experimental Section). When heated in benzene **7** isomerizes into the benzazepine **8** (Scheme II). The structure of **8** was elucidated by NMR spectroscopy, mass spectroscopy, and elemental analysis. The NMR spectrum taken in $CDCl_3$ consists of two singlets at δ 7.25 and 4.12 for the aromatic and methylene protons, respectively, and two broad multiplets centered at δ 2.50 and 1.70. The two multiplets are characteristic of the cyclohexylidine moiety when bonded to nitrogen and they are observed in the NMR spectra of hydrazone derivatives of cyclohexanone[4] and cyclohexanone oxime. Compound **7** when refluxed in benzene containing

a catalytic amount of triethylamine hydrochloride isomerizes into the benzodiazocine **9** (Scheme II).

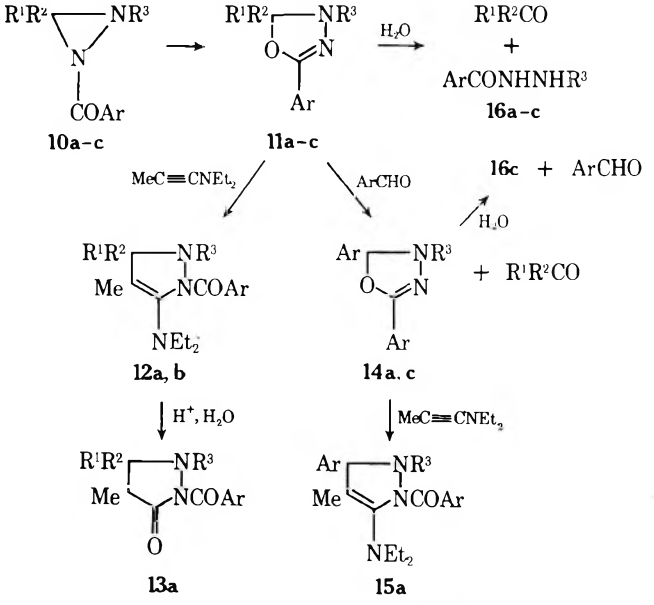
Scheme II



The NMR spectrum of **9** is quite similar to that of **4**. For example, the spectrum shows the presence of a vinylic proton at δ 5.74, an amido proton at δ 8.88, and two broad absorption peaks at δ 2.27 and 1.64 for the aliphatic protons of the cyclohexenyl group. In addition the two nonequivalent methylene groups of the benzodiazocine ring and the aromatic protons appear as multiplets at δ 4.17, 3.47, and 7.18, respectively.

Solutions of 1-aroyl-2,3,3-trialkyldiaziridines **10a–c** in dry methylene chloride, chloroform, or acetonitrile at ambient temperatures gradually change color from pale yellow to red within a few hours. In carbon tetrachloride at 80 °C the change takes place within 10 min. The color change parallels the disappearance of the nuclear magnetic absorption bands of the diaziridines and the appearance of new bands assigned to the 2-aryl-4,5,5-trialkyl-Δ^2-1,3,4-oxadiazolines **11a–c** (Scheme III). Evaporation of the solvent under anhydrous conditions gives solid **11a–c** but exposure of these substnces (or even solutions of these substances) to the atmosphere brings about their immediate hydrolysis to hydrazides **16** and ketones (Scheme III). In only the case of **11a** was it possible to obtain a sample that was stable enough to obtain elemental analyses

Scheme III



a, $R^1 = R^3 = Me$; $R^2 = PhCH_2$
b, $R^1 = R^2 = -(CH_2)_5-$; $R^3 = Me$
c, $R^1 = R^2 = Me$; $R^3 = i\text{-}Pr$
$Ar = p\text{-}O_2NC_6H_4$

although mass spectra for **11a–c** were determined. The hydrolysis of the 2,5-diaryl-4-alkyl-Δ^2-1,3,4-oxadiazolines **14a,c** also occurs rapidly but not as fast as that of the 4,5,5-trialkyl analogues. The hydrolysis of 2,4,5-triaryl-Δ^2-oxadiazolines has been reported to yield hydrazides and aldehydes.[5] The infrared spectra of **11a–c** and **14a,c** and the known 2,4,5-triphenyl-Δ^2-1,3,4-oxadiazolines are quite similar. Significantly there is present an absorption band at 1600 cm^{-1} (Nujol) for the –C=N– moiety and there are no bands attributable to carbonyl absorption.

Addition of 1-(*N,N*-diethylamino)propyne to chloroform solutions of **10a,b** either at the outset of the dissolution of **10a,b** in chloroform or after NMR spectroscopy had revealed the formation of **11a,b** resulted in the formation of the pyrazolines **12a,b** (Scheme III). Analytical and spectral data of **12a,b** together with the hydrolysis of **12a** to the pyrazolone **13a** confirmed their structure. The hydrolysis of 3-diethylamino-3-pyrazolines to pyrazolones is a known reaction.[2] The 2,5-diaryl-Δ^2-1,3,4-oxadiazoline **14a** also reacts with 1-(*N,N*-diethylamino)propyne to give the pyrazoline **15a**.

Treatment of acetonitrile solutions of **10a–c** or **11a–c** with *p*-nitrobenzaldehyde at room temperature gives 2,5-di(*p*-nitrophenyl)-4-alkyl-Δ^2-1,3,4-oxadiazolines **14a,c** and a ketone (Scheme III). Compounds **14a,c** were also prepared by condensing *p*-nitrobenzaldehyde with the appropriate 1-*p*-nitrobenzoyl-2-alkylhydrazine. As mentioned previously **14a,c** hydrolyze to hydrazides **16a,c** and *p*-nitrobenzaldehyde.

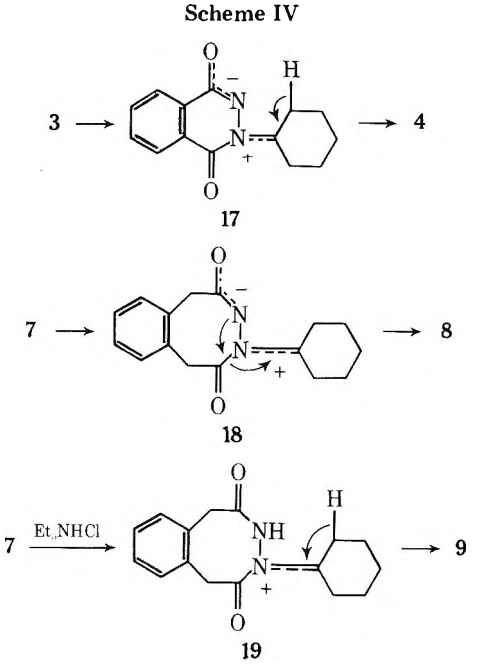
Discussion

One mechanistic scheme to account for the thermal conversions of **3** to **4** and of **7** to **8** involves the intermediacy of the azomethine imides **17** and **18**, respectively. The amido anion of **18** is less encumbered by ring constraint than the corresponding group of **17** and is thus able (unlike **17**) to add to the carbonyl carbon of the other amido group and thereby form **8** (Scheme IV). That this pathway is preferred to the elimination of a proton from the positively charged cyclohexyl group (as is the case with **17**) is borne out by the facile isomerization of the strain-free **1** to **2** via the intermediate $PhCON^+N^-(COPh)C_6H_{11}$.

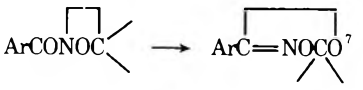
We attribute the conversion of **7** to **9** to the protonation of the amido group, subsequent opening of the diaziridine ring to **19**, followed by an elimination of a proton from **19** (Scheme IV).

The isolation of the labile **11a–c** when the diaziridines

Scheme IV



10a–c were dissolved in acetonitrile or chloroform suggests that **10** ring opened to the azomethine imide **20** which undergoes cyclization to **11** (Scheme V). A 1,3-dipolar species analogous to **20** has been proposed recently to rationalize the isomerization of 1-(anilinoformyl)-2-cyclohexyl-3-phenyl-3-methyldiaziridine to 1-cyclohexyl-4,5-diphenyl-5-methyl-1,2,4-triazolid-3-one.[6] The rearrangement of **10** to **11** bears a close resemblance to the thermal isomerizations of 2-

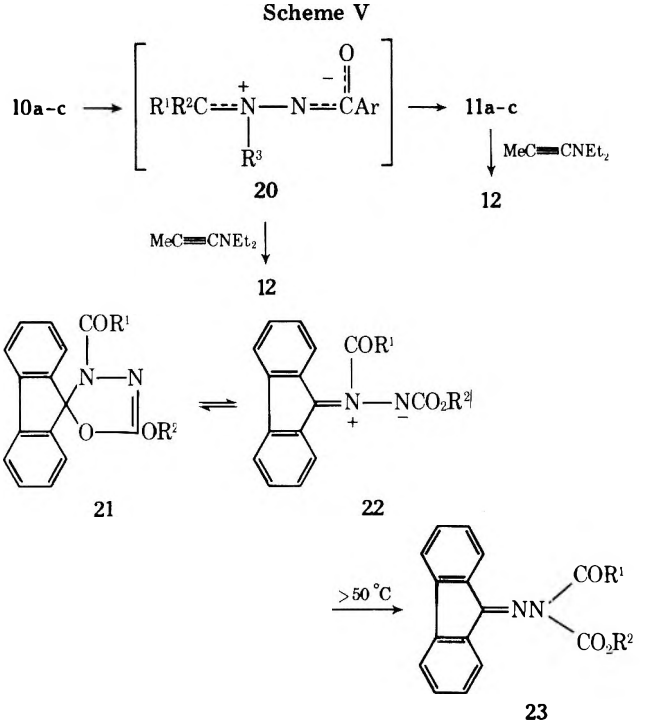


(1)

acyloxaziridines to 1,3,4-dioxazole derivatives and of 1-acylaziridines to Δ^2-oxazolines.[8a,b]

Two mechanisms may be suggested for the formation of the pyrazoline derivatives **12a,b** when **11a,b** reacts with 1-(*N,N*-diethylamino)propyne. One pathway involves an equilibrium between **11** and the azomethine imide **20**. Once formed **20** could undergo a cycloaddition with the ynamine (Scheme V). Such an equilibrium between the Δ^2-1,3,4-oxadiazoline **21** and the azomethine imide **22** has been proposed[9] to explain the rearrangement of **21** to **23** (Scheme V). An alternate reaction scheme for producing **12** is a nucleophilic attack of the ynamine on C-5 to **11** severing the carbon–oxygen bond to give a dipolar intermediate which then cyclizes to **12**.

Scheme V



The reactions of Δ^2-1,3,4-oxadiazolines with aldehydes and other electrophilic reagents are currently under investigation in our laboratories and will be reported at a later date.

It seems likely that the alternate synthesis of **14a** involving the reaction of *p*-nitrobenzaldehyde with a 1-*p*-nitrobenzoyl-2-alkylhydrazine also proceeds through the intermediacy of **20**. Thus Dorn and Otto[10] have isolated stable cyclic azomethine imides in 80–90% yields by condensing 3-pyrazolidones and carbonyl compounds and Oppolzer[11] has even isolated the precursor to an azomethine imide, namely, *N*-hydroxymethyl-*N*-methyl-*N'*-phenacetylhydrazine, when he treated *N*-methyl-*N'*-phenacetylhydrazine with formaldehyde.

Experimental Section

Materials. 1,3-Dimethyl-3-benzyldiaziridine,[12] 1-isopropyl-3,3-dimethyldiaziridine,[13] and 3,3-pentamethylene- and 1-methyl-3,3-pentamethylenediaziridines[14] were prepared according to known procedures.

Synthesis of 4',9'-Dihydrospiro[cyclohexane-1,1'(1*H*)-diazirino[1,2-*c*][3,4]benzodiazocine]-3',10'-dione (7). A solution of 4.62 g (20 mmol) of *o*-benzenediacetyl chloride[15] in 500 ml of dry Et_2O and a solution of 6.73 g (60 mmol) of 3,3-pentamethylenediaziridine in 500 ml of dry Et_2O were simultaneously added dropwise over 7.5 h to a stirred mixture of 10 g of anhydrous $MgSO_4$ in 2.5 l. of dry Et_2O at 5 °C. The reaction mixture was stirred for an additional 19 h and then filtered. Removal of the solvent left crude **7** which was recrystallized from anhydrous hexane (2.20 g, 41%), mp 108–109 °C. An analytical sample of **7** melted at 112–114 °C: NMR ($CDCl_3$) δ 7.25 (s, 4), 3.98 (s, 4), 1.70 (broad s, 10 H).

Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.07; H, 6.73; N, 10.54.

Synthesis of 3-(Cyclohexylideneamino)-1*H*-3-benzazepine-2,4(3*H*,5*H*)-dione (8). A solution of 132 mg of **7** in 10 ml of dry C_6H_6 was refluxed for 2.5 h. Evaporation of the solvent left 130 mg (98.5%) of **8**, mp 140–147 °C. **8** thrice recrystallized from petroleum ether (bp 110–115 °C) melted at 153–157 °C, molecular ion *m/e* 270.

Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.42; H, 6.97; N, 10.36.

Synthesis of 3-(1-cyclohexen-1-yl)-1,3,4,6-tetrahydro-3,4-benzodiazocine-2,5-dione (9). A mixture of 500 mg of **7** and 36 mg of triethylamine hydrochloride in 25 ml of dry C_6H_6 was refluxed for 3 h. The mixture was filtered and the solvent evaporated. The crude **9** (493 mg, 98%) was recrystallized from benzene–petroleum ether (bp 65–110 °C) and then from 95% ethanol, mp 212.5–214 °C.

Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.11; H, 6.90; N, 10.27.

Syntheses of 10a–c. To a stirred mixture of 5.5 mmol of triethylamine and 5 mmol of the appropriate diaziridine (1,3-dimethyl-3-benzyl-1-isopropyl-3,3-dimethyl- and 1-methyl-3,3-pentamethylenediaziridine) in 250 ml of dry Et_2O was added dropwise over a period of 15 min a solution of 4.9 mmol of *p*-nitrobenzoyl chloride in 50 ml of Et_2O. The mixture was stirred for 1 h and the triethylamine hydrochloride filtered. The solvent was concentrated to approximately 5 ml. The crude **10** was filtered and recrystallized. In this manner were obtained **10a** (85%), mp 102–104 °C; **10b** (90%), mp 78–81 °C; **10c** (69%), mp 90–91 °C. Ether was used to recrystallize **10a** and **10c** and cyclohexane was used to recrystallize **10b**.

10a. Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.59; H, 5.50; N 13.49. Found: C, 65.35; H, 5.68; N, 13.45.

10b. Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.06; H, 6.22; N 15.27. Found: C, 61.08; H, 6.25; N, 15.60.

10c. Anal. Calcd for $C_{13}H_{17}N_3O_3$: C, 59.29; H, 6.51; N 15.96. Found: C, 59.17; H, 6.53; N, 16.04.

Isomerization of 10a–c to 11a–c. A solution of 933 mg of **10a** in 25 ml of dry acetonitrile was stored in a desiccator for 24 h. The diaziridine dissolved very slowly. After several hours red crystals of **11a** precipitated and were filtered under dry nitrogen (**11a** hydrolyzes rapidly in air). The melting point (sealed melting point tube) was 120–122 °C. No yield was recorded; ir (Nujol) 1600, 1500, 1300, 1350, 854, 848 cm^{-1}; NMR ($CDCl_3$) δ 1.42 (s, 3, CCH_3), 2.81 (s, 3, NCH_3), 3.13 (s, 2, CH_2), 7.18 (s, 5, C_6H_5) 7.90 (AB q, 4, *p*-$O_2NC_6H_4$-).

Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.59; H, 5.50; N, 13.49. Found: C, 65.69; H, 5.65; N, 13.13.

In a similar fashion a solution of 825 mg of **10b** in 10 ml of CH_3CN isomerized to **11b** in almost quantitative yield. The crystals of **11b** were red and they melted from 85 to 97 °C. Compound **11b** could only be obtained by the complete evaporation of the solvent under a stream of dry nitrogen. **11b** was extremely sensitive to atmospheric moisture. The NMR spectra revealed that all of **10b** had isomerized to **11b**: molecular ion *m/e* 275; ir (Nujol) 1600, 1500, 848, 850 cm^{-1}; NMR ($CDCl_3$) δ 1.74 (broad s, 10, C_5H_{10}), 2.81 (s, 3 NCH_3), 7.96 (AB q, 4, *p*-$O_2NC_6H_4$-).

Compound 11c was prepared in a similar manner to **11b** except that CCl_4 was employed as the solvent and the reaction mixture was heated for 30 min. **11c** was also very rapidly hydrolyzed when exposed to the atmosphere. It melted at 83–85 °C: molecular ion *m/e* 263; ir (Nujol) 1600, 1500, 1360, 1320, 1225, 1100, 1040, 1025 cm^{-1}; NMR ($CDCl_3$) δ 1.28 [d, 6, $CH(CH_3)_2$], 1.55 [s, 6, $C(CH_3)_2$], 3.2 (m, 1, CH), 7.90 (AB q, 4, *p*-$O_2N_6H_4$-).

Preparation of 12a. To a solution of 1.24 g (4 mmol) of **11a** in 20 ml of dry $CHCl_3$ was added 0.44 g (4 mmol) of 1-(*N,N*-diethylamino)propyne. The mixture was kept in a desiccator for 24 h and then the solvent was evaporated. The residue was slurried with a small quantity of 95% ethanol and filtered. The crude **12a** (960 mg, 57%) was filtered and recrystallized from 95% ethanol. The yellow crystals of **12a** melted at 117–119 °C, molecular ion *m/e* 422.

Anal. Calcd for $C_{24}H_{30}N_4O_3$: C, 68.22; H, 7.15; N, 13.26. Found: C, 68.45; H, 7.06; N, 13.06.

Preparation of 12b. To a solution of 550 mg (2 mmol) of **10b** in 10 ml of dry $CHCl_3$ which had been stored in a desiccator for 3 h was added 220 mg of 1-(*N,N*-diethylamino)propyne. After the reaction mixture had stood for an additional 12 h the chloroform was removed by means of a stream of dry nitrogen. The crude **12b** was washed with 1 ml of cold ethanol and filtered to give 400 mg (52%) of crude **12b**, mp 85–91 °C. Recrystallization from 95% ethanol gave 310 mg of **12b**, mp 107.5–109 °C.

Anal. Calcd for $C_{21}H_{30}N_4O_3$: C, 65.25; H, 7.85; N, 14.49. Found: C, 65.62; H, 7.77; N, 14.52.

Conversion of 12a to 13a. To a solution of 350 mg (0.83 mmol) of **12a** in 50 ml of methanol was added 10 ml of 3 N hydrochloric acid. The reaction mixture was heated for 15 min and then neutralized with sodium hydroxide. The solvent was evaporated and the crude **13a** (230 mg, 0.63 mmol, 76%) was filtered. Recrystallization from acetone gave **13a**, mp 234.5–237 °C, molecular ion *m/e* 367.

Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.39; H, 5.76. Found: C, 65.47; H, 5.47.

Conversion of 11a to 14a. A solution of 933 mg (3 mmol) of **10a** in 30 ml of dry acetonitrile was stored in a desiccator overnight. During this time **10a** slowly dissolved and **11a** gradually precipitated. The solution was heated for 5 min to dissolve **11a** and 450 mg (3 mmol) of *p*-nitrobenzaldehyde added. The reaction mixture was kept in a desiccator overnight and then filtered. The crude **14a** (490 mg, 50%) was recrystallized from benzene and melted at 179–181 °C.

Anal. Calcd for $C_{15}H_{12}N_4O_5$: C, 54.85; H, 3.68; N, 17.06. Found: C, 54.85; H, 3.69; N, 16.81.

Alternate Preparation of 14a. In a 50-ml round-bottomed flask equipped with a reflux condenser and a Dean-Stark apparatus was placed a mixture of 390 mg (2.6 mmol) of *p*-nitrobenzaldehyde, 510 mg of 1-*p*-nitrobenzoyl-2-methylhydrazine, and 15 ml of benzene. The reaction mixture was refluxed for 3 h and then cooled. The crude **14a** (750 mg, 88%) was filtered and recrystallized from benzene. It melted at 177–180 °C and was identical in all respects with **14a** prepared by the reaction of **11a** with *p*-nitrobenzaldehyde.

Conversion of 11c to 14c. A tightly stoppered flask containing 262 mg (1 mmol) of **10c** in 5 ml of acetonitrile was kept in a desiccator for 2 days. To this solution was added 151 mg (1 mmol) of *p*-nitrobenzaldehyde and the reaction mixture was allowed to stand for an additional 24 h. The crude **14c** that precipitated during this time was filtered and the volume of the filtrate was concentrated to 2.5 ml and filtered again. The crude **14c** weighed 160 mg (45%) and melted at 146–148 °C. It was purified by partially evaporating the solvent under a stream of dry nitrogen and filtering. The **14a** so obtained melted at 154–156 °C, molecular ion *m/e* 356.

Alternate Preparation of 14c. A mixture of 223 mg (1 mmol) of 1-*p*-nitrobenzoyl-2-isopropylhydrazine, 151 mg (1 mmol) of *p*-nitrobenzaldehyde, and 10 ml of dry chloroform was refluxed overnight. The solvent was evaporated and the residue was slurried with 2 ml of dry ether and was filtered. The **14c** was purified as described above.

Conversion of 14a to 15a. A mixture of 3.28 g (10 mmol) of **14a** and 1.11 g (10 mmol) of 1-(*N,N*-diethylamino)propyne in 50 ml of dry $CHCl_3$ was stored in a desiccator for 12 h. The solvent was evaporated under a stream of dry nitrogen and the crude **15a** (4.24 g, 97%) was recrystallized thrice from absolute ethanol to give **15a**, mp 163–164 °C.

Anal. Calcd for $C_{22}H_{25}N_5O_5$: C, 60.11; H, 5.73; N, 15.93. Found: C, 59.69; H, 5.26; N, 16.15.

Hydrolysis of 11c to 16c. A mixture of 243 mg of **10c** in 10 ml of benzene was refluxed for 40 min during which time it was converted to **11c**. Evaporation of the solvent in the atmosphere gave 204 mg (0.915 mmol, 98%) of **16c**. Recrystallization of **16c** from benzene gave crystals melting at 140–141 °C.

Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.85; N, 18.82. Found: C, 53.55; H, 5.95; N, 18.60.

Alternate Synthesis of 16c. A mixture of 3 g (17 mmol) of *p*-nitrobenzoylhydrazide and 2.7 g (16 mmol) of 2-iodopropane in 20 ml of Me_2SO was kept in the dark for 48 h. After the addition of water (50 ml) the reaction mixture was saturated with sodium chloride and allowed to stand overnight. The precipitated hydriodide of **16c** was filtered and slurried with 50 ml of cold water and filtered again. The hydriodide of **16c** weighed 2.9 g (51%) and decomposed at 250 °C. The 2.9 g of **16c** was dissolved in 40 ml of absolute methanol to which 800 mg of triethylamine had been added. The mixture was stirred for 15 min and the methanol was evaporated. The residue was heated in benzene and the undissolved triethylamine hydriodide was filtered. Evaporation of the benzene gave 1.7 h (48%) of **16c**, mp 138–140 °C.

Synthesis of 16a. A solution of 202 mg (0.65 mmol) of **10a** in 15 ml of benzene was refluxed for 1 h. Evaporation of the solvent in the atmosphere caused rapid hydrolysis of **11a** to **16a** (126 mg, 100%). Crude **16a** melted at 140–141 °C but **16a** recrystallized from chloroform melted at 148.5–152 °C.

Anal. Calcd for $C_8H_9N_3O_3$: C, 49.22; H, 4.64; N, 21.53. Found: C, 49.10; H, 4.85; N, 21.51.

Acknowledgments. We are indebted to Professor Charles C. Sweeley of Michigan State University and Dr. William VandenHeuvel of Merck and Co. for the mass spectra of many of the compounds described in this paper. We thank Messrs. Andy Kofke and Robert Henrie for preliminary studies on compounds 7 and 8, and Dr. Kurt L. Loening for help on nomenclature. This work was supported by Grant CA 15880 from the National Cancer Institute.

Registry No.—**7,** 59811-77-7; 8, 59811-78-8; **9,** 59811-79-9; **10a,** 59811-80-2; **10b,** 59811-81-3; **10c,** 59811-82-4; **11a,** 59811-83-5; **11b,** 59811-84-6; **11c,** 59830-67-0; **12a,** 59811-85-7; **12b,** 59811-86-8; **13a,** 59811-87-9; **14a,** 59811-88-0; **14c,** 59811-89-1; **15a,** 59811-90-4; **16a,** 57676-56-9; **16c,** 59811-91-5; o-benzenediacetyl chloride, 21062-19-1; 3,3-pentamethylenediaziridine, 185-79-5; 1,3-dimethyl-3-benzyldiaziridine, 59872-19-4; 1-isopropyl-3,3-dimethyldiaziridine, 17119-93-6; 1-methyl-3,3-pentamethylenediaziridine, 26177-34-4; *p*-nitrobenzoyl chloride, 122-04-3; 1-(*N,N*-diethylamino)propyne, 4231-35-0; *p*-nitrobenzaldehyde, 555-16-8; *p*-nitrobenzoylhydrazide, 636-97-5; 2-iodopropane, 75-30-9.

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Heterocycles from *N*-Ethoxycarbonylthioamides and Dinucleophilic Reagents. 1. Dihydro-1,2,4-triazolones and 1,2,4-Oxadiazolones

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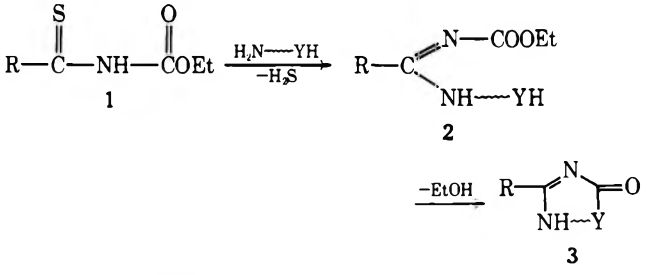
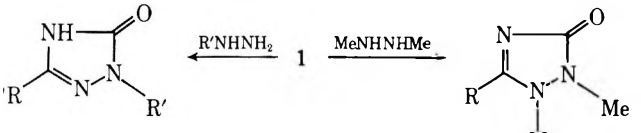
N-Ethoxycarbonylthioamides react with hydrazine or monosubstituted hydrazines to form 2,4-dihydro-3*H*-1,2,4-triazol-3-ones (**4–7**), and with 1,2-dimethylhydrazine to form 1,2-dimethyl-1,2-dihydro-3*H*-1,2,4-triazol-3-ones (**8**). Analogous reactions with hydroxylamine or *N*-methylhydroxylamine yield 1,2,4-oxadiazol-5(4*H*)-ones (**9**) or 2-methyl-1,2,4-oxadiazol-5(2*H*)-ones (**10**), respectively.

Through their condensation–cyclization reactions, alkoxycarbonyl isothiocyanates have proved valuable synthetic tools in heterocyclic chemistry.[1] The carbamates resulting from addition of alcohols or amines to ethoxycarbonyl isothiocyanate[2] and their *S*-methyl derivatives[3] have been found to undergo cyclization reactions with difunctional nucleophilic reagents. However, analogous reactions of the somewhat less easily accessible *N*-ethoxycarbonylthioamides (**1**) have not attracted attention. Treatment of **1** with primary or secondary amines results in elimination of H_2S and formation of *N'*-ethoxycarbonylamidines (**2**).[4] These compounds may be expected to undergo cyclization with loss of EtOH, if the amine used as reagent contains a suitably located, second nucleophilic group YH. The present paper describes such reactions of **1** leading to heterocycles **3** with 1,2,4-triazole and 1,2,4-oxadiazole ring systems.



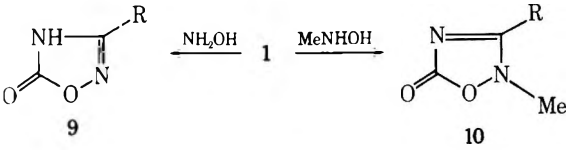
Treatment of an *N*-ethoxycarbonylthioamide (**1**) with hydrazine or a monosubstituted hydrazine causes evolution of H_2S and formation of a 2,4-dihydro-3*H*-1,2,4-triazol-3-one (**4–7**) in good to excellent yield (Tables I–IV). An analogous reaction with 1,2-dimethylhydrazine yields 1,2-dimethyl-1,2-dihydro-3*H*-1,2,4-triazol-3-ones (**8**) in moderate to good yields (Table V). Aqueous sodium hydroxide hydrolyzes carbamoyl derivatives **7** readily to the corresponding **4**.



4, R' = H
5, R' = Me
6, R' = Ph
7, R' = NH_2CO

There is considerable confusion in the literature concerning the location of the double bond in the dihydrotriazolone ring of compounds **4–6**. Some authors place it between positions 1 and 5, others between positions 4 and 5.[5] Structure **4** for the dihydro-1,2,4-triazolones obtained in this study is supported by appearance of the carbonyl band in their ir spectra at a considerably higher wavenumber (1700–1760 cm^{-1}) than for dimethyl derivatives **8** (1655–1660 cm^{-1}), in which the carbonyl group has to be conjugated with the double bond. With regard to monomethyl derivatives **5**, no firm conclusion can be drawn on the basis of the carbonyl band (1670–1690 cm^{-1}). However, the proposed structure is consistent with the close similarity between the uv spectra of **4** (maximum at 265–270 nm) and **5** (maximum at 270–275 nm) and their significant difference from those of the corresponding **8** (maximum at 235–260, shoulder at 275–280 nm). The possibility that derivatives **5** are 1-methyl-1,2-dihydro-3*H*-1,2,4-triazol-3-ones may be excluded, since compounds of such structure are known to exist in the enol form as 3-hydroxy-1,2,4-triazoles. Furthermore, the melting point (216.5–218.5 °C) of the product of the reaction of *N*-ethoxycarbonylthiobenzamide with methylhydrazine agrees well with that of 2-methyl-5-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (218–219 °C)[6] but differs considerably from that of 3-hydroxy-1-methyl-5-phenyl-1,2,4-triazole (195–196 °C)[5], both of which have been prepared by unambiguous routes. In the case of compounds **6** and **7**, the wavenumber of the carbonyl band (1685–1715 and 1700–1760 cm^{-1}, respectively) is again compatible with a structure containing an unconjugated carbonyl. These conclusions concerning the position of the C,N double bond in compounds **4–7** are in complete agreement with the findings of a recent, systematic study of the structure of 5-phenyldihydro-1,2,4-triazol-3-ones.[5]

N-Ethoxycarbonylthioamides (**1**) react similarly with hydroxylamine and *N*-methylhydroxylamine to form 1,2,4-oxadiazol-5(4*H*)-ones (**9**), in excellent yield, and 2-methyl-



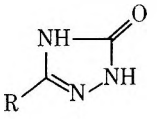
1,2,4-oxadiazol-5(2*H*)-ones (**10**), in moderate yield, respectively (Tables VI, VII). Comparison of the ir spectra of **9** with those of the corresponding **10**, in which there is conjugation between carbonyl and C,N double bond, shows that the carbonyl bands of the former appear at a higher wavenumber than those of the latter. Although the difference (10–45 cm^{-1}) is not always large, it is nonetheless consistent with lack of conjugation in **9**. There are no characteristic differences between the uv spectra of **9** and **10**.

The NMR spectra of the compounds prepared in this study are consistent with the proposed structures and exhibit signals in the ranges of δ 10–13 and 3–4 for NH and NCH_3 protons, respectively.

In all cases, the progress of the reaction is followed easily by testing for evolution of H_2S with lead acetate paper. Because of their simplicity, good yield, and straightforward product isolation, the investigated reactions provide a method of preparation of compounds **4–10** which compares favorably with other approaches to these heterocycles.[7]

With regard to the reaction pathway, it undoubtedly involves initial interaction of the thiocarbonyl of **1** with an amino group of the reagent similar to the earlier mentioned reactions

Table I.[a] 5-R-2,4-Dihydro-3*H*-1,2,4-triazol-3-ones

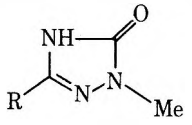


4

Registry no.	R	Yield,[b] %	Mp, °C	Ir, cm^{-1} C=O
939-07-1	C_6H_5	87	323–324 (dec)[c,d]	1750
3214-02-6	4-MeC_6H_4	97	384–386 (dec)[c,e]	1730
59812-14-5	4-EtC_6H_4	94	357–359 (dec)[c]	1700
59812-15-6	4-*i*-PrC_6H_4	98	367–369 (dec)[c]	1700
59812-16-7	4-*t*-BuC_6H_4	99	397–399 (dec)[c]	1700
33199-43-8	4-$MeOC_6H_4$	96	334–335 (dec)[c,f]	1740
59812-17-8	4-$EtOC_6H_4$	91	371–373 (dec)[c]	1720
33199-40-5	4-ClC_6H_4	93	>400[c,g]	1760, 1730
59812-18-9	2-Pyrrolyl	90	333–335 (dec)[h]	1720
27050-49-3	2-Thienyl	95	336–337 (dec)[c,i]	1730
59812-19-0	3-Indolyl	87	375–385 (dec)[c]	1740
931-37-3	Et	97	206–208 (dec)[j,k]	1740

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or partially purified product with melting point lower than that of the analytical sample by 2–5 °C. [c] Recrystallized from *n*-BuOH. [d] Lit. mp 321–322 °C: G. Young and E. Witham, *J. Chem. Soc.*, 224 (1900). [e] Lit. mp 372 °C: B.-G. Baccar and F. Mathis, *C. R. Acad. Sci.*, 261, 174 (1965). [f] Lit. mp 334 °C: ref 7a. [g] Lit. mp 410–412 °C: ref 7c. [h] Recrystallized from water. [i] Lit. mp 337 °C (dec): H. Gehlen, P. Demin, and K. H. Uteg, *Arch. Pharm. (Weinheim Ger.)*, **303**, 310 (1970). [j] Sublimed. [k] Lit. mp 204 °C (dec): C.-F. Kröger, L. Hummel, M. Mutscher, and H. Beyer, *Chem. Ber.*, 98, 3025 (1965).

Table II.[a] 5-R-2-Methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones

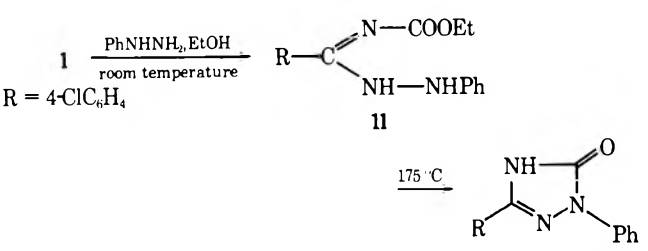


5

Registry no.	R	Yield,[b] %	Mp, °C	Ir, cm^{-1} C=O
54034-38-7	C_6H_5	71	216.5–218.5[c,d]	1675
59812-20-3	4-MeC_6H_4	74	251–252.5[e]	1680
59812-21-4	4-EtC_6H_4	70	196–197[c]	1680
59812-22-5	4-*i*-PrC_6H_4	69	204–206[f]	1680
59812-23-6	4-*t*-BuC_6H_4	77	244–246[f]	1690
59812-24-7	4-$MeOC_6H_4$	63	218–219.5[c]	1680
59812-25-8	4-$EtOC_6H_4$	69	217–219[e]	1680
59812-26-9	2-Pyrrolyl	63	263–264[e]	1670
59812-27-0	2-Thienyl	60	251–252[e]	1675
4114-22-1	Et	86	108–109[e,g]	1690

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or partially purified product with melting point lower than that of the analytical sample by 3–10 °C. [c] Recrystallized from EtOAc. [d] Lit. mp 218–219 °C: ref 6. [e] Recrystallized from EtOH. [f] Recrystallized from EtOH–H_2O. [g] Lit. mp 108–109 °C: C.-F Kröger, L. Hummel, M. Mutscher, and H. Beyer, *Chem. Ber.*, 98, 3025 (1965).

of **1** with simple amines.[4] This is supported by isolation of the expected intermediate **11** from the reaction of *N*-ethoxycarbonyl-4-chlorothiobenzamide with phenylhydrazine when an ethanolic solution of the reagents is allowed to stand at room temperature. The presence of the carbonyl band at 1670 cm^{-1} in the ir spectrum of **11** is indicative of an α,β-unsaturated carbonyl group. When this compound is heated at its melting point, ethanol is eliminated to form the corresponding dihydro-1,2,4-triazolone (**6**, R = 4-chlorophenyl).



Experimental Section[8]

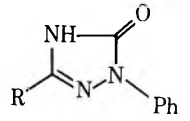
***N*-Ethoxycarbonylthioamides (1). A. Aromatic.** They were prepared by $AlCl_3$-catalyzed thioacylation of aromatic compounds with ethoxycarbonyl isothiocyanate.[9]

B. Heteroaromatic. The 2-pyrrolyl and 2-thienyl derivatives are known compounds.[4] ***N*-Ethoxycarbonyl-3-indolylthioamide.**[10] A mixture of 11.7 g (0.10 mol) of indole and 13.1 g (0.10 mol) of ethoxycarbonyl isothiocyanate was allowed to stand at room temperature for 48 h. The resulting dark-colored solid was crushed into a powder and washed with ice-cold ethyl acetate to give 14.3 g (59%) of crude product, mp 162–163 °C. Recrystallization from ethyl acetate gave the pure compound in the form of yellow crystals: mp 163–164 °C; ir 3250 (NH), 1720 cm^{-1} (C=O); NMR δ 1.3 (t, 3), 4.2 (q, 2), 7.1–7.7 (m, 3), 8.2–8.3 (m, 1), 8.4–8.7 (m, 1), 11.1 (s, 1), 12.1 (s, 1).

Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28. Found: C, 58.10; H, 4.91; N, 11.36.

C. Aliphatic. *N*-Ethoxycarbonylthiopropanamide. A solution of ethylmagnesium bromide was prepared under nitrogen by slow addition (1 h) of 24.0 g (0.22 mol) of ethyl bromide dissolved in 100 ml of ethyl ether to 4.80 g (0.20 mol) of magnesium turnings covered by 50 ml of ethyl ether.

Table III.[a] 5-R-2-Phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones

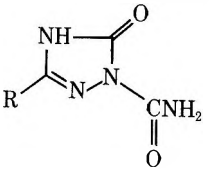


6

Registry no.	R	Yield,[b] %	Mp, °C	Ir, cm^{-1} C=O
3346-44-9	C_6H_5	94	232.5–233.5[c,d]	1700
3214-05-9	4-MeC_6H_4	88	267–268[c,e]	1715
59812-28-1	4-EtC_6H_4	98	249–250[c]	1705
59812-29-2	4-*i*-PrC_6H_4	97	236.5–238[c]	1700
59812-30-5	4-*t*-BuC_6H_4	93	287–288[c]	1685
59812-31-6	4-$MeOC_6H_4$	96	235–237[c]	1700
59812-32-7	4-$EtOC_6H_4$	93	239–240.5[c]	1705
27423-54-7	4-ClC_6H_4	73	283–284[c]	1700
59812-33-8	2-Pyrrolyl	91	237–238[f]	1700
19382-16-2	2-Thienyl	96	260–261	1680
59811-92-6	3-Indolyl	86	349–350 (dec)[g]	1710
28669-27-4	Et	60	121–122[f,h]	1700

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or partially purified product with melting point lower than that of the analytical sample by 2–5 °C. [c] Recrystallized from EtOH. [d] Lit. mp 229 °C: R. Fusco and C. Musante, *Gazz. Chim. Ital.*, 68, 147 (1938). [e] Lit. mp 264 °C: C. Gastaldi and E. Principalle, *ibid.*, 56, 557 (1926). [f] Recrystallized from EtOH–H_2O. [g] Recrystallized from *n*-BuOH. [h] Lit. mp 122–123 °C: ref 7b.

Table IV.[a] 5-R-2-Carbamoyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones

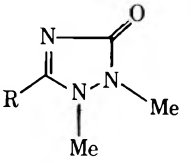


7

Registry no.	R	Yield,[b] %	Mp, °C	Ir, cm^{-1} C=O
59811-93-7	4-MeC_6H_4	98	329–330 (dec)[c]	1740 1700
59811-94-8	2-Pyrrolyl	95	325–327 (dec)[d]	1760, 1730, 1715

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for the compounds listed in this table. [b] Crude or partially purified product with melting point lower than that of the analytical sample by 2–5 °C. [c] Recrystallized from EtOH–H_2O. [d] Recrystallized from H_2O.

Table V.[a] 5-R-1,2-Dimethyl-1,2-dihydro-3*H*-1,2,4-triazol-3-ones



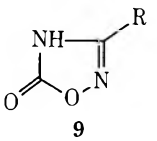
8

Registry no.	R	Yield,[b] %	Mp, °C	Ir, cm^{-1} C=O
50369-46-5	C_6H_5	42	241–243[c,d]	1660
59811-95-9	4-MeC_6H_4	60	214–215.5[c]	1660
59811-96-0	4-EtC_6H_4	65	226–227[c]	1660
59811-97-1	4-*i*-PrC_6H_4	61	225–227[c]	1660
59811-98-2	4-*t*-BuC_6H_4	57	213–214[e]	1660
59811-99-3	4-$MeOC_6H_4$	64	235–236.5[c]	1655
59812-00-9	4-$EtOC_6H_4$	60	210.5–212.5[c]	1655

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or partially purified product with melting point lower than that of the analytical sample by 2–5 °C. [c] Recrystallized from EtOH. [d] Lit. mp 255–256 °C: ref 5. [e] Recrystallized from EtOAc.

After the stirred solution had been cooled to −35 to −45 °C (dry ice–$CHCl_3$ bath), 23.6 g (0.18 mol) of ethoxycarbonyl isothiocyanate in 200 ml of ethyl ether was added slowly (1 h) while the temperature was kept at −35 to −45 °C. The reaction mixture was stirred for an additional 3 h at the same low temperature and then was allowed to warm up to room temperature. The precipitated salt was collected by filtration and washed with four 50-ml portions of ethyl ether. It was then mixed with 200 ml of ether and hydrolyzed with 200 ml of saturated aqueous ammonium chloride. Following separation of layers, the aqueous layer was extracted with two 50-ml portions of

Table VI.[a] 3-R-1,2,4-Oxadiazol-5(4*H*)-ones

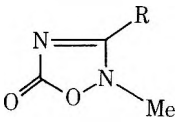


9

Registry no.	R	Yield,[b] %	Mp, °C	Ir, cm^{-1} C=O
1456-22-0	C_6H_5	96	202–203[c,d]	1755
31827-28-8	4-MeC_6H_4	98	221–222.5[c,e]	1760
59812-01-0	4-EtC_6H_4	85	190.5–192[c]	1770, 1730
59812-02-1	4-*i*-PrC_6H_4	98	197–198[c]	1775, 1735
59812-03-2	4-*t*-BuC_6H_4	98	234–236[c]	1775, 1735
59812-04-3	4-$MeOC_6H_4$	97	211–212[f]	1795 1730
59812-05-4	4-$EtOC_6H_4$	93	222.5–224[f]	1745
59812-06-5	2-Pyrrolyl	89	215–217 (dec)[g]	1760
35637-09-3	2-Thienyl	83	202–205.5[g]	1790 1725
59812-07-6	3-Indolyl	90	233–234 (dec)[h]	1800 1720
57689-63-1	Et	50	69–70.5[i,j]	1770

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or partially purified with melting point lower than that of the analytical sample by 2–5 °C. [c] Recrystallized from EtOH. [d] Lit. mp 198 °C: C. Musante, *Gazz. Chim. Ital.*, 68, 331 (1938). [e] Lit. mp 220 °C: L. H. Schubart, *Ber.*, 22, 2433 (1889). [f] Recrystallized from EtOH–H_2O. [g] Recrystallized from H_2O. [h] Recrystallized from *n*-BuOH. [i] Following removal of EtOH from the reaction mixture, the residue was extracted with Et_2O and the dried ($MgSO_4$) extract was evaporated to a new residue which was distilled under reduced pressure (bp 154–156 °C, 3 Torr). [j] Recrystallized from benzene–petroleum ether (bp 30–60 °C).

Table VII.[a] 3-R-2-Methyl-1,2,4-oxadiazol-5(2*H*)-ones



10

Registry no.	R	Yield,[b] %	Mp, °C	Ir, cm^{-1} C=O
59812-08-7	4-MeC_6H_4	34[c,d]	121.5–122.5[e]	1750
59812-09-8	4-$MeOC_6H_4$	50[d]	146–148[e]	1750
52531-61-0	4-ClC_6H_4	51[d]	168–170[f,g]	1750
59812-10-1	2-Pyrrolyl	50[c]	214–215[e]	1745

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or partially purified product with melting point lower than that of the analytical sample by 2–5 °C. [c] NaOAc used to free MeNHOH from its salt. [d] NaOMe used to free MeNHOH from its salt. [e] Recrystallized from H_2O. [f] Recrystallized from *i*-PrOH. [g] Lit. mp 168.5–170 °C: ref 7d.

ethyl ether and the combined ethereal solutions were dried over anhydrous magnesium sulfate. After removal of ether, the product was distilled at 3 Torr and the fraction boiling between 82 and 85 °C was collected. There was obtained 15.4 g (54%) of product as a yellow oil: ir 3400, 3300, 3200 (NH), 1760 cm^{-1} (C=O); NMR δ 1.0–1.4 (m, 6), 2.9 (q, 2), 4.1 (q, 2), 11.4 (s, 1).

Anal. Calcd for $C_6H_{11}NO_2S$: C, 44.70; H, 6.88; N, 8.69. Found: C, 44.54; H, 7.11; N, 8.64.

***N*-Ethoxycarbonylphenylthioacetamide.** This was obtained in 50% yield following the procedure used for preparation of the previous compound. Thus, benzylmagnesium chloride from 6.30 g (0.050 mol) of benzyl chloride and 1.20 g (0.050 mol) of magnesium was allowed to react with 5.90 g (0.045 mol) of ethoxycarbonyl isothiocyanate in a total of 100 ml of ether at −45 to −35 °C. The crude product (5.0 g, mp 39–42 °C) was recrystallized from petroleum ether (bp 35–60 °C) to give the pure compound as yellow crystals: mp 45–47 °C; ir 3400, 3300, 3180 (NH), 1760 cm^{-1} (C=O); NMR δ 1.2 (t, 3), 4.1 (q, 2), 4.2 (s, 2), 7.1 (s, 5), 11.8 (s, 1).

Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.32; H, 5.82; N, 6.32.

5-Substituted 2,4-Dihydro-3*H*-1,2,4-triazol-3-ones (4). To a solution of 0.010 mol of *N*-ethoxycarbonylthioamide in 20 ml of ethanol was added 0.020 mol of 95% hydrazine in 5 ml of ethanol. The reaction mixture was heated on a steam bath until evolution of hydrogen sulfide had ceased (10–30 min), then it was cooled and filtered to yield the product.

5-Substituted 2-Methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (5). Methylhydrazine (1.0 ml) was added to 0.0050 mol of *N*-ethoxycarbonylthioamide dissolved in 5 ml of tetrahydrofuran and the solution was refluxed for 15 min, then cooled and poured into icewater. The resulting mixture was neutralized with acetic acid and the precipitated solid was collected by filtration. (In the case of the 5-ethyl derivative, which is water soluble, equimolar amounts of reagents were used and the product was isolated by evaporation to dryness.)

5-Substituted 2-Phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (6). To 0.010 mol of *N*-ethoxycarbonylthioamide dissolved in 20 ml of ethanol was added 0.020 mol of phenylhydrazine in 5 ml of ethanol and the solution was refluxed until evolution of hydrogen sulfide had ceased (2–6 h). After the mixture had been cooled, any solid product was collected by filtration. The filtrate was concentrated to a small volume and chilled or mixed with ice to yield a new precipitate which was combined with the first one.

***N'*-Ethoxycarbonyl-*N*-phenylamino-4-chlorobenzamidine (11).** A mixture of 1.1 g (0.0050 mol) of *N*-ethoxycarbonyl-4-chlorothiobenzamide, 25 ml of 95% ethanol, and 1.1 g (0.010 mol) of phenylhydrazine was let stand at room temperature for 12 h. The precipitated material was collected by filtration and washed with ice-cold ethanol to yield 1.0 g (63%) of pure **11** as white crystals: mp 171 °C (partial melting followed by solidification and further melting at 283–284 °C; recrystallization from ethanol did not change the melting behavior); ir 3340, 3280 (NH), 1670 cm^{-1} (C=O); NMR δ 1.2 (t, 3), 4.0 (q, 2), 6.5–7.5 (m, 9), 8.8 (s, 1), 9.4 (s, 1).

Anal. Calcd for $C_{16}H_{16}N_3O_2Cl$: C, 60.47; H, 5.08; N, 13.22. Found: C, 60.67; H, 5.15; N, 13.22.

Conversion of 11 into 2-Phenyl-5-(4-chlorophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one. Compound **11** (0.20 g) was heated in an oil bath at 170–180 °C for 5 min. After it had been cooled and recrystallized from ethanol, the product was identified as 2-phenyl-5-(4-chlorophenyl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one on the basis of its melting point, as well as its ir and NMR spectra.

5-Substituted 2-Carbamoyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones (7). To 0.010 mol of *N*-ethoxycarbonylthioamide dissolved in 15 ml of ethanol was added a solution of 0.020 mol of semicarbazide hydrochloride and 0.020 mol of sodium acetate in 10 ml of aqueous ethanol and the resulting mixture was stirred magnetically until completion of hydrogen sulfide evolution (15–24 h). The precipitated product was collected by filtration and combined with a new precipitate formed when the filtrate had been concentrated to a small volume and mixed with ice.

Hydrolysis of 7 into 4. A mixture of 0.40 g of **7** and 10 ml of 10% aqueous sodium hydroxide was boiled for 10 min and the resulting solution was neutralized with dilute hydrochloric acid to yield a precipitate which was collected by filtration and washed with cold water. The products, obtained in 75% yield, were identified by their melting points, as well as their ir and NMR spectra.

5-Substituted 1,2-Dimethyl-1,2-dihydro-3*H*-1,2,4-triazol-3-ones (8). A mixture of 0.0050 mol of 1,2-dimethylhydrazine dihydrochloride, 0.010 mol of sodium methoxide, 0.0050 mol of *N*-ethoxycarbonylthioamide, and 5 ml of methanol was refluxed for 1 h. The resulting mixture was cooled and treated with a slight excess of 10% aqueous sodium hydroxide to yield a solid product which was collected by filtration and washed with a little ice-cold water.

3-Substituted 1,2,4-Oxadiazol-5(4*H*)-ones (9). A mixture of 0.010 mol of *N*-ethoxycarbonylthioamide, 0.020 mol of hydroxylamine hydrochloride, 0.020 mol of sodium acetate trihydrate, and 20 ml of aqueous ethanol was refluxed until evolution of hydrogen sulfide had ceased (2–3 h). The resulting solution was concentrated to a small volume and mixed with ice to form a precipitate which was collected by filtration.

3-Substituted 2-Methyl-1,2,4-oxadiazol-5(2*H*)-ones (10). To a solution of 0.010 mol of *N*-ethoxycarbonylthioamide in 10 ml of ethanol was added 0.010 mol of *N*-methylhydroxylamine hydro-

chloride and 0.010 mol of sodium acetate dissolved in aqueous ethanol. The resulting solution was refluxed until evolution of hydrogen sulfide had ceased (1–2 h). In some cases (indicated in Table VII), sodium methoxide was used instead of sodium acetate. Then the reaction was carried out in 10 ml of methanol and the mixture was stirred magnetically (22–24 h).

Acknowledgments. Financial support by the Research Corporation, the Research Allocations Committee of the University of New Mexico, and the Department of Chemistry of the University of New Mexico is gratefully acknowledged.

Registry No.—1 (R = 3-indolyl), 59812-11-2; 1 (R = Et), 59812-12-3; 1 (r , ph), 5499-31-0; 11 (R = 4-ClC_6H_4), 59812-13-4; indole, 120-72-9; ethoxycarbonyl isothiocyanate, 16182-04-0; ethyl bromide, 74-96-4; benzyl chloride, 100-44-7; methylhydrazine, 60-34-4; phenylhydrazine, 100-63-0; *N*-ethoxycarbonyl-4-chlorothiobenzamide, 57774-74-0; semicarbazide HCl, 563-41-7; 1,2-dimethylhydrazine 2HCl, 306-37-6; hydroxylamine HCl, 7803-49-8; *N*-methylhydroxylamine HCl, 4229-44-1.

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(8) Melting points lower than 300 °C were determined in a Thomas-Hoover apparatus, and those higher than 300 °C by use of a heated metal block; all are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 337 spectrophotometer using mineral oil mulls. NMR spectra were obtained on a Varian EM360 spectrophotometer using solutions in Me_2SO-d_6 or in Me_2SO-d_6 + CF_3COOD with tetramethylsilane as internal standard. Ultraviolet spectra were recorded in a Perkin-Elmer 402 spectrophotometer using solutions in 95% ethanol.
(9) E. P. Papadopoulos, *J. Org. Chem.*, **41**, 962 (1976).
(10) Originally prepared and characterized by S. A. Brueggemann, Department of Chemistry, University of New Mexico.

Nitrones and Nitroxides Derived from Oxazolines and Dihydrooxazines[1]

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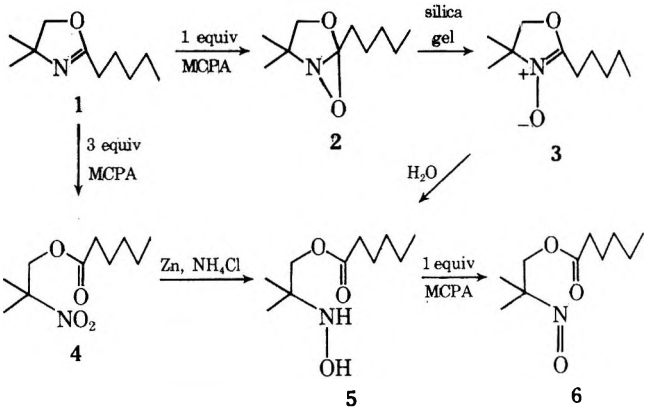
A new synthetic route to several doxyl nitroxides **14** and two tetrahydro-1,3-oxazine nitroxides **26** and **27** is described. Oxidation of the representative oxazoline **1** with 1 equiv of MCPA gave oxaziridine **2**. Excess MCPA led to nitro ester **4** and nitroso ester **6**. Isomerization of **2** on silica gel afforded nitrone **3**, reaction of which with moisture produced ester **5**. Analogous reactions applied to dihydrooxazine **7** led to oxaziridine **8**, nitroso ester **10**, nitro ester **11**, nitrone **9**, and ester **12**. Treatment of **3** with a series of organometallic reagents followed by Cu^{2+}-catalyzed air oxidation of the intermediate **13** led to doxyl nitroxides. In contrast, reaction of **3** with vinylmagnesium bromide or vinyllithium at 25 °C gave dienes **19** and **21**. With excess 1-lithio-1-hexyne at −15 °C, nitrone **3** gave open-chain nitrone **22**. Allylmagnesium bromide and **3** at 25 °C followed by oxidation gave nitroxide **23**. Analogous reactions at 25 °C of nitrone **9** with methyllithium and butyllithium afforded the nitroxides **26** and **27**.

Doxyl (4,4-dimethyloxazolidine-*N*-oxyl) nitroxide spin labels[3] have played an important role in studies of biological systems using the spin labeling technique.[4] Alternative, flexible synthetic entries to new stable nitroxides are central to continued progress in the spin labeling field. We recently communicated a new procedure for assembling doxyl nitroxides which bypasses the usual ketone precursors and which permits the synthesis of doxyl nitroxides having unsaturation in the doxyl chains (**1** → **3** → **14**).[1] This procedure takes advantage of the wide variety of oxazolines made available through the elegant work of Meyers.[5,6,7] We now present experimental details relating to our new doxyl synthesis, starting with the representative oxazoline **1**. We also describe for the first time analogous reactions of dihydrooxazine **7** and its conversion into a second series of stable nitroxide free radicals.[17]

Results and Discussion

The addition of an organometallic reagent to the requisite nitrone constitutes the key step in the new doxyl synthesis.[8] Since the nitrones are derived from the corresponding oxazoline or dihydrooxazine, we have investigated the oxidation of these latter substances in some detail.[9] Thus, oxidation of oxazoline **1** with 1 equiv of *m*-chloroperoxybenzoic acid (MCPA) in ether at −10 °C produced oxaziridine **2** (~95%) (Chart I). Small amounts of blue nitroso ester **6** could be observed visually and by NMR in samples of crude **2**, although

Chart I

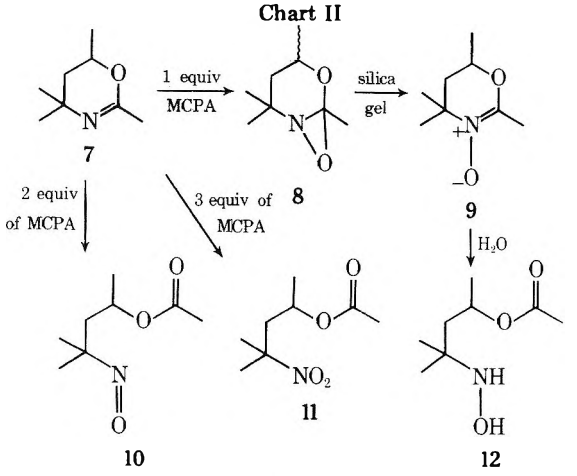


reaction of **1** with 2 equiv of MCPA still gave mostly **2** with minor amounts of **6** and nitro ester **4**. Prolonged reaction of **1** with 3 equiv of MCPA gave a good yield of nitro ester **4**. In order to confirm the identity of compounds **4** and **6**, nitro ester **4** was synthesized by acylation of the corresponding alcohol with hexanoic acid and then reduced with zinc and NH_4Cl to *N*-hydroxy ester **5**. Reaction of **5** with 1 equiv of MCPA gave blue nitroso ester **6** in good yield. Structure assignments throughout this paper are based on the highly characteristic NMR spectra together with other analytical data found in the Experimental Section.

Initial attempts to prepare nitrone **3** were patterned after Padwa's isomerization of certain oxaziridines into nitrones in acetonitrile at 80 °C.[10] Under these conditions, oxaziridine **2** afforded a mixture which was shown by its NMR spectrum to consist of nitrone **3** (8%), nitro ester **6** (31%), nitro ester **4** (11%), oxazoline **1** (48%), and *N*-hydroxy ester **5** (3%). Fortunately, during an attempted purification of oxaziridine **2**, it was discovered that chromatography over silica gel effected smooth isomerization of **2** to the desired nitrone **3**.

The oxidation of dihydrooxazine **7** (Chart II) with 1 equiv of MCPA in ether afforded oxaziridine **8** in good yield. When 2 equiv of MCPA was used, nitroso ester **10** was the major

Chart II

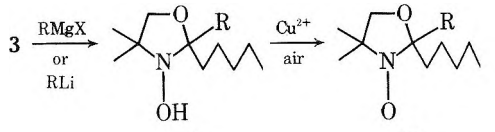


7 8 9 10 11 12

product while 3 equiv of MCPA led in good yield to nitro ester **11**. Oxaziridine **8**, like its five-membered ring counterpart **2**, also underwent smooth isomerization to its corresponding nitrone **9**.

Nitrones **3** and **9** were quite hygroscopic. Nitrone **9** was obtained from the silica gel column as a white, crystalline solid which quickly melted on exposure to air. The NMR spectrum invariably contained peaks attributed to *N*-hydroxy ester **12**. When samples were carefully protected from moisture, nitrones **3** and **9** could be isolated with only trace amounts of the corresponding *N*-hydroxy ester derivatives **5** and **12**. Oxaziridines **2** and **8**, however, may be conveniently stored at −20 °C for months without evidence of decomposition. Thus, the starting nitrones for the reactions described below were always freshly prepared from the oxaziridine immediately prior to use.

The reaction of nitrone **3** with a two- to threefold excess of organometallic reagent in ether solution at reduced temperatures afforded, after cold aqueous workup, the corresponding *N*-hydroxyoxazolidine **13** (eq 1). The crude mixture was immediately taken up in methanol containing a trace of $Cu(OAc)_2 \cdot H_2O$[11] and stirred under air in order to form the corresponding doxyl nitroxides **14**. Several doxyl nitroxides



(1)

13 14

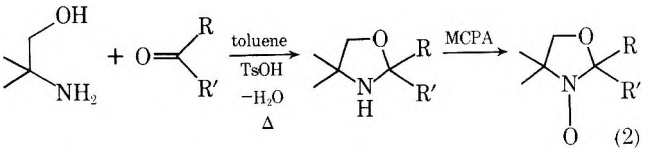
prepared in this way are summarized in Table I. In those instances where the doxyl nitroxide may also be prepared from the requisite ketone utilizing our earlier method (eq 2),[3] the yields by this present nitrone procedure are comparable. The nitrone procedure can afford at times two major advantages, however: (a) the synthesis does not depend on the availability of the requisite ketone and (b) addition to the nitrone produces the easily oxidized *N*-hydroxy amine intermediate.

Table I. Doxyl Nitroxides Prepared from Nitrone 3

Doxyl derivative **14**	Organometallic reagent	Temp, °C	Rxn time	Yield,[c] %
R = CH_3[a]	CH_3Li	25	1 h	43
R = CH_3CH_2[b]	CH_3CH_2MgBr	−15	5 min	27[d]
R = $CH_3(CH_2)_6$[b]	$CH_3(CH_2)_6MgBr$	−15	5 min	27[d]
R = CH_2=CH	CH_2=CHLi	−78	2 h	29[d]

[a] Identical by ir with a sample prepared by our earlier method.[3] [b] All doxyl derivatives showed the expected mass spectral fragmentation patterns[12] and each showed the typical three-line nitroxide ESR spectrum. [c] Isolated yield, based on starting nitrone. [d] Analytical sample obtained by preparative VPC on a 2-ft 5% SE-30/Firebrick column.

Thus doxyls may be prepared which contain functional groups sensitive to MCPA (e.g., entry 4, Table I).



(2)

Interestingly, the course of the reaction between the nitrones and the organometallic reagents depended markedly on the reaction temperature and on the structure of the organometallic reagent. In general, when the organometallic reagent was added to the nitrone at −78 °C and then the mixture was allowed to warm to 25 °C, workup afforded significant quantities of recovered nitrone and its hydrolysis product. Thus, at lower temperatures the organometallic reagents tended to act as bases, generating the inert (to addition) anion of the nitrone. Quite possibly, this side reaction could be used to advantage through alkylation reactions, for example.

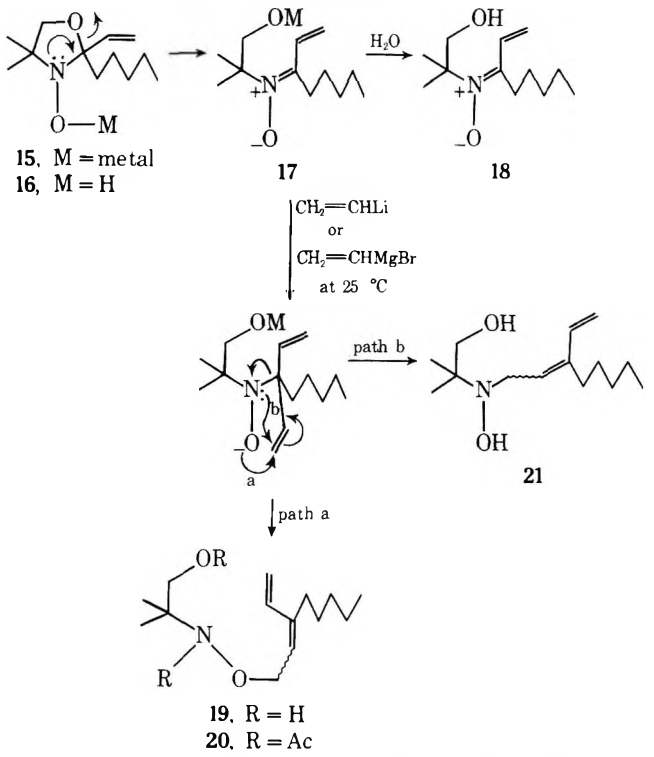
A second pronounced effect of temperature was observed in reactions between nitrone **3** and organometallic reagents containing unsaturation near the metal atom. With temperatures in excess of −15 °C, the intermediate *N*-hydroxyoxazolidine (as the metal salt) apparently was capable of undergoing a ring-opening isomerization reaction in the reaction medium to give the corresponding open-chain nitrone (**15** → **17**). This latter substance in certain instances suffered addition of a second equivalent of organometallic reagent, leading to a new branched chain nitroxide after oxidation (**3** → **23**). These reactions are illustrated by the following examples.

Reaction (Chart III) of nitrone **3** with vinyllithium at −78 °C followed by a cold aqueous workup afforded *N*-hydroxyoxazolidine **16**, uncontaminated by its ring-opened isomer **18** (by NMR). While a quite pure sample of **16** could be obtained by rapid chromatography over alumina, chromatography over silica gel invariably afforded a mixture of **16** and **18**, in which the latter predominated. It was also not possible to prepare a sample of **18**, free of **16**.

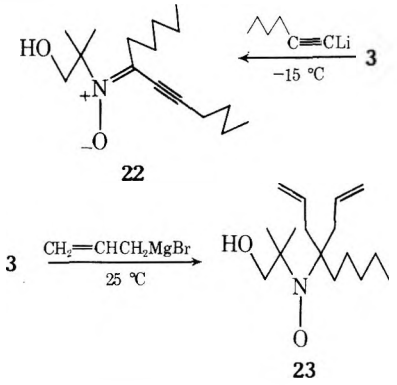
The addition of vinyllithium or vinylmagnesium bromide to **3** at 25 °C gave two stable products which were isolated by column chromatography and were tentatively assigned the interesting structures **19** and **21** based on their spectral properties and the observation that the predominant product **19** afforded an *O,N*-diacetyl derivative **20** upon treatment with acetic anhydride in pyridine. Alcohols **19** and **21** were likely formed by the route outlined in Chart III.

The reaction of two other unsaturated organometallic reagents with nitrone **3** with briefly investigated. Treatment of nitrone **3** with excess 1-lithio-1-hexyne at −15 °C gave open-chain nitrone **22** in 13% yield, while at −78 °C, starting **3** was recovered unchanged. The reaction of excess allylmagnesium

Chart III



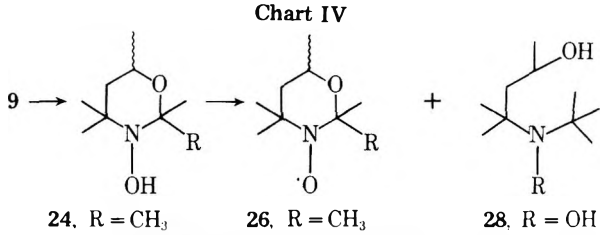
bromide with **3** at 25 °C followed by air oxidation gave nitroxide **23** in 20% yield.



In general, the *N*-hydroxyoxazolidines produced by the addition (>−15 °C) of saturated alkyl groups to nitrone **2** showed much less tendency toward isomerization to the corresponding open-chain nitrones. Indeed, the best yield (43%) of **14** (R = CH_3) was obtained when the reaction was done at 25 °C. The product resulting from the addition of 2 mol of methyllithium was not detected. Even so, with the higher homologues, minor absorptions attributed to the open-chain nitrones could be observed in the NMR spectra of the crude *N*-hydroxyoxazolidines obtained from reactions done at 25 °C.

Several reactions of the six-membered ring nitrone **9** with organometallic reagents have also been examined. Reactions involving Grignard reagents gave complex mixtures of products. The reaction (Chart IV) of **9** with methyllithium at 25

Chart IV



°C for 1 h followed by $Cu(OAc)_2 \cdot H_2O$-catalyzed air oxidation gave, in addition to nitroxide **26**, some nitroxide **29** resulting from the addition of 2 mol of methyllithium. Comparison of the NMR spectrum of the crude product mixture after workup of the methyllithium addition with the NMR spectra of *N*-hydroxy compounds **24** and **28** obtained via reduction of the corresponding nitroxides with phenylhydrazine[13] indicated a relatively clean mixture of **24** and **28**. Much **26** was lost during isolation owing to its volatility. Nitroxide **27** was similarly prepared in 18% yield using butyllithium. As in earlier experiments, the objective was the preparation of the nitroxide and while several minor products were formed they were not isolated or characterized. None of the nitroxide resulting from the addition of 2 mol of the reagent was detected in the butyllithium reaction.

Nitroxides **26** and **27** are members of a recently described[17] class of stable nitroxides which possess a tetrahydrooxazine ring system. Such nitroxides may prove useful in spin labeling studies though at present their overall synthesis starting from dihydrooxazine **7** is not as convenient as the five-membered ring doxyl synthesis herein described, and the presence of the ring methyl group leads to pesky isomer possibilities.

Experimental Section[14]

2-Pentyl-4,4-dimethyloxazoline 2,3-Oxide (2). To a solution of 1.69 g (10.0 mmol) of oxazoline 1[15] in 20 ml of dry ether at −10 °C was added dropwise with stirring under N_2 a solution of 2.03 g (10.0 mmol) of 85% MCPA dissolved in 30 ml of ether. After standing at 8 °C for 48 h the solution was washed well with aqueous 10% Na_2CO_3 and dried over K_2CO_3. Evaporation of the solvent gave 1.67 g (99%) of crude (94% by NMR) oxaziridine **2** as a pale blue oil: NMR δ 1.13 (3 H, s, *gem*-Me), 1.36 (3 H, s, *gem*-Me), 2.1 (2 H, m, α-CH_2), 3.46 [1 H, d (*J* = 8 Hz), CH_2O], 3.61 [1 H, d (*J* = 8 Hz), CH_2O]; mass spectrum *m/e* (rel intensity) 185 (3), 184 (7), 170 (3), 156 (11), 142 (31), 129 (100), 114 (10), 99 (20), 71 (12), 56 (36), 43 (38), 41 (18). Crude **2** was used for subsequent reactions.

2-Nitro-2-methylpropyl Hexanoate (4). A. From 1. To a solution of 169 mg (1.00 mmol) of **1** in 5 ml of ether at 0 °C was added a solution of 608 mg (3.00 mmol) of 85% MCPA dissolved in 3 ml of ether. After standing for 6 days at 8 °C the colorless solution was washed well with aqueous 10% Na_2CO_3 and brine and then dried over K_2CO_3. Evaporation of the solvent gave 206 mg (95%) of a yellow oil which was ~78% nitro ester **4** by NMR. The analytical specimen was obtained as an oil by preparative VPC: NMR δ 1.61 (6 H, s, *gem*-Me), 2.33 [2 H, t (*J* = 7 Hz), α-CH_2], 4.41 (2 H, s, CH_2O); ir 1745, 1550 cm^{-1}. Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.56; H, 8.82; N, 6.18.

B. From 2-Nitro-2-methylpropanol. A mixture of 2.38 g (20 mmol) of 2-nitro-2-methylpropanol, 1.162 g (10 mmol) of hexanoic acid, and 50 mg of $TsOH \cdot H_2O$ in 50 ml of benzene was brought to reflux for 24 h, water being collected in a Dean-Stark trap containing K_2CO_3. The benzene solution was washed with water, aqueous saturated $NaHCO_3$, and brine and then dried over K_2CO_3. Evaporation of the solvent and distillation of the yellow residue gave 1.215 g (61%) of **4**, bp 85–87 °C (0.06 mm).

2-(Hydroxyamino)-2-methylpropyl Hexanoate (5). A solution of 464 mg (2.14 mmol) of **4** and 114 mg (2.14 mmol) of NH_4Cl in 20 ml of H_2O was cooled to <10 °C in an ice bath. To the stirred solution was added 688 mg (10.7 mmol) of powdered zinc. After stirring for 4 h at <15 °C, the mixture was filtered and the zinc cake was washed with methanol. The solution was concentrated and extracted with several portions of ether. The ether solution was dried over K_2CO_3 and evaporated to yield a blue oil, chromatography of which gave 120 mg (28%) of *N*-hydroxy ester **5** as a colorless oil: NMR δ 1.10 (6 H, s, *gem*-Me), 2.37 [2 H, t (*J* = 7 Hz), α-CH_2], 4.07 (2 H, s, CH_2O); ir 3280 (OH), 1735 cm^{-1} (ester); mass spectrum *m/e* (rel intensity) 203.153 (2) (calcd for $C_{10}H_{21}NO_3$, 203.152), 172 (27), 99 (26), 74 (100), 71 (19), 58 (39), 56 (26), 55 (12), 43 (22), 42 (18), 41 (16).

2-Nitroso-2-methylpropyl Hexanoate (6). To a solution of 17.2 mg (0.085 mmol) of *N*-hydroxy ester **5** in 3 ml of ether at 0 °C was added dropwise with stirring under N_2 a solution of 17.2 mg (0.085 mmol) of 85% MCPA dissolved in 1.0 ml of ether. After 10 min, the solution was diluted with ether and washed several times with aqueous 10% Na_2CO_3 and brine. Evaporation of the solvent gave a blue oil which was chromatographed on a silica gel column to yield 13.1 mg (77%) of purified **6**. An analytical sample of **6** as a dark blue oil was

prepared by preparative VPC: NMR δ 1.13 (6 H, s, *gem*-Me), 2.22 [2 H, t (J = 7 Hz), α-CH_2], 4.80 (2 H, s, CH_2O); ir 1745 (ester), 1567 cm^{-1} (N–O). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.85; H, 9.66; N, 6.69.

2,4,4,6-Tetramethyl-5,6-dihydro-1,3-oxazine 2,3-Oxide (8). To a solution of 821 mg (5.82 mmol) of 7[16] in 20 ml of dry ether at −23 °C under N_2 was added with stirring dropwise over 20 min a solution of 1.18 g (5.82 mmol) of 85% MCPA dissolved in 20 ml of ether. The bath was allowed to warm to −10 °C and then aqueous 10% Na_2CO_3 was added. The ether layer was separated, washed with chilled aqueous 10% Na_2CO_3, and dried over K_2CO_3. Evaporation of the solvent gave 570 mg (64%) of the crude (84% by NMR) oxaziridine 8 as a blue oil (some loss due to volatility): NMR δ 1.26 (6 H, s, *gem*-Me), 1.17 [3 H, d (J = 6 Hz), Me at C_6], 1.65 (3 H, s, Me at C_2), 4.05 (1 H, m, H at C_6). Crude 8 was used for subsequent reactions.

2-Nitroso-2-methyl-4-acetoxypentane (10) and Dimer. To a solution of 119 mg (0.84 mmol) of 7 in 2 ml of dry ether at 0 °C was added dropwise over 15 min with stirring under N_2 a solution of 341.2 mg (1.68 mmol) of 85% MCPA dissolved in 3 ml of ether. The solution was allowed to warm to 25 °C and was stirred for 5 h, after which the ether solution was washed with four portions of aqueous 10% Na_2CO_3 and then with brine. Evaporation of the solvent and chromatography on silica gel yielded 115 mg (79%) of nitrosc ester 10 as a dark blue oil. Upon standing at −20 °C, colorless crystals of the dimer separated out. These were washed with cold CCl_4 and sublimed (50 °C, 0.025 mm) to obtain the analytical specimen: mp 65–67 °C; NMR δ 1.57 (6 H, s, *gem*-Me), 1.22 [3 H, d (J = 6 Hz)], 2.02 (3 H, s, acetyl), 4.95 (1 H, m, methine H). Anal. Calcd for $C_{16}H_{30}N_2O_6$: C, 55.47; H, 8.73; N, 8.09. Found: 55.26; H, 8.76; N, 7.93.

Complete dissociation to the blue monomer occurred in $CDCl_3$ in 1 h: NMR (monomer) δ 1.06 (3 H, s, *gem*-Me), 1.13 (3 H, s, *gem*-Me), 1.21 [3 H, d (J = 6 Hz)], 1.87 (3 H, s, acetyl), 4.94 (1 H, m, methine H); ir (CCl_4) 1745 (ester), 1565 cm^{-1} (N–O).

2-Nitro-2-methyl-4-acetoxypentane (11). To a solution of 238 mg (1.68 mmol) of 7 in 10 ml of ether was added at 25 °C a solution of 1.01 mg (5.00 mmol) of 85% MCPA dissolved in 10 ml of ether. After standing for 12 h the ether solution was washed well with aqueous 10% Na_2CO_3 and dried over K_2CO_3. Evaporation gave 200 mg (64%) of 11 as a pale yellow oil. The analytical specimen was obtained by preparative VPC: NMR δ 1.58 (6 H, s, *gem*-Me), 1.23 [3 H, d (J = 6 Hz)], 1.96 (3 H, s, acetyl), 5.09 (1 H, m, methine H); ir (CCl_4) 1750 (ester), 1555 cm^{-1} (nitro); mass spectrum (30 eV) m/e (rel intensity) 189.102 (0.02) (calcd for $C_8H_{15}NO_4$, 189.100), 174 (1), 143 (3), 129 (4), 118 (4), 99 (5), 83 (53), 56 (11), 55 (24), 43 (100), 41 (29).

General Procedure for Isomerization of Oxaziridines 2 and 8. A solution of ~150 mg of crude oxaziridine in 2 ml of $CHCl_3$ was placed on top of a dry silica gel column (1.5 × 10 cm). After standing for 30 min, the column was successively eluted with 20 ml of $CHCl_3$, 20 ml of acetone, and finally 15 ml of methanol. Evaporation of the methanol at 20 °C afforded the nitrone (>85%).

2-Pentyl-4,4-dimethyloxazoline *N*-oxide (3) was obtained as a pale yellow oil: NMR δ 1.50 (6 H, s, *gem*-Me), 2.62 [2 H, t (J = 7 Hz), α-CH_2], 4.29 (1 H, s, CH_2O); uv (EtOH) 244 nm (ε 4540); mass spectrum m/e (rel intensity) 185.139 (3) (calcd for $C_{10}H_{19}NO_2$, 185.142), 172 (9), 154 (25), 126 (29), 113 (100), 99 (35), 74 (45), 58 (62), 43 (43).

2,4,4,6-Tetramethyl-5,6-dihydro-1,3-oxazine *N*-oxide (9) was obtained as low-melting white crystals: NMR δ 1.51 (6 H, s, *gem*-Me), 1.38 [3 H, d (J = 6 Hz)], 2.25 (3 H, s, Me at C_2), 4.63 (1 H, m, methine H); mass spectrum m/e (rel intensity) 157.111 (13) (calcd for $C_8H_{15}NO_2$, 157.110), 141 (9), 115 (40), 100 (81), 83 (53), 74 (52), 73 (34), 58 (23), 56 (20), 55 (16), 43 (100).

Usually evident in samples of 9 by NMR was a small contaminant of *N*-hydroxy ester 12: NMR δ 1.09 (6 H, s, *gem*-Me), 1.25 [3 H, d (J = 6 Hz)], 2.03 (3 H, s, Me at C_2), 5.12 (1 H, m, methine H); ir (CCl_4) 3280 (OH), 1740 cm^{-1} (ester).

2-Pentyl-2,4,4-trimethyloxazolidine-*N*-oxyl (14, R = CH_3). To a solution of 150 mg (0.800 mmol) of freshly prepared nitrone 3 in 5 ml of dry ether at 25 °C with stirring under N_2 was added 3 equiv of 2 M methylmagnesium iodide in ether. After 1 h, aqueous saturated NH_4Cl was added, the ether layer was separated, and the residue was washed thoroughly with fresh ether. Evaporation of the combined ether solutions afforded crude *N*-hydroxyoxazolidine 13 (R = CH_3), which was taken up in 10 ml of methanol containing ~2 mg of $Cu(OAc)_2 \cdot H_2O$ and stirred under air for 30 min at 25 °C. Evaporation of the solvent and column chromatography on silica gel afforded the nitroxide (14 R = CH_3). The pure specimen was obtained by preparative VPC and its infrared spectrum was identical with that of 14 (R = CH_3) prepared by our earlier method.[3]

2-Pentyl-2-ethyl-4,4-dimethyloxazolidine-*N*-oxyl (14, R = CH_2CH_3). Similarly prepared using ethylmagnesium bromide at −15 °C was 14 (R = CH_2CH_3): mass spectrum m/e (rel intensity) 214 (7), 186 (5), 158 (16), 143 (21), 129 (100), 72 (22), 56 (33). Anal. Calcd for $C_{12}H_{24}NO_2$: C, 67.25; H, 11.29; N, 6.54. Found: C, 67.38; H, 11.69; N, 6.34.

2-Pentyl-2-heptyl-4,4-dimethyloxazolidine-*N*-oxyl [14, R = $(CH_2)_6CH_3$]. Similarly prepared using heptylmagnesium iodide at −15 °C was 14 [R = $(CH_2)_6CH_3$]: mass spectrum m/e (rel intensity) 284 (3), 228 (11), 210 (41), 199 (81), 198 (62), 186 (45), 170 (46), 99 (40), 85 (32), 71 (73), 57 (100), 43 (90). Anal. Calcd for $C_{17}H_{34}NO_2$: C, 71.78; H, 12.05; N, 4.92. Found: C, 71.99; H, 12.54; N, 4.69.

2-Pentyl-2-vinyl-4,4-dimethyloxazolidine-*N*-oxyl (14, R = Vinyl). To a solution of 100 mg (0.540 mmol) of freshly prepared 3 in 10 ml of dry ether at −78 °C was added with stirring dropwise under N_2 a twofold excess of vinyllithium (2 M in THF). After 2 h, some ether saturated with water was added and then the mixture was allowed to warm to 25 °C. Water was added and the ether phase separated. The aqueous phase was extracted with ether and the combined ether solutions were dried (K_2CO_3) and evaporated, affording crude *N*-hydroxyoxazolidine 13 (R = vinyl) along with some mineral oil from the vinyllithium reagent. The crude product was dissolved in 10 ml of MeOH containing ~2 mg of $(Cu(OAc)_2 \cdot H_2O$ and stirred under air at 25 °C for 2 h. The solvent was evaporated to yield a yellow oil. Column chromatography over silica gel followed by preparative TLC over silica gel afforded 33 mg (29%) of pure title nitroxide. The analytical specimen was obtained as an orange oil by preparative VPC: mass spectrum m/e (rel intensity) 212 (8), 156 (12), 142 (16), 127 (100), 70 (17), 56 (36), 55 (32). Anal. Calcd for $C_{12}H_{22}NO_2$: C, 67.89; H, 10.44; N, 6.60. Found: C, 67.33; H, 10.81; N, 6.41.

Reaction of Nitrone 3 with Vinylmagnesium Bromide at 25 °C. To a solution of 85 mg of freshly prepared 3 in 10 ml of dry ether at 0 °C was added with stirring under N_2 2 equiv of vinylmagnesium bromide (2 M in THF). After the mixture was allowed to warm to 25 °C, the usual workup with aqueous saturated NH_4Cl gave a yellow oil which consisted of two major components by TLC. Chromatography over silica gel using $CHCl_3$ as the eluent gave 41 mg (37%) of diene 19 as a colorless oil which crystallized upon standing at −20 °C: mp 30–31 °C; NMR δ 1.04 (6 H, s, *gem*-Me), 2.25 (2 H, m, allylics), 3.46 (2 H, s, CH_2O), 4.33 [2 H, d (J = 7 Hz), C=C–CH_2O], 5.60 [1 H, t (J_{trans} = 18 Hz), terminal vinyl], 6.30 (1 H, dd, terminal vinyl); mass spectrum m/e (rel intensity) 241.201 (4) (calcd for $C_{14}H_{27}NO_2$, 241.204), 210 (2), 137 (35), 95 (38), 81 (71), 74 (37), 67 (100), 55 (17), 41 (18); ir ($CHCl_3$) 3300–3600 (NH and OH), 1600 cm^{-1} (C=C); uv (EtOH) 232 nm (ε 18 200).

Further elution with ether gave 14 mg (12%) of diene 21 as a colorless oil: NMR δ 1.20 (6 H, s, *gem*-Me), 2.27 (2 H, m, allylics), 3.54 (2 H, s, CH_2O), 3.44 [2 H, d (J = 7 Hz), CH_2N], 5.64 (1 H, t (J = 7 Hz), vinyl], 5.02 [1 H, d (J_{cis} = 11 Hz), terminal vinyl], 5.21 [1 H, d (J_{trans} = 18 Hz), terminal vinyl], 6.32 (dd, terminal vinyl); mass spectrum m/e (rel intensity) 241.202 (1) (calcd for $C_{14}H_{27}NO_2$, 241.204), 210 (32), 194 (13), 137 (18), 95 (38), 81 (67), 67 (100), 55 (43), 41 (40).

When the reaction and workup for the vinyl Grignard addition were done at 0 °C rather than 25 °C, the major component by NMR was the open-chain nitrone 18: NMR δ 1.60 (6 H, s, *gem*-Me), 2.65 (2 H, m, N=C–CH_2), 3.73 (2 H, s, CH_2O, 5.54 [1 H, d (J_{cis} = 11 Hz), terminal vinyl], 5.52 [1 H, d (J_{trans} = 17 Hz), terminal vinyl], 5.99 (1 H, dd, terminal vinyl). It was not possible to obtain a sample of 18 free from 16.

Acetylation of Diene 19. To a solution of 8.5 mg (0.036 mmol) of 19 in 1 ml of acetic anhydride was added 1 drop of pyridine. The solution was left standing at 25 °C for 5 days and then the solvent was evaporated. Preparative TLC on silica gel gave 5.0 mg (44%) of diacetate 20 as a light yellow oil: NMR δ 1.44 (6 H, s, *gem*-Me), 2.06 (3 H, s, acetyl), 2.16 (3 H, s, acetyl), 4.47 (2 H, s, OCH_2), 4.51 (2 H, m, C=C–CH_2O), 5.16 [1 H, d (J_{cis} = 11 Hz), terminal vinyl], 5.32 [1 H, d (J_{trans} = 18 Hz), terminal vinyl], 5.56 (1 H, t (J = 7 Hz), vinyl], 6.32 (1 H, dd, terminal vinyl); ir 1745 (ester), 1670 cm^{-1} (amide).

Reaction of Nitrone 3 with 1-Lithio-1-hexyne. To a solution of 41 mg (0.50 mmol) of 1-hexyne in 5 ml of dry ether at 0 °C under N_2 was added 1 equiv of methyllithium (1.7 M in ether). After 30 min at 25 °C, the solution was cooled to −15 °C and treated with 65 mg (0.35 mmol) of freshly prepared nitrone 3 in 2 ml of ether. After 5 min, the reaction mixture was worked up in the usual manner. Column chromatography of the crude product followed by preparative TLC produced 12 mg (13%) of oily nitrone 22: NMR δ 1.69 (6 H, s, *gem*-Me), 2.52 [4 H, t (J = 7 Hz), α-CH_2], 3.73 (2 H, s, CH_2O); ir (CCl_4) 3350 (OH), 1580 cm^{-1} (N–O); mass spectrum m/e (rel intensity) 267.220 (8) (calcd for $C_{16}H_{29}NO_2$, 267.220), 220 (34), 196 (41), 180 (66), 139 (26), 99 (100), 87 (32), 79 (90), 74 (50), 59 (95), 58 (66), 43 (63).

3-Aza-4,4-diallyl-2,2-dimethyl-1-hydroxynonane-*N*-oxyl (23). To a solution of 50 mg (0.27 mmol) of nitrone 3 in 4 ml of ether at 25 °C with stirring under N_2 was added 3 equiv of 1 M allylmagnesium bromide in ether. After 30 min, aqueous saturated NH_4Cl was added,

the ether layer was separated, and the residue was washed thoroughly with fresh ether. Evaporation of the combined ether portions gave a yellow oil which after Cu^{2+}-catalyzed air oxidation and TLC on silica gel gave 15 mg (20%) of **23**: ir 3360 (OH), 1640 cm^{-1} (C=C); mass spectrum *m/e* (rel intensity) 268.229 (6) (calcd for $C_{16}H_{30}NO_2$, 268.228), 228 (18), 212 (19), 196 (27), 180 (30), 164 (41), 156 (43), 123 (42), 109 (56), 95 (85), 93 (84), 81 (100), 67 (84), 55 (74), 41 (73).

2,2,4,4,6-Pentamethyltetrahydrooxazine-*N*-oxyl (26) and 3-Aza-6-hydroxy-2,2,4,4-tetramethylheptane-*N*-oxyl (29). To a solution of 76 mg (0.48 mmol) of **9** in 5 ml of dry ether with stirring at 25 °C was added 4 equiv of 2 M methyllithium in ether. After 1 h, aqueous 20% K_2CO_3 was added and the ether phase was separated and combined with several ether washings of the aqueous residue. Evaporation of the solvent gave a nearly colorless oil (79.5 mg) which was taken up in 5 ml of CH_3OH and stirred under air with 2 mg of $Cu(OAc)_2 \cdot H_2O$ for 30 min. Evaporation of the solvent and preparative tlc on silica gel gave 15 mg (18%) of nitroxide **26** (considerable loss due to volatility), mass spectrum *m/e* (rel intensity) 172.133 (5) (calcd for $C_9H_{18}NO_2$, 172.134), 157 (5), 142 (5), 114 (20), 84 (49), 69 (100), 59 (35), 43 (55), 41 (47); and 22 mg (24%) of nitroxide **29**, ir 3430 cm^{-1} (OH), mass spectrum 188.163 (12) (calcd for $C_{10}H_{22}NO_2$, 188.165), 158 (6), 132 (13), 114 (23), 88 (40), 84 (30), 83 (36), 74 (33), 56 (22), 57 (100), 45 (41), 43 (20), 41 (38).

Treatment of **26** with phenylhydrazine in $CDCl_3$[13] gave the corresponding *N*-hydroxylamine **24**: NMR δ 1.18 [3 H, d (*J* = 6 Hz)], 1.28 (6 H, s, *gem*-Me), 2.45 (3 H, s, *gem*-Me), 2.47 (3 H, s, *gem*-Me), 5.04 (1 H, m, CHO).

Treatment of **29** with phenylhydrazine in $CDCl_3$ gave the corresponding *N*-hydroxylamine **28**: NMR δ 1.28 [3 H, d (*J* = 6 Hz)], 1.30 (3 H, s, *gem*-Me), 1.34 (9 H, s, *tert*-butyl), 4.20 (1 H, m, CHO).

2-Butyl-2,4,4,6-tetramethyltetrahydrooxazine-*N*-oxyl (27). Similarly prepared by the method above was nitroxide **27** in 18% yield: mass spectrum *m/e* (rel intensity) 214.183 (12) (calcd for $C_{12}H_{24}NO_2$, 214.181), 199 (3), 157 (25), 114 (43), 101 (32), 84 (84), 69 (83), 55 (29), 43 (93), 41 (100).

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Registry No.—**1**, 55011-28-4; **2**, 55011-29-5; **3**, 55011-30-8; **4**, 59813-15-9; **5**, 59813-16-0; **6**, 59813-17-1; **7**, 26939-18-4; **8**, 59813-18-2; **9**, 59813-19-3; **10**, 59813-13-7; **10** dimer, 59813-14-8; **11**, 59813-20-6; **12**, 59813-21-7; **13** (R = CH_2CH_3), 55011-32-0; **13** [R = $(CH_2)_6CH_3$], 55011-33-1; **13** (R = vinyl), 55011-34-2; **14** (R = CH_2CH_3), 55011-35-3; **14** [R = $(CH_2)_6CH_3$], 55011-36-4; **14** (R = vinyl, 55011-37-5; **18**, 56348-28-8; **19**, 59813-22-8; **20**, 59813-23-9; **21**, 59813-24-0; **22**, 59813-25-1; **23**, 59813-26-2; **24**, 59813-27-3; **26**, 55179-45-8; **27**, 59813-28-4; **28**, 59813-29-5; **29**, 59813-30-8; 2-nitro-2-methylpropanol, 76-39-1; hexanoic acid, 142-62-1; oxaziridine, 6827-26-5; 1-hexyne, 693-02-7; phenylhydrazine, 100-63-0.

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Mobile Activated Allyl Systems. 19.[1] Reactions of Amines with α-(Bromomethyl)cinnamonitrile

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The reactions of a variety of amines with α-(bromomethyl)cinnamonitrile (**1**) in solvents of different polarities are reported. The ratio of the two products formed, namely the substitution-rearrangement (S–R) product **2** and the substitution product **3**, was found to vary with the polarity of the solvent as well as with the basicity and the steric effectiveness of the amine used. Except for the *tert*-butylamine reaction product **2a** and the diisopropylamine reaction product **2e**, all S–R products **2** isomerized to the thermodynamically more stable substitution products **3** in a polar solvent. Product **2a** was found to be susceptible to the attack of free amines to give the appropriate amine exchange product **3**. Product **2e**, however, was inert even to the highly reactive nucleophile piperidine.

Although primary allyl halides react with amines to give normal substitutions, Cromwell and Rebman[2] observed substitution–rearrangement (S–R) products upon treatment of *trans*-α-(bromomethyl)chalcone (Ia) with *tert*-butylamine and piperidine in hydrocarbon solvents. The amine reaction has been extended to other mobile allyl systems, namely, α-(bromomethyl)benzalacetone (Ib)[3] and methyl α-(bromomethyl)cinnamate (Ic).[4] In hydrocarbon solvents, morpholine and piperidine react with the above-mentioned mobile allyl systems to give both substitution and S–R products. With *tert*-butylamine, only the S–R products were isolated. It has been shown that the amine molecule attacks the mobile keto allyl system in an S_N2' manner, giving initially the S–R product (II). The substitution product (III) is a result of either

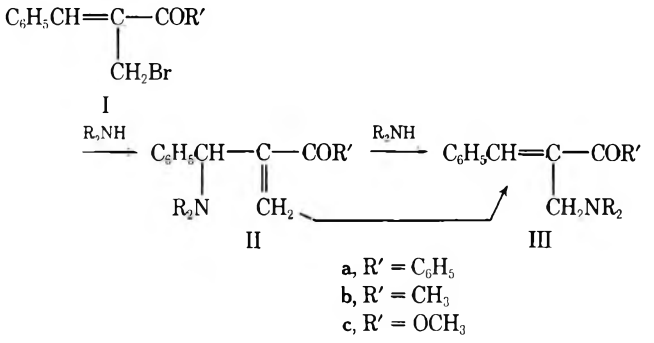
Table I. 60-HMz Proton Magnetic Resonance Data[a]

Compd	Aromatic[b]	C_6H_5CH	$C{=}CH_2$	CH_2N	Amine group
2a	7.26	4.45	5.82, 6.04		1.08 (s), *tert*-butyl
3a	7.05–7.80			3.43	1.12 (s), *tert*-butyl
2b	7.10–7.90	3.80	5.77, 5.88		2.17–2.50 (m), $-H_2CNCH_2-$
					1.50 (m), $-CH_2CH_2CH_2-$
3b	7.00–7.90			3.18	2.20–2.60 (m), $-CH_2NCH_2-$
					1.50 (m), $-(CH_2)_3-$
2c	7.12–7.90		5.87, 6.01		3.53–3.85 (m),[c] $-CH_2OCH_2-$
					2.26–2.62 (m) $-CH_2NCH_2-$
3c	7.00–7.90			3.21	3.56–3.78 (m) $-CH_2OCH_2$
					2.35–2.60 (m) $-CH_2NCH_2-$
2d	7.05–8.00	4.34	5.84, 5.92		2.60 (q), CH_2CH_3
					0.98 (t), $-CH_2CH_3$
3d	7.00–7.90			3.30	2.57,[d] $-CH_2CH_3$, 1.00,[e] $-CH_2CH_3$
2e	7.15–7.90	4.80	5.97, 6.02		3.07 (h), $-CH(CH_3)_2$
					0.90 (d), 1.12 (d),
					Nonequivalent $-CH_3$
3e	7.16–7.92			3.38	3.07 (h), $-CH(CH_3)_2$
					1.02 (d), $-CH(CH_3)_2$

[a] Chemical shift in δ units from internal Me_4Si. [b] Benzal proton hidden in this region also. [c] Benzyl proton hidden in this region. [d] Overlap of 2 quartet. [e] Overlap of 2 triplet, believed to be attributable to the existence of two geometrical isomers of **3d**.

the autocatalytic rearrangement of the S–R product in a more polar solvent like chloroform, or the attack of a second mole of the appropriate amine on the S–R product in a second rearrangement–substitution. The processes are summarized in Scheme I.

Scheme I

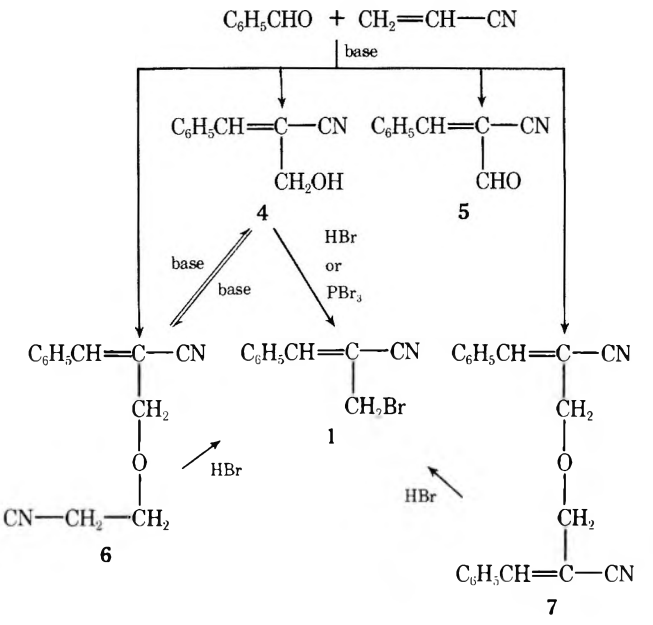


In the case of β-keto secondary allyl halides, the SN2′ mechanism is by no means the only way an amine can attack the mobile allyl system. Previously it has been reported that the direct attack of an amine at the allylic position proceeded parallel with the expected SN2′ reaction for the reaction of *tert*-butylamine with 2-(α-bromobenzyl)-4,4-dimethyl-1,4-dihydro-1-ketonaphthalene.[5] It occurred to us that studies of the reaction of amines with α-(bromomethyl)cinnamonitrile, where the β-carbonyl group has been replaced by a nitrile group, might provide further insight into the nature of the competitive reaction pathways available to these mobile allyl systems.

Results

Preparation of the starting material α-(bromomethyl)cinnamonitrile (1) was performed by modifying the procedure reported by Wasserman et al.[6] The base-catalyzed condensation of benzaldehyde and acrylonitrile yielded four products (Scheme II), three of which can be converted to **1**. Instead of isolating the useful compounds one by one, **4**, **6**, and **7** were separated from the resulting crude oil by vacuum distillation as a mixture. The mixture was then refluxed with 48% aqueous hydrobromic acid in glacial acetic acid. Compound **1** precipitated when the reaction mixture was poured into ice water.

Scheme II



Recrystallization from hot hexane gave white, scaly crystals.

The reactions of **1** with 2 molar equiv of amines were carried out in a number of solvents. The amine hydrobromide formed during the reaction precipitated upon replacement of the solvent with ether and was removed by filtration. Evaporation of the solvent in vacuo yielded the product(s), which was analyzed immediately by ^1H NMR spectroscopy.

The two substitution products are readily distinguished from each other by ^1H NMR spectroscopy (Table I). Compound **2** exhibits three singlets (slightly broadened due to geminal and allylic coupling), assigned to the benzylic and vinylic protons. For **3**, the vinyl and methylene proton bands are characteristic (Table I).

Except in the cases when acetonitrile was used as solvent, **2** was found to be the exclusive or major product. A summary of the results is listed in Table II.

The S–R products **2b**, **2c**, and **2d** were observed to rearrange to their thermodynamically more stable isomers, i.e., the substitution products **3b**, **3c**, and **3d**, on standing in a polar

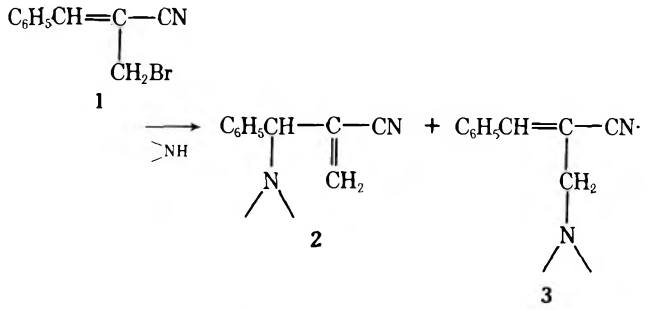
Table II. Amine Reaction with 1

Amount of substrate, mol	Amine	Amount of amine, mol	% amine hydrobromide	Solvent (ml)	Reaction time, h	Product
0.018	*tert*-Butylamine	0.071	90	*n*-Hexane (350)	48	**2a** (100)
0.0045	*tert*-Butylamine	0.009	92	Benzene (50)	48	**2a:3a** (>95:<5)
0.0045	*tert*-Butylamine	0.009	95	Chloroform (50)	48	**2a:3a** (70:30)
0.0045	*tert*-Butylamine	0.009	100	Acetonitrile (50)	8	**2a:3a** (30:70)
0.0045	Piperidine	0.009	98	*n*-Hexane (150)	0.25	**2b:3b** (>95:<5)
0.0045	Piperidine	0.009	100	Chloroform (50)	0.25	**2b:3b** (80:20)
0.0045	Morpholine	0.009	92	*n*-Hexane (150)	5.5	**2c:3c** (>95:<5)
0.0045	Morpholine	0.009	95	Chloroform (50)	3	**2c:3c** (>95:<5)
0.0045	Diethylamine	0.009	100	*n*-Hexane (150)	5.5	**2d** (100)
0.0045	Diethylamine	0.009	98	Chloroform (50)	3	**2d:3d** (70:30)
0.0045	Diisopropylamine	0.015	0	Benzene (100)	13	No reaction
0.0045	Diisopropylamine	0.015	78	Benzene (reflux) (100)	60	**2e:3e** (30:70)
0.0045	Diisopropylamine	0.015	53	*n*-Hexane (reflux) (300)	11 days	**2e** (100)
0.0045	Diisopropylamine	0.015	100	Acetonitrile (100)	3 days	**3e** (100)

Table III. Elemental Analysis and Infrared Data

	Calcd			Found				
Comp	C	H	N	C	H	N	$\nu_{C\equiv N}$	Mp, °C
2a[a]	67.06	7.50	11.17	67.00	7.73	11.40	2240	169
3a[a]	67.06	7.50	11.17	67.02	7.79	11.30	2220	244
3b[a]	68.57	7.20	10.67	68.58	7.39	10.77	2220	218
3c[b]	52.52	4.16	15.31	52.57	4.29	15.34	2220	237
3d[b]	54.18	4.70	15.80	54.13	4.83	15.78	2230	118
3e[b]	56.05	5.31	14.86	55.96	5.07	14.82	2222	197

[a] Hydrochloride. [b] Picrate.



solvent ($CDCl_3$), in the absence of additional appropriate free amine. The rate of conversion was fastest for **2b** → **3b**, while that of **2d** → **3d** was found to be the slowest among the three. However, **2a** and **2e** were found not to convert to their other isomers autocatalytically.

The reaction of **2a** with amines at room temperature in carbon tetrachloride was followed by ^1H NMR spectroscopy. The results are listed in Table IV. S–R product **2a** reacted with piperidine and morpholine to produce **3b** and **3c**, quantitatively. However, treatment of **2a** with the sterically bulky diethylamine and *tert*-butylamine did not effect such a change under these conditions. Substitution product **3a** was successfully prepared by the reaction of a large excess of *tert*-butylamine with **2a** in acetonitrile over a period of 50 days.

On standing in a polar solvent with or without the presence of excess free amine, the sterically restricted **2e** was observed not to convert to **3e** which might be expected to be the thermodynamically more stable isomer. Compound **3e** was inert even to piperidine.

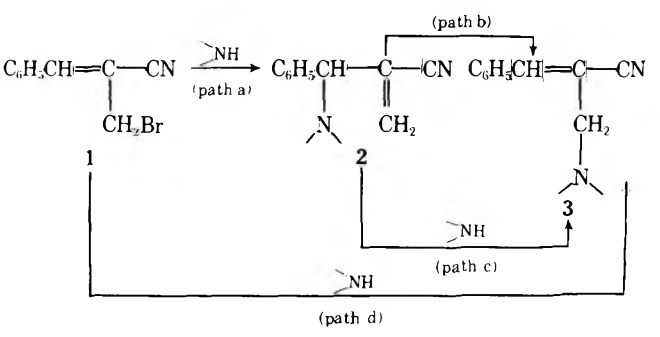
Discussion

Attack of amines on **1** can occur in two ways, namely, the amine molecule may attack the benzal carbon in a SN2′ manner, yielding **2** (Scheme III, path a), or the amine may attack the allylic position directly, yielding **3** (Scheme III, path d). The former route, which is the normal case in most of the mobile ketoallyl systems being studied, is shown by the reaction of various amines with **1** in nonpolar solvents. Compound **2** was observed to be the exclusive or major product in all cases. The latter route, although rare in other studies of similar systems, appears to occur with the mobile cyanoallyl system. Here when **1** is treated with *tert*-butylamine or di-

Table IV. Amine Exchange Reaction with 2a

Amine used	[Amine]/[precursor]	Time necessary for >90% conversion
tert-Butylamine	>3	No significant reaction
Piperidine	~3	11 h
Morpholine	~2.5	48 h
Diethylamine	~3	No significant reaction

Scheme III



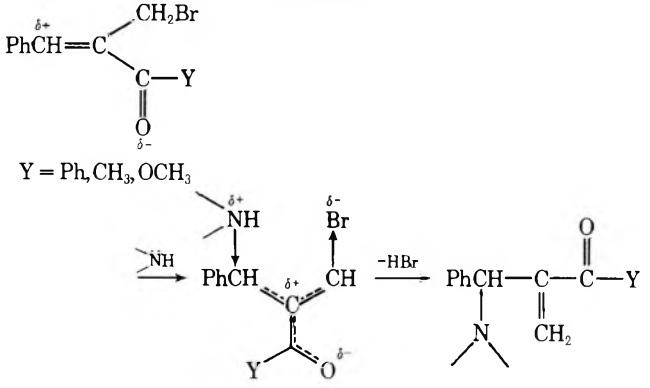
isopropylamine in a solvent more polar than a saturated hydrocarbon, both **2** and **3** were observed to form in parallel reactions. The rate for **2a** to convert to **3a** was negligible in the absence of free amine, and was slow compared to the formation of **3a** when the reaction of amine with **1** was run in a polar solvent. Also, under no circumstances could **2e** be converted to **3e.** Evidently, both pathways (path a and path d) occur in a parallel manner in the reaction of *tert*-butylamine and diisopropylamine with **1** in polar solvents.

Product **3,** arising from a second SN2′ reaction, was also observed in the mobile cyano system (Scheme III, path c). Such a mechanistic pathway for **2** → **3** conversion was established previously with β-ketoallylamines.[7,8] Results of the amine exchange reaction of different amines with **2a** are summarized in Table III. The rate of conversion was found to be a function of the basicity of the amine used. The reaction of **1** with piperidine is much faster than the reaction of **1** with other amines with lower basicity. However, basicity is not the only factor that has to be taken into account in understanding these reactions. Steric size of the free amine used plays an important role also. Diethylamine is more basic than morpholine, but diethylamine is resistant to displacing the *tert*-butylamine from **2a,** while morpholine is able to accomplish this, though slowly. Also, the fact that **2a** converts to **3a** with difficulty (in large excess of free amine and after a period of 50 days) and **2e** does not convert to **3e** (even in the presence of free amine) is believed to be attributable to the steric effectiveness of the alkyl group of the two amino groupings. This point is further illustrated by **2e** being inert even to piperidine.

Isomer **3** can also arise from autorearrangement of **2**[10] (Scheme III, path b, no excess amine present). Compounds **2b, 2c,** and **2d** were observed to isomerize in this fashion to **3b, 3c,** and **3d,** respectively, the thermodynamically more stable isomers. The fact that **2a** and **2e** do not isomerize, respectively, to **3a** and **3e** is attributed again to the steric requirements of the alkyl group of the amino function.

The formation of S–R products from the reaction of amines with β-carboallyl halides has been considered to be a variant of an SN2′ mechanism, in which carbon–nitrogen bond formation proceeds ahead of carbon–halogen bond breakage,[3,4,9] Scheme IV. The oxygen atom of the β-carbo group accepts

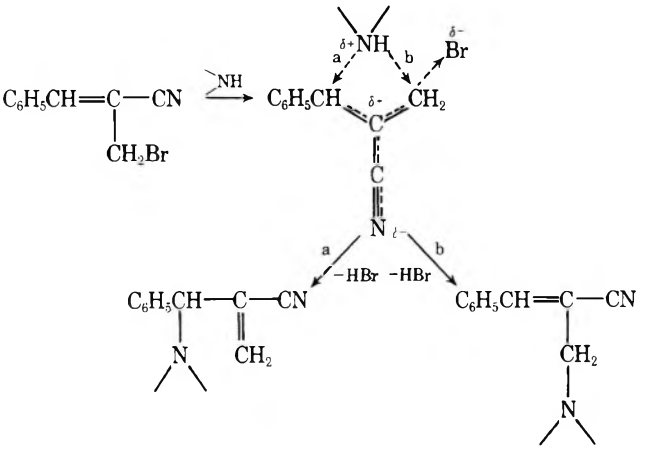
Scheme IV



much of the developing negative charge which is ultimately carried away by the leaving halide ion.

Owing to the noninterconvertibility of **2a** and **2e,** respectively, to **3a** and **3e,** autocatalytically, we suggest another mode of amine attack on the activated allyl halide in the reaction of *tert*-butylamine and diisopropylamine with the mobile cyano allyl bromide **1.** It is possible that in the more polar solvents, the carbon–bromine bond lengthens at a rate so fast that direct attack of the amine at the allylic carbon becomes a competitive pathway to the well-established SN2′ pathway as described before; see Scheme V.

Scheme V



Experimental Section

Melting points were determined from a Mel-Temp apparatus, and were uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 621 spectrophotometer. The proton magnetic resonance spectra were determined from a Varian Model A-60 spectrometer, utilizing tetramethylsilane as an internal standard. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill., or by Chemalytics, Inc., Tempe, Ariz. ^{1}H NMR data obtained in deuteriochloroform are listed in Table I.

Preparation of α-(Bromomethyl)cinnamonitrile (1). To a mixture of 106 g (1 mol) of benzaldehyde and 5 ml of 30% KOH/MeOH solution in 100 g of *tert*-butyl alcohol at the temperature of ice was added 106 g (2 mol) of acrylonitrile over a period of 1.5 h. The mixture was then stirred at room temperature for 8 h. The viscous solution was acidified with hydrochloric acid to pH 2–3. The solution was diluted with 500 ml of diethyl ether, and was washed repeatedly with water. The ethereal solution was washed with saturated brine and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo yielded a yellow, viscous oil, which was then subjected to vacuum distillation (0.3–1 mmHg). At 120 °C, a colorless oil, which solidified on cooling, was distilled, ir $\nu_{C=O}$ 1700 cm^{-1}. Between 134 and 220 °C, 148 g of yellow oil was distilled over, ir ν_{C-O} 1115 cm^{-1}.

A sample of 25.6 g of the yellow oil obtained in the previous reaction was refluxed with 140 ml of 48% hydrobromic acid and 200 ml of glacial acetic acid for 2 h. The cooled yellow solution was poured into ice water with vigorous stirring. The precipitate thus formed was filtered off, and was washed with a large quantity of water to remove the acid. Recrystallization from light petroleum yielded 19.39 g of **1** as white crystals: mp 44–49 °C (lit. 54–55 °C); ir (KBr) ν (Nujol) 2225, 540 cm^{-1}; ^{1}H NMR (CCl_4) 4.18 (s, 2 H, $-CH_2Br$), 7.17 (s, 1 H, benzal proton), 7.25–7.90 ppm (m, 5 H, aromatic protons). A total of 106 g (48%, with respect to the benzaldehyde used) of **1** was obtained for a number of trials under similar conditions.

General Procedure for the Reaction of Amines with 1. A measured quantity of **1** dissolved in a specified quantity of solvent was treated with 2 molar equiv of the appropriate amine. After the reaction was complete the mixture was filtered to remove the amine hydrobromide, the weight of which was determined to estimate the percent yield of the reaction. In case a polar solvent, like chloroform or acetonitrile, was used, the solvent was replaced by an apolar solvent to precipitate the inorganic salt. The product oil was analyzed by ^{1}H NMR spectroscopy. Upon standing in chloroform for several days the stable product formed and was fully characterized. See Tables I–III for results and data.

Reaction of Diisopropylamine with 1 in Hexane and Then in Acetonitrile. To a solution of 1 g (4.50×10^{-3} mol) of **1** in 300 ml of *n*-hexane was added 1.5 g (1.43×10^{-2} mol) of diisopropylamine. The solution was stoppered and stirred for 12 h. No inorganic salt precipitated, implying that no reaction was taking place. The solution was then refluxed for 11 days and 440 mg (53%) of the amine hydrobromide salt was removed by filtration. Removal of the solvent in vacuo yielded a yellow oil, which was immediately identified to be a mixture of **2e** and starting material.

The acetonitrile solution of the above mixture was treated with another 1.5 g of diisopropylamine. The solution was stoppered and stirred for 4 days. The solvent was removed in vacuo. Treatment of the residue with diethyl ether yielded another 380 mg (47%) of amine hydrobromide salt. Removal of the ether in vacuo yielded a yellow oil, which was identified to be a mixture of **2e** and **3e.** It was observed that

the absorption in the ^{1}H NMR spectrum corresponding to the vinyl protons of **2e** did not change in intensity after treatment with diisopropylamine the second time.

Attempted Conversion of 2a to 3a. A 70:30 mixture of **2a:3a** was allowed to stand in deuteriochloroform for several days. No significant change was observed in the ^{1}H NMR spectrum of the product mixture. The mixture was then refluxed in chloroform (15 h) and then in acetonitrile (7 h). In neither case could significant changes be observed in the ^{1}H NMR spectrum.

General Procedure for the Amine Exchange Reaction. To a solution of 164 mg (0.000738 mol) of **2a** in 1.5 ml of carbon tetrachloride was added quickly approximately 2–3 molar equiv of the appropriate amine. The solution was filtered into a ^{1}H NMR tube. The concentration of the amine could be estimated by the intensity of the ^{1}H NMR signal relative to that of **2a**. The reaction was monitored by the relative intensity of the signals corresponding to respectively the vinylic protons of the precursor and the allylic protons of the product. Another tube holding only **2a** in carbon tetrachloride was used as a control to the experiment. See Table IV for results and data.

Attempted Reaction of 2e with Diisopropylamine. To a solution of 160 mg (0.00061 mol) of a 30:70 mixture of **2e** and **3e** in 30 ml of acetonitrile was added 287 mg (0.0028 mol) of diisopropylamine. The solution was stoppered and stirred for 13 h. Removal of the solvent and unreacted amine yielded a yellowish oil (quantitative), which was spectrally equivalent to the unreacted precursor.

Attempted Reaction of 2e with Piperidine. To a solution of 100 mg (0.00045 mol) of a 30:70 mixture of **2e** and **3e** in 10 ml of benzene was added 360 mg (0.0042 mol) of piperidine. The solution was stoppered and stirred for 13 h. Removal of the solvent and the unreacted amine yielded a yellowish oil (quantitative) which was spectrally equivalent to the unreacted precursor.

Reaction of *tert*-Butylamine with a Mixture of 2a and 3a in Acetonitrile. To a solution of 220 mg (0.001 mol) of a mixture of **2a** and **3a** (**2a:3a**, 70:30) in 30 ml of acetonitrile was added 690 mg (0.0094 mol) of *tert*-butylamine. The solution was stoppered and stirred for 53 h. Significant changes in the ratio of the two isomers were observed in the ^{1}H NMR spectrum of the worked up material. Under similar conditions, the solution was stirred for another 50 days. Removal of the solvent and excess amine yielded **3a** as a yellow oil (200 mg, 91%).

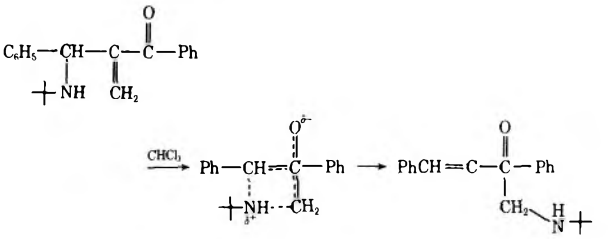
A hexane solution of the product was exposed to a stream of hydrogen chloride gas. A white solid was isolated, which on recrystallization from methanol–ether mixture yielded the crystalline amine hydrochloride salt of **3a**.

Acknowledgment. This investigation was supported by Grant CA 02931 from the National Cancer Institute of the U.S. Public Health Service.

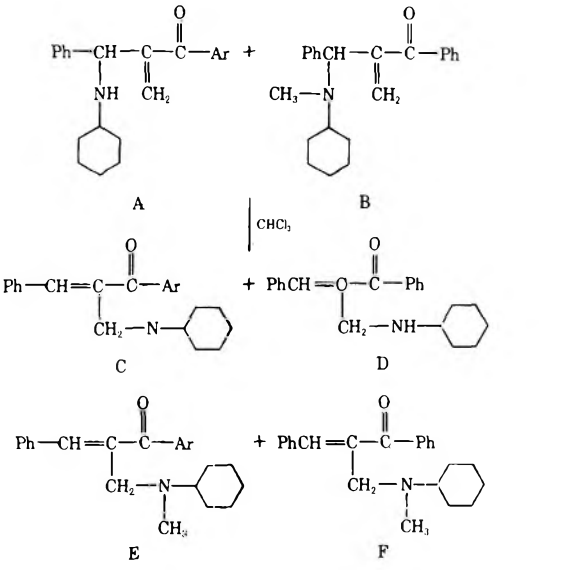
Registry No.—**1**, 59728-94-8; **2a**, 59728-95-9; **2a** HCl, 59728-96-0; **2b**, 59728-97-1; **2c**, 59728-98-2; **2d**, 59728-99-3; **2e**, 59729-00-9; **3a**, 59729-01-0; **3a** HCl, 59729-02-0; **3b**, 4933-37-3; **3b** HCl, 59729-03-2; **3c**, 59729-04-3; **3c** picrate, 59729-05-4; **3d**, 59729-06-5; **3d** picrate, 59729-07-6; **3e**, 59729-08-7; **3e** picrate, 59729-09-8; benzaldehyde, 100-52-7; acrylonitrile, 107-13-1; *tert*-butylamine, 75-64-9; piperidine, 110-89-4; morpholine, 110-91-8; diethylamine, 109-89-7; diisopropylamine, 108-18-9.

References and Notes

(1) For the previous paper in this series, see R. J. Murray and N. H. Cromwell, *J. Org. Chem.*, in press. The general title of the series has now been broadened from "Mobile Keto Allyl Systems" to "Mobile Activated Allyl Systems" to allow coverage of activating groupings other than the keto groups.
(2) R. P. Rebman and N. H. Cromwell, *J. Org. Chem.*, **32**, 3830 (1967).
(3) M. C. Eagen and N. H. Cromwell, *J. Org. Chem.*, **39**, 911 (1974).
(4) M. C. Eagen and N. H. Cromwell, *J. Org. Chem.*, **39**, 3863 (1974).
(5) (a) N. H. Cromwell and E-M. Wu, *J. Org. Chem.*, **33**, 1895 (1968); (b) G. Glaros and N. H. Cromwell, *ibid.*, **37**, 862 (1972); (c) *ibid.*, **37**, 867 (1972).
(6) H. H. Wasserman, B. Suryanarayana, and D. D. Gassetti, *J. Am. Chem. Soc.*, **78**, 2808 (1956).
(7) N. H. Cromwell, K. Matsumoto, and A. D. George, *J. Org. Chem.*, **36**, 272 (1971).
(8) G. Maury, E-M. Wu, and N. H. Cromwell, *J. Org. Chem.*, **33**, 1900 (1968).
(9) A. D. George, E. Doomes, and N. H. Cromwell, *J. Org. Chem.*, **36**, 3918 (1971).
(10) Rebman and Cromwell[1,11] postulated an intramolecular mechanism for the autocatalytic rearrangement of α-(α-*tert*-butylaminobenzyl)acrylophenone. Doomes,[12] on the basis of some rough kinetic data, suggested



that the process was not unimolecular. Eagen,[13] by a crossover experiment, showed that Doomes' suggestion was correct. An equimolar mixture of α-(α-cyclohexylaminobenzyl)-4′-phenylacrylophenone (A) and α-(α-*N*-methylcyclohexylaminobenzyl)acrylophenone (B) was dissolved in chloroform. The rates of rearrangement of A and B, respectively, to their



thermodynamically more stable direct-substitution isomers are somewhat comparable. The solution of A + B was allowed to stand to at room temperature for 72 h. The ^{1}H NMR spectrum of the reaction mixture showed four compounds, C, D, E, and F, to be present.
(11) R. P. Rebman and N. H. Cromwell, *Tetrahedron Lett.*, 4833 (1965).
(12) E. Doomes, Ph.D. Thesis, University of Nebraska, 1968.
(13) M. Eagen, Ph.D. Thesis, University of Nebraska, 1972.

Vinyl Carbanions. 2. Simultaneous Hydrogen–Deuterium Exchange and Addition of Ethyl [^{2}H]Alcohol to *trans*-Cinnamonitrile Catalyzed by Sodium Ethoxide

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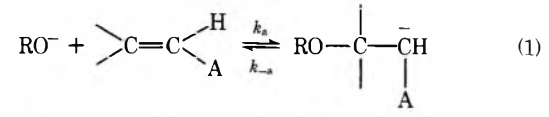
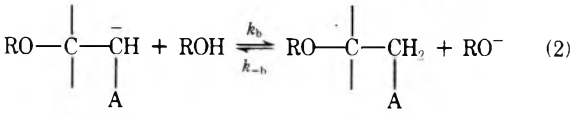
Received February 23, 1976

The kinetics of the simultaneous addition of ethyl [^{2}H]alcohol to *trans*-cinnamonitrile and the H–D exchange at C_α catalyzed by sodium ethoxide have been studied. The observed rate equation for the addition is $R = A$[*trans*-cinnamonitrile] $+ B$, where A and B are constants which depend on the initial concentrations of olefin and base. The forward (k_1) and the backward (k_{-1}) rate constants of the nucleophilic addition step are $(3.72 \pm 0.51) \times 10^{-4}$ l. mol^{-1} s^{-1} and $(9.58 \pm 1.20) \times 10^4$ s^{-1}, respectively. The equilibrium constant for the overall addition reaction is $K = (3.9 \pm 0.2) \times 10^{-2}$ l. mol^{-1}. The H–D exchange is faster than the addition reaction and takes place via the vinyl carbanion derived from the olefin. Cis to trans isomerization occurs during the addition of ethyl [^{2}H]alcohol to *cis*-cinnamonitrile. Based on kinetic data, it is suggested that this isomerization takes place by an addition–elimination mechanism.

Kinetic studies of the addition of alcohols to activated olefins catalyzed by the derived sodium alkoxides have established that the rate-determining step is a nucleophilic attack of the alkoxide ion on the double bond followed by a fast protonation[1–4] as follows:



(1)



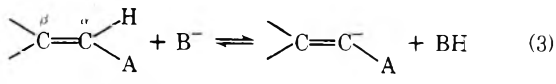
(2)

A = electronegative group

Equilibrium is established if the rate of decomposition of the intermediate carbanion is comparable with the rate of its protonation. This is the case in the addition of alcohols to vinyl sulfones,[5] to alkyl vinyl ketones,[6–9] and to β-nitrostyrene.[10]

Rate constants of the rate-limiting step (k_a) only and overall equilibrium constants were obtained from kinetic studies of the above-mentioned and some other Michael addition systems.[11] An appropriate treatment of the kinetic data in the case of the ethoxide-catalyzed addition of ethanol to β-nitrostyrene[10] made it possible to obtain the values of both k_a and k_{-a} as well as the overall equilibrium constant. This approach is being also used in the present work.

An acid–base type reaction may occur in Michael addition reaction systems in which an active olefin having an α-vinyl hydrogen is involved (eq 3). Recent kinetic and stereochemical



(3)

studies with β,β-disubstituted olefins have confirmed that vinyl carbanions are intermediates in the base-catalyzed hydrogen–deuterium exchange of 2,2,4,6,6-pentamethylcyclohexylineneacetonitrile,[12] of the corresponding ketone,[13] and of fluorene-9-ylideneacetonitrile.[14] Active olefins which are not sterically hindered at C_β are subjected to nucleophilic attacks at this position, but vinyl carbanions are also involved in competing base-catalyzed reactions of such olefins. This has been suggested to be the case in the dimerization of acrylic[15] and crotonic[16] esters to yield such dimers as CH_2=C(COOR)CH_2CH_2COOR and CH_3CH=C(COOR)$CH(CH_3)CH_2$COOR, respectively. A vinyl carbanion is also involved in a chain transfer reaction to monomer in the anionic polymerization of acrylonitrile.[17]

The acid–base type equilibrium (eq 3) has not been taken into account in any of the previous kinetic studies of Michael addition reactions. It was the purpose of the present work to study kinetically both the hydrogen–deuterium exchange at C_α and the nucleophilic addition reaction with such an olefin where these two may occur simultaneously.

Results and Discussion

The addition of ethyl [^{2}H]alcohol to *trans*-cinnamonitrile catalyzed by sodium ethoxide was accompanied by a simultaneous hydrogen–deuterium exchange reaction to yield the α-deuterated olefin *trans*-PhCH=CDCN. The rate of the exchange reaction was followed by infrared spetroscopy, and the rate of the addition reaction was followed by determined the concentrations of both the total (exchanged and unexchanged) olefin and the addition product by VPC. The rate of addition R_t was measured both as $-$d[TCN]/dt and d[add]/dt, where [TCN] and [add] are the concentrations at time t of the total olefin and of the addition product, respectively. For each run a plot of R_t against [TCN] and against [add] gave straight lines with slopes A and A' and intercepts B and B', respectively (Figures 1 and 2). The experimental rate equations are

$$R_t = -\text{d[TCN]}/dt = A[\text{TCN}] + B \quad (4)$$

$$R'_t = \text{d[add]}/dt = A'[\text{add}] + B' \quad (5)$$

The values of R_t and R'_t for each run are the slopes of the conversion curves at different t values. On integration of eq 4 and 5, eq 6 and 7 are obtained:

$$[\text{TCN}] = \frac{(A[\text{TCN}]_0 + B)e^{-At} - B}{A} \quad (6)$$

$$[\text{add}] = B'(e^{-A't} - 1)/A' \quad (7)$$

Using a computer, the best conversion curves were plotted according to eq 6 and 7, and the values of A, B, A', and B' were calculated. The deviations of the measured values of [TCN] from those computed according to eq 6 were small (±1%) indicating the reliability of the experimental method used. The same deviations for the adduct were somewhat higher (±3%). Detailed data for some of the kinetic runs are presented in the Experimental Section (Table II).[24]

In view of the evidence presented regarding the formation of vinyl carbanions in nucleophilic addition reactions to activated olefins,[12–17] the following reaction scheme may represent the ethoxide–*trans*-cinnamonitrile–ethyl [^{2}H]alcohol system.

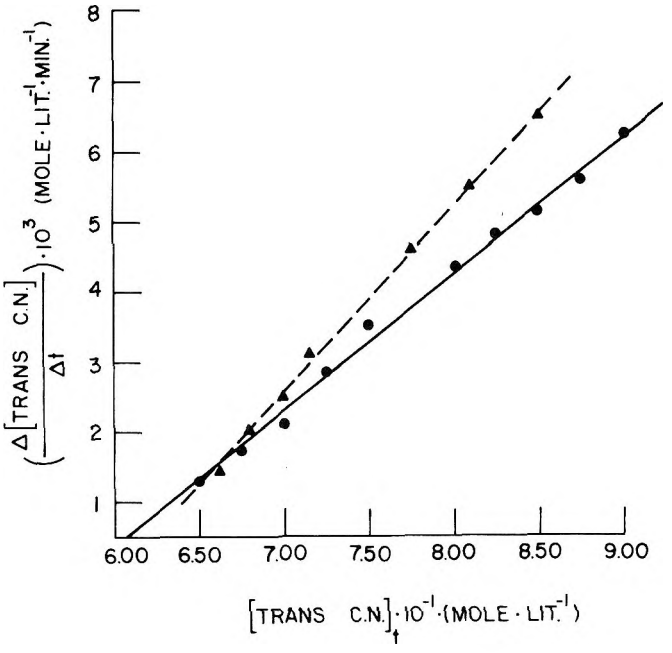
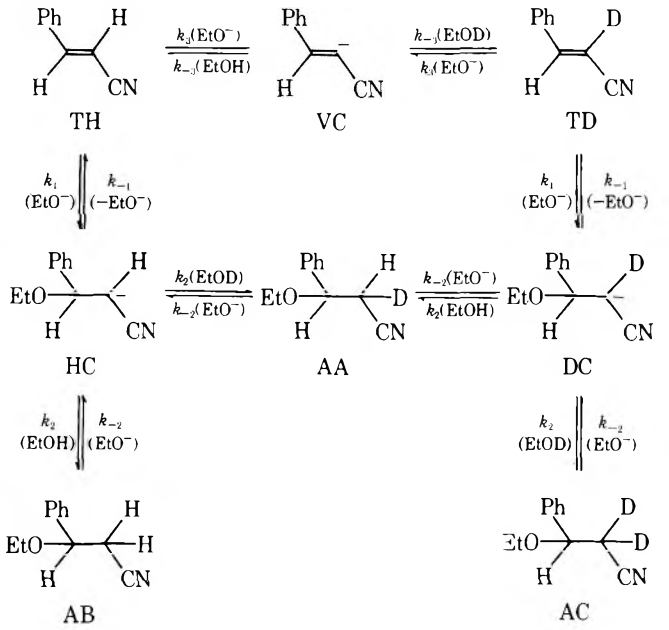


Figure 1. Plots of R_t, rate of addition of ethyl [^{2}H]alcohol to *trans*-cinnamonitrile (TCN), against $[TCN]_t$: ●, run 10; ▲, run 11.



This scheme takes into account only the nucleophilic addition and the hydrogen–deuterium exchange reactions, assuming that the trans to cis isomerization occurs to a negligible extent. This assumption will be justified later on presenting and discussing the problem of isomerization. The kinetic isotope effect is also being neglected for both the vinyl carbanion formation and the nucleophilic addition reaction. This is justified by the very low isotope effects observed in base-catalyzed hydrogen–isotope exchange in carbon acids.[18,19] This is also the case, for example, in the hydrogen–deuterium exchange of 2-methyl-3,3-diphenylpropionitrile[20] (k_H/k_D = 2.60), of 2,2-diphenylcyclopropanecarbonitrile[20] (k_H/k_D = 1.50), and of the α,β-unsaturated nitrile 2,2,4,6,6-pentamethylcyclohexylideneacetonitrile[12] (k_H/k_D = 2.05). Regarding the nucleophilic addition, it is quite reasonable to assume that the rate constants for this reaction involving either the hydrogen or the deuterium derivatives of the olefin are practically the same.

According to the above reaction scheme, the rates by which

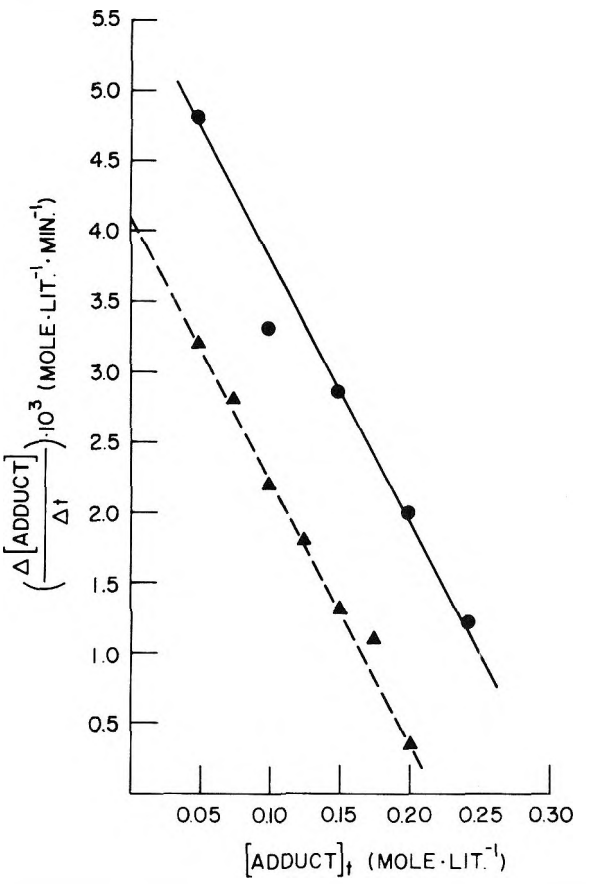


Figure 2. Plots of R_t, rate of addition of ethyl [^{2}H]alcohol to *trans*-cinnamonitrile, against $[adduct]_t$, the concentration of the addition product at time t: ●, run 6; ▲, run 7.

the olefins and adducts react are given by the following equations:

$$-d[TH]/dt = (k_1 + k_3)[EtO^-][TH] - k_{-1}[HC] - k_{-3}[VC][EtOH] \quad (8)$$

$$-d[TD]/dt = (k_1 + k_3)[EtO^-][TD] - k_{-1}[DC] - k_{-3}[VC][EtOD] \quad (9)$$

$$-d[AA]/dt = k_{-2}[EtO^-][AA] - k_2([EtOD][HC] + [EtOH][DC]) \quad (10)$$

$$-d[AB]/dt = k_{-2}[EtO^-][AB] - k_2[EtOH][HC] \quad (11)$$

$$-d[AC]/dt = k_{-2}[EtO^-][AC] - k_2[EtOD][DC] \quad (12)$$

The overall rate of addition of EtOD to *trans*-cinnamonitrile is given by

$$R_t = -d[TCN]/dt = -d[TH]/dt - d[TD]/dt \quad (13)$$
$$= (k_1 + k_3)([TH] + [TD])[EtO^-] + k_1([HC] + [DC]) - k_3[VC][S]$$

where [TCN] is the total concentration of *trans*-cinnamonitrile at time t and [S] = [EtOH] + [EtOD]. Assuming steady state conditions for the intermediate carbanions, namely d[HC]/dt = 0, d[DC]/dt = 0, and d[VC]/dt = 0, the corresponding expressions for the values of [HC], [DC], and [VC] can be derived. By substituting these values in eq 13 the following rate equation is obtained

$$-\frac{d[TCN]}{dt} = k_1[TCN][EtO^-] - \frac{k_1k_{-1}[TCN] + k_{-1}k_{-2}[add]}{k_2[S] + k_{-1}}[EtO^-] \quad (14)$$

Table I. Rate Constants for the Addition of Ethyl [^{2}H]Alcohol to *trans*-Cinnamonitrile Catalyzed by Sodium Ethoxide at 39 °C

Run no.	$[TCN]_0$, mol l.$^{-1}$	$[EtO^-Na^+]$, mol l.$^{-1}$	$10^2 A$ $10^3 B$	$10^4 A'$ $10^3 B'$	$10^4 k_1$,[a] l. mol^{-1} s^{-1}	$10^{-4} k_{-1}$,[a] s^{-1}	$10^4 k'_1$,[a] l. mol^{-1} s^{-1}	$10^{-4} k'_{-1}$,[a] s^{-1}	$10^2 \frac{-B}{[TCN]_0[EtO^-]}$
1	0.318	0.215	0.98 −1.71	−1.91 2.08	3.06	7.75	8.40	16.60	2.51
2	0.477		0.81 −2.22	−0.97 2.53	2.72	6.13	4.03	5.85	2.15
3	0.637	0.180	0.94 −3.21		3.07	7.13			2.78
4	0.637	0.215	1.13 −4.08	−1.80 4.18	3.33	9.20	5.08	15.10	3.00
5	0.795		1.63 −7.43	−1.83 5.58	5.07	12.93	5.72	14.38	4.35
6	0.954		1.21 −6.71	−1.51 5.28	3.75	9.58	4.28	12.68	3.27
7	1.114		1.27 −7.68	−1.49 6.67	4.30	9.42	4.63	11.80	3.21
8	0.954	0.180	1.23 −6.85	−1.20 4.45	4.73	11.38	4.32	11.60	4.00
9		0.240	1.44 −7.92	−0.92 3.80	3.53	10.83	2.77	6.22	3.47
10		0.320	2.00 −11.70	−3.15 11.14	4.18	11.46	6.38	18.42	4.02
11		0.414	2.21 −12.40	−3.45 11.18	3.30	9.52	4.72	15.58	3.47

[a] The average values of the rate constants are $k_1 = (3.72 \pm 0.51) \times 10^{-4}$ l. mol^{-1} s^{-1}; $k'_1 = (4.75 \pm 0.70) \times 10^{-4}$ l. mol^{-1} s^{-1}; $k_{-1} = (9.58 \pm 1.20) \times 10^4$ s^{-1}; $k'_{-1} = (12.8 \pm 3.20) \times 10^4$ s^{-1}.

where [add] is the total concentration of the addition products at time t: $[add] = [AA]_t + [AB]_t + [AC]_t$. Since an addition product is formed, it may be assumed that $k_2[S] \gg k_{-1}$. Taking this into account and substituting $[TCN]_0 - [TCN]$ for [add], eq 14 changes into a rate equation which is similar to the experimental rate eq 4

$$-\frac{d[TCN]}{dt} = \left(k_1 + \frac{k_{-1}k_{-2}}{k_2[S]}\right)[EtO^-][TCN] - \frac{k_{-1}k_{-2}}{k_2[S]}[EtO^-][TCN]_0 \quad (15)$$

where the constants A and B of eq 4 are given by

$$A = \left(k_1 + \frac{k_{-1}k_{-2}}{k_2[S]}\right)[EtO^-] \quad (16)$$

$$B = -k_{-1}k_{-2}[EtO^-][TCN]_0/k_2[S] \quad (17)$$

A rate equation (eq 18) for the formation of the addition product can be derived in a similar way from the general reaction scheme:

$$d[add]/dt = -(k_1 + k_{-1}k_{-2}/k_2[S])[EtO^-][add] + k_1[EtO^-][TCN]_0 \quad (18)$$

This rate equation is similar to the experimental rate eq 5 where A' and B' are therefore given by

$$A' = -(k_1 + k_{-1}k_{-2}/k_2[S])[EtO^-] \quad (19)$$

$$B' = k_1[EtO^-][TCN]_0 \quad (20)$$

Since the value of A, B, A', and B' were obtained experimentally for each kinetic run, the values of k_1 and k_{-1} could be calculated using eq 21 and 22, respectively, which were

$$k_1 = \left(A + \frac{B}{[TCN]_0}\right)/[EtO^-] = B'/[EtO^-][TCN]_0 \quad (21)$$

$$k_{-1} = -k_2B[S]/k_{-2}[EtO^-][TCN]_0 = k_2[S]\left(A' + \frac{B}{[TCN]_0}\right)/k_{-2}[EtO^-] \quad (22)$$

derived from eq 16, 17, 19, and 20. It can be shown that the ratio k_2/k_{-2} needed for these calculations is given by $k_2/k_{-2} = K_{a(EtOD)}/K_{a[PhCH(OEt)CH_2CN]}$. Since $K_{a(EtOD)} \approx 10^{-18}$ and assuming that $K_{a[PhCH(OEt)CH_2CN]}$ is equal to that of acetonitrile ($pK_a = 10^{-25}$), a value of $k_2/k_{-2} \approx 10^7$ is obtained. The calculated values of k_1 and k_{-1} for each run (Table I) are quite constant. This indicates that the reaction scheme and the derived rate equations (eq 15 and 18) indeed represent correctly the presently studied addition reaction of ethyl [^{2}H]alcohol to *trans*-cinnamonitrile. Experimentally found values of A, B, and B' and known concentrations of reagents appear in eq 21. As a result, the calculated values of k_1 should be quite accurate. k_{-1} is not as accurate as k_1 because only an approximate value of k_2/k_{-2} is available.

Four distinct conditions may be associated with the suggested reaction scheme, from which rate eq 15 has been derived, namely (a) $k_1 \gg k_{-1}$, $k_2 \gg k_{-2}$; (b) $k_1 \gg k_{-1}$, $k_2 \ll k_{-2}$; (c) $k_1 \ll k_{-1}$, $k_2 \gg k_{-2}$; (d) $k_1 \ll k_{-1}$, $k_2 \ll k_{-2}$. If condition a holds, the result will be that $k_1 \gg k_{-1}k_{-2}/k_2[S]$ and $k_1[EtO^-][TCN] \gg B$, so that rate eq 15 will change to a second-order rate equation $R = k_1[EtO^-][TCN]$, which is different from the observed rate eq 4. Condition a was found to apply in case of the addition of methanol and/or ethanol to acrylonitrile,[2,4] acrylic esters,[4] and methacrylonitrile,[4] catalyzed by the derived sodium alkoxides. Conditions b and d cannot be applied at all since k_2 should be much larger than k_{-2} as $pK_{a(AA)} \gg pK_{a(EtOD)}$. As a consequence, condition c is the one which may hold for this reaction system. It requires that k_1 should be much smaller than k_{-1}, which is indeed the case.

The addition of ethyl alcohol to acrylonitrile catalyzed by sodium ethoxide was almost quantitative and much faster ($k_1 = 11.7 \times 10^{-2}$ l. mol^{-1} s^{-1} at 25 °C)[4] than the presently investigated addition of ethyl [^{2}H]alcohol to *trans*-cinnamonitrile [$k_1 = (3.72 \pm 0.51) \times 10^{-4}$ l. mol^{-1} s^{-1}]. This is of course due to the fact that $k_{-1} \gg k_1$ ($k_1/k_{-1} \approx 10^{-8}$) resulting from the phenyl group at C_β. However, such steric hindrance does not necessarily lead to k_{-1} being larger than k_1. The reverse order was found for the addition of ethyl alcohol to β-ni-

trostyrene catalyzed by sodium ethoxide ($k_1/k_{-1} \approx 10^6$).[10] indicating that the electronegativity of the substituent at C_α also affects this ratio to a large extent. One can, in fact, predict the relation between k_1 and k_{-1} for such equilibrium nucleophilic additions of BH to activated olefins catalyzed by the conjugate base, by comparing the acidities of BH and of the addition product. It is obvious, in line with the above-mentioned conditions associated with the reaction scheme, that if the addition product is more acidic than BH ($k_2 \gg k_{-2}$) k_1 should be larger than k_{-1}, and if the reverse is true ($k_2 \gg k_{-2}$), k_1 should be smaller than k_{-1}. In accordance with these considerations, it was found for the addition of ethyl alcohol to β-nitrostyrene[10] (for which $k_2 \ll k_{-2}$) that $k_1 \gg k_{-1}$.

The equilibrium concentrations of the addition product and of *trans*-cinnamonitrile are given by $[\text{add}]_{eq} = B'/A'$ and $[\text{TCN}]_{eq} = B/A$, respectively (eq 4 and 5). The equilibrium constant K for the overall addition reaction (eq 23) is given by

$$\textit{trans}\text{-Ph} + \text{CH=CH} + \text{CN} + \text{C}_2\text{H}_5\text{OD} \xrightleftharpoons{K(\text{EtO}^-)} \text{C}_2\text{H}_5\text{O} + \text{CH(Ph)} + \text{CH}_2\text{CN} \quad (23)$$

$$K = [\text{add}]_{eq}/[\text{TCN}]_{eq}[\text{S}] = \text{A'B'/A'B[S]} \quad (24)$$

By substituting the expressions of A, B, A', and B' (as derived from eq 17, 18, 20, and 21) in eq 24 this equation is changed to

$$K = k_1k_2/k_{-1}k_{-2} \quad (25)$$

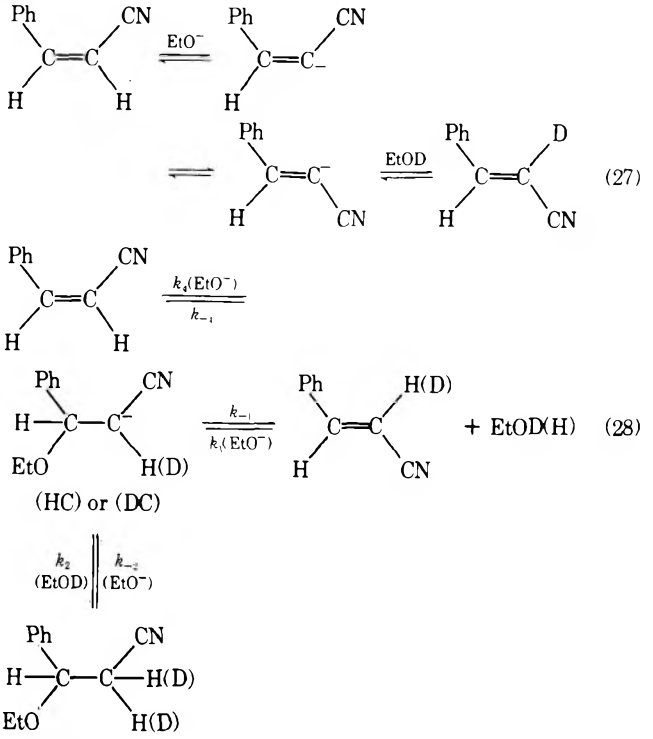
The value of $K = (3.9 \pm 0.2) \times 10^{-2}$ l. mol^{-1} obtained from eq 24 is relatively more accurate than the value of $K = (4.1 \pm 0.7) \times 10^{-2}$ l. mol^{-1} obtained from eq 25. This is due to the fact that A, A', B, and B' are experimentally obtained data, whereas some inaccuracy is involved in the values of k_{-1} and k_2/k_{-2}.

Hydrogen–Deuterium Exchange. As mentioned, a simultaneous hydrogen deuterium exchange of the α-vinyl hydrogen occurred during the addition of ethyl [^{2}H]alcohol to *trans*-cinnamonitrile catalyzed by sodium ethoxide. Two alternative pathways are possible for this exchange, namely via the derived vinyl carbanion[12-14] or by an addition–elimination mechanism (see scheme). The exchange reaction is faster than the addition reaction, as can be seen from the corresponding conversion curves (Figure 3).[24] This by itself cannot be regarded as evidence in favor of the vinyl carbanion mechanism. It is obvious that such a behavior may also result from an addition–elimination mechanism, only if the addition product is unstable and decomposes at a relatively high rate to *trans*-cinnamonitrile. This, in turn, can be the case only if the condition $k_1 \ll k_{-1}k_{-2}/k_2[\text{S}]$ holds for the rate eq 26.

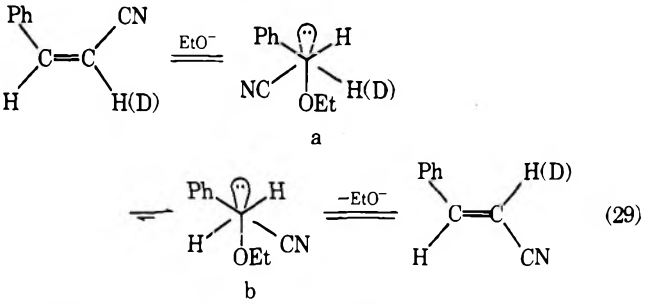
$$-\text{d[TCN]}/\text{d}t = (k_1[\text{TCN}] - k_{-1}k_{-2}[\text{add}]/k_2[\text{S}])[\text{EtO}^-] \quad (26)$$

Equation 26 is obtained from eq 15 by substituting $[\text{add}] = [\text{TCN}]_0 - [\text{TCN}]$. It follows from eq 17 that $k_{-1}k_{-2}/k_2[\text{S}] = -B/[\text{TCN}]_0[\text{EtO}^-]$, so that the value of $k_{-1}k_{-2}/k_2[\text{S}]$ can be calculated for each run. It was found by this way that $k_{-1}k_{-2}/k_2[\text{S}] \approx k_1$ (see Table I), which means that the above-mentioned condition does not apply for the exchange reaction. It should, therefore, be concluded that the hydrogen–deuterium exchange in the presently investigated system and its relatively higher rate as compared to that of the addition reaction is not due to an addition–elimination mechanism, but to the alternative vinyl carbanion mechanism. This depression of the addition–elimination mechanism is due to the combined effects of the steric hindrance to the nucleophilic attack ($k_1 \ll k_{-1}$, see Table I), to the fact that $k_2 \gg k_{-2}$, and to the lower value of k_{-2} as compared to k_3 (which is assumed by us to be so).

Isomerization. Isomerization was observed while carrying out kinetic rate measurements of the addition of ethyl [^{2}H] alcohol to *cis*-cinnamonitrile. In a typical run, starting with the cis isomer, the percentage of *trans*-cinnamonitrile in the mixture of the unreacted cis and trans isomers increased gradually up to a value of 55% at equilibrium (Figure 4).[24] It has been shown that vinyl carbanions derived from α,β-unsaturated nitriles have a very high configurational stability.[12-14] It may be therefore assumed that this cis to trans isomerization does not occur via the derived vinyl carbanion (eq 27) but rather by an addition–elimination mechanism (eq 28).



The isomerization involves an inversion of the carbanionic intermediate and rotation of the C_α–C_β bond (eq 29). The



activation energy for the inversion of the carbanion is very low ($\sim 10^{-2}$ kcal/mol).[21]

It is obvious that the conformational equilibrium of the anionic intermediates a and b is highly in favor of b. In accordance with this, very small amounts of the cis isomer were detected while measuring the rates of addition of ethyl [^{2}H]alcohol to *trans*-cinnamonitrile. At equilibrium the mixture of olefins consisted only of 4–6% of the cis isomer, its concentration being practically constant for each run during the whole reaction period (Table II).[24]

The transformation of the carbanionic intermediate a to b may be regarded as practically irreversible so that the backward reaction (k_{-4}) of (HC) or (DC) (eq 28) to the cis isomer is assumed to be negligible. The rate of the nucleophilic addition involving *cis*-cinnamonitrile (CCN) should therefore be given by

$$-\text{d[CCN]}/\text{d}t = k_4[\text{EtO}^-][\text{CCN}] \quad (30)$$

A detailed representative kinetic run is given in Table II.[24] First-order rate plots of log $[CCN]_t/[CCN]_0$ against t yielded straight lines in all cases studied (Figure 5).[24] The second-order rate constants were determined by dividing the pseudo-first-order rate constants by base concentration.

It may be argued that the trans olefin does indeed isomerize to the cis olefin, but that the very minor accumulation of the cis isomer is due to its faster consumption in the addition reaction, as compared to that of the trans olefin. This, however, is not the case as is evident from the fact that the second-order rate constants for the nucleophilic attack step of the ethoxide anion on the *cis*- and on the *trans*-cinnamonitrile are about the same: $k_4 \approx 3.50 \times 10^{-4}$ l. mol^{-1} s^{-1} and $k_1 = (3.72 \pm 0.51) \times 10^{-4}$ l. mol^{-1} s^{-1}.

Experimental Section

The infrared spectra were obtained with a Perkin-Elmer Model 257 spectrophotometer. NMR spectra were recorded on a JEOL 60 MHz spectrometer. VPC measurements were done on a Varian Aerograph Model 1800 gas chromatograph. Mass spectra were recorded on a Hitachi Perkin-Elmer Model RMV-6 (70 eV) mass spectrometer.

Materials. A mixture of *cis*- and *trans*-cinnamonitrile was synthesized[22] and separated by distillation on a spinning band column. The cis and trans isomers were each obtained at 98% purity (VPC). Absolute dry ethyl [^{2}H]alcohol (Miles-Yeda), 99.9% isotopically pure, was used. Ethanolic sodium ethoxide solutions were prepared by adding sodium metal to ethyl [^{2}H]alcohol under reflux and nitrogen. The base concentration was determined by titration with hydrochloric acid. Liquid materials and solutions were kept under pure nitrogen in flasks fitted with self-sealing rubber caps. Aliquot portions were removed from these flasks with syringes by applying nitrogen pressure.

Kinetic Runs. The reactions of *trans*-cinnamonitrile with ethyl [^{2}H]alcohol catalyzed by sodium ethoxide were carried out in a 150-ml flask connected to high vacuum and nitrogen lines. The flask was fitted with a self-sealing rubber cap through which liquids were introduced by syringes. The system was dried, evacuated, and flushed with dry nitrogen prior to the introduction of solvent and reactants. The required amounts of cinnamonitrile and ethyl [^{2}H]alcohol were introduced into the flask which was then immersed in a constant-temperature bath at (39 ± 0.5) °C. A solution of sodium ethoxide in ethyl [^{2}H]alcohol was then introduced and time recorded. Portions of the homogeneous mixture were withdrawn at measured intervals through a capillary stopcock, by applying a nitrogen pressure. The samples withdrawn were quenched with excess acetic acid and subjected to quantitative VPC and ir measurements. Some representative results of kinetic rate measurements of the addition reaction are presented in Table II.[24] The kinetic rate measurements of the addition of ethyl [^{2}H]alcohol to *cis*-cinnamonitrile and its simultaneous isomerization to the trans isomer were followed by VPC.

Quantitative Ir Analysis. The baseline density method[23] was used to determine the percentage of deuterium (% D) in the samples withdrawn from the reaction mixture. The ir spectrum of each of several mixtures composed of weighted amounts of α-deuterated and nondeuterated *trans*-cinnamonitrile was recorded using no solvent in sodium chloride cells (0.025 cm thickness). The transmittance T at 975 cm^{-1} (due to the C=CH bond) and the transmittance T' at 955 cm^{-1} (due to the C=CD bond) were determined. The % D of each of the same samples was determined from their mass spectra. A standard curve for the quantitative ir analysis was prepared by plotting log T/T' against % D. Solvents (ethyl [^{2}H]alcohol and acetic acid) were evaporated from each of the quenched samples withdrawn from the reaction mixture and the residue was distilled under vacuum into a cooled trap. This distillate consisted of a mixture of the addition product of ethyl [^{2}H]alcohol to *trans*-cinnamonitrile and the α-deuterated and nondeuterated olefins. The ir spectrum of the liquid was recorded, log T/T' determined, and the % D then directly read from the standard curve.

Registry No.—Ethyl [^{2}H]alcohol, 925-93-9; *trans*-cinnamonitrile, 1885-38-7; sodium ethoxide, 141-52-6; *cis*-cinnamonitrile, 24840-05-9.

Supplementary Material Available. Figures 3, 4, and 5 and Table II describing the addition of ethyl [^{2}H]alcohol to *trans*- and *cis*-cinnamonitrile (4 pages). Ordering information is given on any current masthead page.

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(24) See paragraph at end of paper regarding supplementary material.

Regioselective Nucleophilic Addition to 3,4-Lutidine

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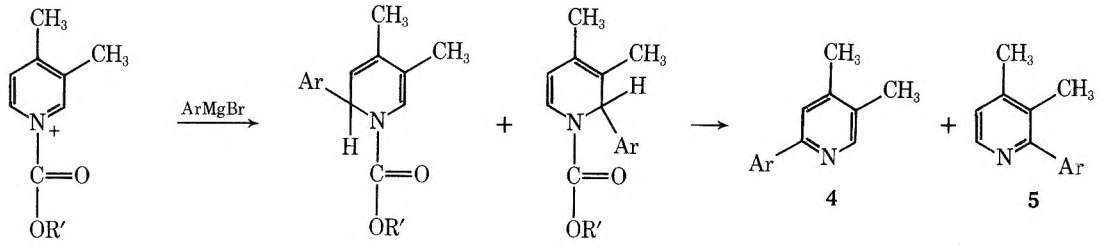
The usual orientation of nucleophilic addition at the 2 position of a 3-alkylpyridine can be changed by increasing the steric requirements of the nitrogen substituent. Thus the addition of phenylmagnesium bromide to the alkyl chloroformate ester salts of 3,4-lutidine is regioselective giving up to 90% addition of the aryl group at the 6 position. The large steric requirements of the 1-phenoxycarbonyl group or an ortho-substituted phenyl Grignard reagent gave 95% or greater regioselectivity of reaction at the less hindered α position of the 3,4-lutidine salt.

The reactions of nucleophiles with pyridines and pyridine derivatives may occur by addition at the 2, 4, or 6 position of the ring.[1] When the nucleophile is an organometallic reagent the addition usually takes place adjacent to the nitrogen, at the 2 or 6 positions,[2] and with the unsymmetrical ring having a 3-alkyl group, the addition is primarily at the 2 position.

Table I



Compd	R′	Ar	4/5	Overall yield, %	Solvent
a	CH_3CH_2	C_6H_5	78/22	31	Ether
b	i-C_4H_9	C_6H_5	75/25	27	THF
c	i-C_3H_7	C_6H_5	90/10	32	Ether
d	C_6H_5	C_6H_5	92/8	35	THF
e	CH_3CH_2	p-ClC_6H_4	62/38	40	THF
f	C_6H_5	p-ClC_6H_6	95/5	55	THF
g	CH_3CH_2	o-$CH_3C_6H_4$	95/5	46	THF
h	C_6H_5	o-$CH_3C_6H_4$	>95[a]	56	THF

[a] Only a trace of 5 could be detected in the NMR spectrum.

Thus the reactions of phenyllithium with 3-picoline,[3] 3-alkyl-1-ethoxypyridinium bromides with Grignard reagents,[4] and 3,4-lutidine methiodide with benzylmagnesium chloride[2c,5] all give as the sole or major product compounds resulting from addition of the organometallic reagent at the 2 position. This unexpected regiospecificity has been rationalized as resulting from an "ortho" effect of the 3-alkyl group probably related to London forces.[3]

The requirement for a series of 2-aryl-4,5-lutidines for a synthetic problem in this laboratory would be facilitated if the regiospecificity of the addition of an organometallic reagent to a 3,4-lutidine derivative could be controlled to give predominently reaction at the less hindered, 6 position. To make use of this steric factor to govern the regiospecificity of the nucleophilic addition it was evident from the literature that a group with large steric requirements would have to be introduced on the nitrogen. Since the pyridines were the desired product, the nitrogen substituent must be easily lost in the aromatization of the intermediate dihydropyridine. The activation of the pyridine ring to reaction with a Grignard reagent by salt formation with a chloroformate, recently reported by Fraenkel and co-workers[6] with 4-substituted pyridines, seemed to provide a possible method for controlling the regiospecificity.

The steric requirements of the nitrogen substituent were varied by changing the nature of the alkyl group of the ester of the chloroformate, and the various 1-alkoxycarbonyl-3,4-lutidinium salts (**1**) were treated with an aryl Grignard reagent. The NMR spectrum of the mixture of 1-alkoxycarbonyl-2-aryl-1,2-dihydro-3,4-lutidine (**3**) and 1-alkoxycarbonyl-2-aryl-1,2-dihydro-4,5-lutidine (**2**) was not resolved sufficiently to allow analysis of the product. Thus aromatization of the mixture by heating with sulfur gave the pyridines **4** and **5** which could be analyzed by the NMR. The results of the study are given in Table I.

Results and Discussion

The reaction of 3,4-lutidine with the chloroformates gave the salts which in turn were treated with a Grignard reagent to give a mixture of dihydropyridines (**2** and **3**). Except for the product from the reaction of p-chlorophenylmagnesium bromide and the phenyl chloroformate salt of 3,4-lutidine, which was largely the solid 1-phenoxycarbonyl-2-p-chlorophenyl-4,5-dimethyl-1,2-dihydropyridine (**2f**), the oily mixtures of dihydropyridines were not analyzed. The products were aromatized by heating with sulfur rather than by reaction with n-butyllithium, the procedure previously described,[6] since the former procedure is more convenient for preparative scale reactions.

The reactions of unhindered aryl Grignard reagents with the lutidine salts from ethyl and isobutyl chloroformate, alkyl groups with no branching near the carbonyl group, gave significant amounts of reaction at the 2 position of the pyridine ring (**1a,b,e**). The alkoxycarbonyl salts of 3,4-lutidine (**1**) gave a much greater ratio of addition of the aryl Grignard reagent at the 6 position than did other derivatives of 3,4-lutidine or the base itself. An increase in the steric requirements of the ester (**1c,d,f**) or in the Grignard reagent (**g**) gave much greater regioselectivity with nearly exclusive reaction at the 6 position. Thus with the hindered Grignard reagent, o-tolylmagnesium bromide, even the smallest ester, ethoxycarbonyllutidinium salts, gave nearly exclusively a single isomer. This orientation is particularly noteworthy when compared with the reaction of o-tolyllithium or o-ethylphenyllithium with 3-picoline which was reported to give about 95% addition at the 2 position.[7] Similar high regiospecificity was achieved with any aryl Grignard reagent with the phenyl chloroformate salt of 3,4-lutidine.

These results clearly show that orientation of nucleophilic arylation of 3-alkylpyridines can be controlled to give substitution at the position ortho to the alkyl group using the base or by using *our* procedure to give substitution "para" to the alkyl substituent.

Experimental Section

Melting points were determined using a Thomas-Hoover capillary melting point apparatus or a Mel-Temp apparatus and were not corrected for thermometer stem exposure. Elemental analyses were determined using an F and M Model 185 C, H, and N analyzer. Infrared spectra were determined using Perkin-Elmer Model 137 or 337 spectrometers with samples prepared as mulls or KBr pellets. The nuclear magnetic resonance spectra were determined using a JEOL Model MH-100 spectrometer.

2-Aryl-3,4- and -4,5-dimethylpyridines (4 and 5). A solution of 3,4-lutidine (5.36 g, 0.05 mol) in 150 ml of dry THF (ether) under nitrogen was cooled in a carbon tetrachloride–dry ice bath. An alkyl chloroformate (0.05 mol) was added dropwise over 5 min to the stirred solution, forming a white precipitate. An aryl Grignard reagent (0.06 mol) in 55 ml of THF (ether) was then added dropwise at such a rate as not to allow the temperature to rise above 0 °C. After the addition was completed, the mixture was stirred at 0–5 °C (ice bath) for 1 h and hydrolyzed with 50 ml of 20% ammonium chloride solution. The or-

ganic layer was washed with 50-ml portions of 5% NaOH, water, 5% HCl, water, and brine, and then was dried (K_2CO_3). Evaporation of the solvent gave yellow oils as a residue which were treated with 1 equiv of sublimed sulfur at 190–200 °C for 45 min. The reaction mixture was cooled, dissolved in 150 ml of ether, and extracted with three 50-ml portions of 10% hydrochloric acid. The acid extracts were washed with 50 ml of ether, made basic with 20% NaOH, and extracted with four 50-ml portions of ether. The organic layer was washed with brine and dried (K_2CO_3). The solution was filtered and concentrated and the residue was distilled, giving a mixture of 2-aryl-3,4-dimethylpyridine (**5**) and 2-aryl-4,5-dimethylpyridine (**4**). The percentages of the isomeric pyridines **4** and **5** were determined from the NMR spectrum of the mixture. The combined quantities of **4** and **5** were given from the integration of the signal for the α protons which were accidentally identical at δ 8.54 for Ar = C_6H_5 or p-ClC_6H_4 or at δ 8.64 for Ar = o-$CH_3C_6H_4$. The relative amount of **5** in the mixture was obtained from the integration of the signal for the 5 proton, a doublet at δ 7.14 for Ar = p-ClC_6H_4 or o-$CH_3C_6H_4$ or at δ 7.08 for Ar = C_6H_5.

1-Phenoxycarbonyl-2-*p*-chlorophenyl-4,5-dimethyl-1,2-dihydropyridine (2f). A solution of 3,4-lutidine (10.71 g, 0.1 mol) in 200 ml of dry THF under nitrogen was cooled in a carbon tetrachloride–dry ice bath. Phenyl chloroformate (15.66 g, 0.1 mol) was added dropwise over 5 min to the stirred solution giving a white precipitate. A solution of p-chlorophenylmagnesium bromide (0.12 mol) in 100 ml of THF was added dropwise at a rate which kept the temperature below 0 °C. After the addition was completed, the mixture was stirred at 0–5 °C (ice bath) for 1 h and then was hydrolyzed with 100 ml of 20% NH_4Cl solution. The organic layer was washed with 50 ml of 5% NaOH solution and 50 ml of saturated brine solution and then was dried (K_2CO_3) and evaporated. The residual yellow oil crystallized on standing under pentane to give 25.7 g (73%) of **2f** as a light yellow solid. The product was recrystallized twice from isopropyl alcohol to give an analytical sample of **2f:** mp 111–114 °C; NMR ($CDCl_3$) δ 7.08–7.80 (m, 9 H), 6.92 (br s, 1 H), 6.03 (d, 1 H), 5.68 (d, 1 H), 1.70–2.08 (2 s, 6 H); ir (KBr) 1705 cm^{-1}.

Anal. Calcd for $C_{20}H_{18}ClNO_2$: C, 70.69; H, 5.34; N, 4.12. Found: C, 70.95; H, 5.26; N, 4.07.

2-Phenyl-4,5-dimethylpyridine (4d). A solution of 3,4-lutidine (5.36 g, 0.05 mol) in 150 ml of dry THF under nitrogen was cooled in a carbon tetrachloride–dry ice bath. Phenyl chloroformate (7.83 g, 0.05 mol) was added dropwise over 5 min to the stirred solution, forming a white precipitate. A solution of phenylmagnesium bromide (0.06 mol) in 55 ml of THF was added dropwise at a rate to keep the temperature below 0 °C. After the addition was complete, the mixture was stirred at 0–5 °C (ice bath) for 1 h and then was hydrolyzed with 50 ml of 20% NH_4Cl solution. The organic layer was washed with 50-ml portions of 5% NaOH, water, 5% HCl, water, and brine, and then was dried (K_2CO_3). The mixture was filtered and evaporated to yield 12.32 g of a yellow oil. The crude yellow oil was treated with sublimed sulfur (1.29 g, 40.37 mmol) at 190–200 °C for 45 min. The reaction mixture was cooled, dissolved in 150 ml of ether, stored over sodium hydroxide pellets overnight, and filtered. The filtrate was washed with 50 ml of 10% sodium hydroxide and 50 ml of water, and was extracted with three 50-ml portions of 10% hydrochloric acid. The acid extracts were washed with 50 ml of ether, made basic with 20% sodium hydroxide and extracted with four 50-ml portions of ether. The organic layer was washed with water and brine and was dried (K_2CO_3). The solution was filtered, concentrated, and distilled, giving 3.23 g (35%) of **4d** as a light yellow oil: bp 117–120 °C (0.35 mm); picrate mp 203–204 °C [lit.[8] bp 146–150 °C (6 mm), picrate mp 202–203 °C]; NMR ($CDCl_3$) δ 8.58 (s, 1 H), 8.12–8.28 (m, 2 H), 7.44–7.70 (m, 4 H), 2.16 (s, 6 H).

2-*p*-Chlorophenyl-4,5-dimethylpyridine (4f). A mixture of 15.0 g (44.14 mmol) of crude **2f** and 1.27 g (39.73 mmol) of sublimed sulfur was heated with stirring at 190–200 °C for 45 min. The reaction mixture was cooled, dissolved in 150 ml of ether, and placed over sodium hydroxide pellets overnight. The solution was filtered and washed with 50 ml of 20% sodium hydroxide solution and 50 ml of water. The solution was extracted with three 50-ml portions of 10% hydrochloric acid. The acid extracts were filtered, washed with 25 ml of ether, made basic with 20% sodium hydroxide, and extracted with four 50-ml portions of ether. The ether extracts were washed with saturated brine solution, dried (K_2CO_3), and evaporated to give a brown solid. Distillation of the solid (bp 125–130 °C, 0.06 mm) yielded 6.9 g (72%) of **4f** as a light yellow solid. The solid was recrystallized twice from hexane–Norite to give **4f** as white crystals: mp 61.5–62 °C; NMR ($CDCl_3$) δ 8.48 (s, 1 H), 8.00 (d, 2 H), 7.46 (d, 2 H), 7.43 (s, 1 H), 2.20 (s, 6 H).

Anal. Calcd for $C_{13}H_{12}ClN$: C, 71.72; H, 5.56; N, 6.43. Found: C, 71.71; H, 5.65; N, 6.56.

2-(*o*-Tolyl)4,5-dimethylpyridine (4g). Using the procedure for the preparation of **4f,** 10.71 g (0.1 mol) of 3,4-lutidine, 11.19 g (0.1 mol) of ethyl, chloroformate, and 0.12 mol of o-tolylmagnesium bromide in 100 ml of THF gave, after vacuum distillation, 16.2 g of a yellow oil. Treatment with 1.91 g (59.7 mmol) of sublimed sulfur gave, after vacuum distillation, 9.0 g (46%) of a yellow oil. The oil was treated with Norite–chloroform and redistilled to give an analytical sample of **4g:** bp 110–115 °C (0.35 mm); picrate, mp 166–167 °C; NMR ($CDCl_3$) δ 8.64 (s, 1 H), 7.35–7.68 (m, 4 H), 7.30 (s, 1 H), 2.43 (s, 3 H), 2.24 (s, 6 H).

Anal. Calcd for $C_{14}H_{15}N$: C, 85.24; H, 7.66; N, 7.10. Found: C, 85.28; H, 7.65; N, 7.12.

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Registry No.—2f, 59463-69-3; **4d,** 27063-84-9; **4d** picrate, 27063-85-0; **4f,** 59463-70-6; **4g,** 59463-71-7; 3,4-lutidine, 583-58-4; phenyl chloroformate, 188-14-9; p-chlorophenyl bromide, 106-39-8; phenyl bromide, 108-86-1; o-tolyl bromide, 95-46-5; ethyl chloroformate, 541-41-3.

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Synthesis of Cyclic and Acyclic Tri- and Tetrasubstituted Hydroxyguanidines

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Acyclic trisubstituted and previously unknown tetrasubstituted hydroxyguanidines **6** have been prepared from *C*-chloroformamidinium chlorides **3** (available from ureas or thioureas) via reaction with *O*-(tetrahydro-2-pyranyl)-hydroxylamine (**4**), followed by removal of the protecting group by acid hydrolysis. Cyclic tri- and tetrasubstituted hydroxyguanidines **11** have been prepared by the reaction of phosgene-*O*-(tetrahydro-2-pyranyl)oxime (**7**) or phosgene-*O*-(*N*-methylcarbamoyl)oxime (**8**) with a diamine, followed by removal of the protecting group by acid or base hydrolysis.

Hydroxyguanidines and their derivatives may be active pharmaceutical agents and agrichemicals.[2] Synthetic routes to acyclic 1,1,3-trisubstituted hydroxyguanidines[3] are limited and the 1,1,3,3-tetrasubstituted analogues are unknown. Known cyclic hydroxyguanidines are limited to the acid salts of 1,3-ethylene- and 1,3-trimethylene-2-hydroxyguanidine; the neutral compounds are unstable.[4] This paper describes two useful methods for preparing these compounds.

While selected acyclic 1,1,3-trisubstituted hydroxyguanidines have been made by nucleophilic displacement of either a chlorine or *S*-methyl group of **1** with hydroxylamine[3] (eq 1), yields of **2** are low and the urea is a major by-product.

$$R^1N{=}C(X)NR^2R^3 + NH_2OH$$

1a, X = Cl
b, X = SCH_3

$$\xrightarrow{CH_3OH} R^1N(H)-\overset{\overset{NOH}{\|}}{C}-NR^2R^3 + R^1NH\overset{\overset{O}{\|}}{C}NR^2R^3 \quad (1)$$

2

These problems can be avoided and the scope of synthesis expanded to tetrasubstituted and cyclic compounds as follows. *C*-Chloroformamidinium chloride salts **3** are prepared in the standard way from reaction of the appropriate urea (or thiourea) with phosgene.[5] Reaction of **3** with *O*-(tetrahydro-2-pyranyl)hydroxylamine (**4**)[6] (a masked hydroxylamine soluble in most aprotic solvents) and a tertiary amine base gives *O*-(tetrahydro-2-pyranyl)hydroxyguanidines **5**. The yield is high for acyclic compounds, and low for cyclics.[7] The protecting group can then be cleaved by acid to generate the desired product **6** (eq 2, 3, 4). Acyclic examples are given in Table I.

$R^1R^2NCONR^3R^4$
or $+ COCl_2$
$R^1R^2NCSNR^3R^4$

$$\xrightarrow{C_6H_5CH_3} [R^1R^2N-\overset{\overset{Cl}{|}}{C}-NR^3R^4]^+Cl^- \quad (2)$$

3

$$3 + NH_2-O-\text{(tetrahydropyranyl)} + 2NEt_3$$

4

$$\xrightarrow[\text{or } CHCl_3]{CH_3CN} R^1R^2N-\overset{\overset{N-O-\text{(tetrahydropyranyl)}}{\|}}{C}-NR^3R^4 \quad (3)$$

5

$$5 \xrightarrow{H_3O^+} R^1R^2NC(=NOH)NR^3R^4 \quad (4)$$

6

A better route to the cyclic hydroxyguanidines has been developed. Reaction of either phosgene *O*-(tetrahydro-2-pyranyl)oxime (**7**) or phosgene *O*-(methylcarbamoyl)oxime (**8**)[8] (carbonyl oxime synthons) with the appropriate diamine and tertiary amine base, followed by acid or base hydrolysis, gives **11** (eq 5 and 6). Cyclic examples are given in Table II.

$$\text{Cl}_2C{=}NOX + R^1NH(CH_2)_nNHR^2 + 2NEt_3 \xrightarrow[\text{reflux}]{CHCl_3} R^1N(NOX)(CH_2)_nNR^2 \quad (5)$$

n = 2,3

7, X = O-(tetrahydropyranyl)
8, X = $CONHCH_3$

9, X = O-(tetrahydropyranyl)
n = 2,3
10, X = $CONHCH_3$
n = 2,3

9 —(3 N HCl)→ **11**, R^1 = alkyl, aryl; R^2 = alkyl, H; n = 2,3

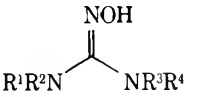
10 —(CH_3ONa/CH_3OH or KOH/CH_3OH)→ **11**, R^1 = alkyl, aryl; R^2 = alkyl, H; n = 2,3 (6)

Experimental Section

General. Melting points were taken on a Mel-Temp melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian A-60 in deuteriochloroform unless otherwise stated. All shifts are reported in δ with tetramethylsilane as an internal standard. Mass spectra were determined with a Du Pont CEC 110 B. Analyses were performed by the Central Research and Development Department Analytical Section.

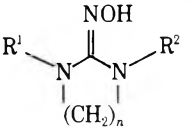
All experiments were carried out under a dry nitrogen atmosphere unless otherwise noted. Solvents were dried with 4A molecular sieve. All equipment was dried with a heat gun while under vacuum. All new compounds were purified by chromatography on SilicAR CC-7, and shown to be single compounds by two different thin layer solvent systems. Oils were converted into their hydrochloride salt with dry hydrogen chloride in ether.

Table I. Acyclic Tri- and Tetrasubstituted Hydroxyguanidines



R^1	R^2	R^3	R^4	Yield, %	Mp, °C (registry no.)	NMR	Mass spectrum, *m/e*
C_6H_5	CH_3	CH_3	CH_3	31	112–114 (59812-83-8)	2.67 (s, 6 H), 3.17 (s, 3 H), 6.65–7.40 (m, 6 H) (phenyl and NOH)	Calcd for $C_{10}H_{15}N_3O$: 193.1214 Found: 193.1220
$C_6H_5CH_2$	CH_3	C_2H_5	C_2H_5	50	HCl salt 149 dec (59812-84-9)	1.12 (t, J = 7 Hz, 6 H), 2.70 (s, 3 H), 2.93–3.45 (m, 4 H), 4.35 (s, 2 H), 7.23 (s, 5 H)	Calcd for $C_{13}H_{21}N_3O$: 235.1683 Found: 235.1689
$C_6H_5CH_2$	CH_3	CH_3	H	42	HCl salt 132–137 (59812-85-0)	1.62 (bs, 2 H), 2.52 (s, 3 H), 2.83 (s, 3 H), 4.15 (s, 2 H), 7.34 (s, 5 H)	Calcd for $C_{10}H_{15}N_3O$: 193.1214 Found: 193.1202
C_6H_5	CH_3	CH_3	H	48	HCl salt 164–168 (59812-86-1)	2.47 (s, 3 H), 3.15 (s, 3 H), 6.43–7.40 (m, 6 H)	Calcd for $C_9H_{13}N_3O$: 179.1058 Found: 179.1041
C_6H_5	CH_3	C_2H_5	H	65	86–88 (59226-52-7)	0.98 (t, J = 7 Hz, 3 H), 2.86 (q, J = 7 Hz, 2 H), 3.16 (s, 3 H)	Calcd for $C_{10}H_{15}N_3O$: 193.1214 Found: 193.1224

Table II. Cyclic Tri- and Tetrasubstituted Hydroxyguanidines



R^1	R^2	n	NMR	Mp, °C (registry no.)	Mass spectrum, *m/e*
$C_6H_5CH_2$	CH_3	3	1.40–2.20 (m, 2 H) 2.86 (s, 3 H) 2.87–3.30 (m, 4 H) 4.45 (s, 2 H) 7.28 (s, 5 H)	108–110 (59812-87-2)	Calcd for $C_{12}H_{17}N_3O$: 219.1371 Found: 219.1369
$C_6H_5CH_2$	CH_3	2	2.84 (s, 3 H) 3.08 (ns, 4 H) 4.58 (s, 2 H) 7.33 (s, 5 H)	94–96 (59812-88-3)	Calcd for $C_{11}H_{15}N_3O$: 205.1214 Found: 205.1202
$C_6H_5CH_2$	H	2	3.12–3.28 (A^2B^2, 4 H)	118–120 (59812-89-4)	Calcd for $C_{10}H_{13}N_3O$: 190.1058 Found: 190.1045

All new compounds have been characterized by spectral techniques and their structures are consistent with spectral data.

General Procedure for Preparation of Acyclic Tri- and Tetrasubstituted Hydroxyguanidines via 2-Chloroformamidinium Chlorides. Preparation of 1-Phenyl-1,3,3-trimethyl-2-hydroxyguanidine. Starting materials are either the corresponding urea or thiourea prepared by standard procedures using either isocyanates or isothiocyanates and amines, or carbamoyl chlorides and amines.

N-Phenyl-*N*,*N*′,*N*′-trimethylurea (8.9 g, 0.05 mol) was dissolved in 50 ml of toluene and cooled to −22 °C. To it was added 4.9 g (0.05 mol) of liquid phosgene. The reaction was run overnight and the 2-chloroformamidinium chloride (3) formed as a white solid. The moisture-sensitive white solid could be either isolated by filtration in a drybox or, after decanting the liquid, redissolved in dry acetonitrile and carried on to the next step.

In some instances the salt did not crystallize but formed an oil and was carried on to the next step.

After removal of toluene, followed by solution in 50 ml of acetonitrile, the salt solution was added dropwise to a cool (−22 °C) solution of 5.85 g (0.05 mol) of *O*-tetrahydropyranylhydroxylamine (4)[6] and 10.1 g (0.1 mol) of triethylamine. The reaction mixture was warmed to 25 °C, stirred for 2 h, then poured into 100 ml of methylene chloride. The methylene chloride layer was extracted six times with 100 ml of water and dried, and the solvent was removed. The resultant liquid was dissolved in 55 ml of 1 N HCl and 100 ml of water and heated on a steam bath for 1 h. The aqueous phase was extracted twice with 100 ml of methylene chloride, then made basic with 60 ml of 1 N NaOH and extracted twice with 100 ml of methylene chloride. The organic layer was dried over $MgSO_4$ and evaporated to give a white solid: 3.0 g (31%); mp 112–114 °C; NMR ($CDCl_3$) δ 2.67 (s, 6 H), 3.17 (s, 3 H), 6.65–7.40 (m, 5 H); mass spectrum 193.1220 (calcd for $C_{10}H_{15}N_3O$, 193.1214).

Preparation of Phosgene *O*-(Tetrahydro-2-pyranyl)oxime (7). Dihydropyran (2.52 g, 0.03 mol) and phosgene oxime[9] (3.6 g, 0.03 mol) were dissolved in 100 ml of dry tetrahydrofuran. Two drops of phosphorus oxychloride was added, and the mixture was heated at reflux for 4–12 h. The reaction was followed by TLC. The solvent was then evaporated and the residue distilled. A colorless liquid (3.4 g, 58% yield) was collected: bp 62–63 °C (0.7 mm); NMR ($CDCl_3$) δ 1.32–2.10 (m, 6 H), 3.40–4.20 (m, 2 H), 5.35 (bs, 1 H); mass spectrum M^+ *m/e* 197 (too small to measure), 139, 113, 96, 85, measured for $C_3H_3NOCl_2$ 138.9590, calcd 138.9591, for $(CH_2{=}CHON{=}CCl_2)^+$.

General Procedure for Preparation of Tri- and Tetrasubstituted Cyclic Hydroxyguanidines. I. Preparation of 1-Benzylimidazolidin-2-one Oxime from a Diamine and 8. To a refluxing solution of *N*-benzylethylenediamine (1.40 g, 0.01 mol) and triethylamine (2.02 g, 0.02 mol) in 100 ml of chloroform was added dropwise (0.5 h) 1.70 g (0.01 mol) of 8[8] in 50 ml of chloroform. The solution was allowed to reflux for 12 h and cooled, and the organic layer was worked up with 2 × 100 ml of water. After drying ($MgSO_4$), 2.33 g (94% yield) of brown oil was recovered. The oil was dissolved in 100 ml of methanol and 1.08 g (0.02 mol) of potassium hydroxide was added. The

solution was heated to reflux for 24 h, poured into 500 ml of water, acidified to pH 1, and extracted with 2 × 100 ml of methylene chloride. The aqueous layer was then made basic (pH 9) and extracted with 2 × 100 ml of methylene chloride; the extracts were dried ($MgSO_4$) and evaporated, then chromatographed to give an off-white crystalline substance (0.6 g, 31% yield).

II. 1-Benzylimidazolidin-2-one Oxime from a Diamine and 7. To a refluxing solution of *N*-benzylethylenediamine (0.75 g, 0.005 mol) and triethylamine (1.01 g, 0.01 mol) in 100 ml of chloroform was added dropwise over 5 h 1.0 g (0.0051 mol) of **7** in 10 ml of chloroform. After the solution was heated at reflux for 4 h, the solvent was evaporated and the residue hydrolyzed with 20 ml of 1 N HCl on a steam bath for 1 h. The workup is the same as part I (from acidification step). The yield was 0.55 g (58%).

Registry No.—**7**, 59812-90-7; **8**, 24248-83-7; **10** (n = 2), 59812-91-8; dihydropyran, 110-87-2; phosgene oxime, 1794-86-1; *N*-benzylethylenediamine, 4152-09-4.

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Fully Automated Solid Phase Synthesis of Protected Peptide Hydrazides on Recycling Hydroxymethyl Resin

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A fully automated solid phase synthesis of Boc-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-$HNNH_2$ (I) on hydroxymethyl resin (II) is described. All of the operations, including esterification of the first amino acid residue to the resin, deprotection of α-amino protecting group followed by coupling reaction with the next amino acid residue, as well as hydrazinolytic cleavage of I from the solid support, have been automated. The regenerated resin II was reused several times for the synthesis of the same compound to give automatically several batches of I. Results of this process are compared with results of other solid phase and classical syntheses of the Gly-Phe-Phe-Tyr-Thr sequence.

In solid phase peptide synthesis,[1] the process of assembling the peptide chain anchored to a polymer support has been quite effectively automated.[2] However, the attachment of the first amino acid residue to the resin and the cleavage of the anchoring linkage in order to release the products from the solid support have to be carried out individually in separate vessels.[3-5] In the following, a completely automatic recycled synthesis of the protected pentapeptide hydrazide Boc-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-$HNNH_2$[6] (I) on the hydroxymethyl resin[7,8] (II) is described. The results of five consecutive syntheses of I on the same batch of resin II are presented and compared with results of several experiments in which the same pentapeptide sequence Gly-Phe-Phe-Tyr-Thr was prepared by different procedures.

For the fully automated synthesis of I, a Beckman Model 990 peptide synthesizer[9] was programmed to perform all operations described below within the same reaction vessel. Boc-Thr(Bzl)-OH was esterified to resin II by the 4-dimethylaminopyridine catalyzed dicyclohexylcarbodiimide (DCC) procedure.[8] After benzoylation to block remaining unreacted alcoholic functions on the resin, Boc-Tyr(Bzl)-OH, Boc-Phe-OH, Boc-Phe-OH, and Boc-Gly-OH were sequentially coupled to the growing peptide chain on the resin according to general principles of the solid phase method.[1-5] In each coupling cycle, the *tert*-butyloxycarbonyl group was removed by a 20-min treatment with 33% trifluoroacetic acid in CH_2Cl_2 and the coupling reaction was effected with 2.5-fold excess each of Boc-amino acid and DCC for 2 h. Upon completion of the chain assembly the pentapeptide resin was stirred with 10% H_2NNH_2 in DMF for 16 h. Product I released from the polymer support was obtained in crystalline form after evaporation of the reaction and wash fluids collected from the vessel outlet. The hydrazinolysis reaction served also to regenerate resin II which remained in the reaction vessel. It was recycled four times through the entire synthetic protocol to give a total of five batches of I, which was purified by recrystallization. Overall yields from each run were approximately 60% with no sign of decreasing (see Table I). The resin particles survived all operations as evident from inspection of the beads before and after these experiments under a microscope. There was no indication of any disintegration of resin particles. The completeness of the hydrazinolytic cleavage was checked after each run by ir spectrophotometry.[8] The rate of hydrazinolysis was found to be surprisingly rapid with a half-life of about 45 min.

Thus, with the possible exception of aspartic or glutamic acid containing peptides, the process described above appears to be rather versatile and generally applicable to rapid synthesis of protected oligopeptide hydrazides. These are useful intermediates for polypeptide synthesis by the azide method[10] allowing effective combination of solid phase techniques and classical procedures[11,12] with retention of the best features of each.[4]

In Table II, the results of recycled automated synthesis of I are compared with those of other processes for the synthesis of the same sequence.[13] A dramatic increase in speed, efficiency, and simplicity can be noted.

The manual solid phase synthesis of I on hydroxymethyl

Table I. Recycled Automated Synthesis of Boc-Gly-Phe-Phe-Tyr(Ezl)-Thr(Bzl)-$HNNH_2$ on $HOCH_2$-C_6H_4-Resin[a]

Run no.	Product wt, g	Yield, %[b]	Mp, °C	$[\alpha]^{25}D$, deg		Anal.	
				Calcd	67.30 C	6.63 H	10.56 N
1	1.80	54.0	229–230	−2.24	67.10	6.68	10.43
2	2.09	62.4	228–230	−2.12	67.05	6.73	10.32
3	2.01	60.2	229–230	−2.35	67.32	6.76	10.39
4	2.04	61.1	229–230	−2.38	67.04	6.63	10.43
5	2.05	61.4	229–230	−2.16	67.47	6.52	10.33

[a] Hydroxymethylated copolystyrene–1% divinylbenzene (6.0 g, 0.70 mmol/g) was used. The degree of substitution was 0.55 mmol Thr/g. [b] Theoretical yield, 3.6 mmol = 3.34 g.

Table II. Synthesis of Gly-Phe-Phe-Tyr-Thr Sequence by Solid Phase Techniques and Classical Method

Compd	Synthetic method	Time consumed	Overall yield, %
Boc-Gly-Phe-Phe-Tyr-Thr-$HNNH_2$ (I) (mp 229–230 °C, cryst)	$HOCH_2$—Resin(automated)	30 h	59.2[a]
Boc-Gly-Phe-Phe-Tyr-Thr-$HNNH_2$ (I) (mp 227–229 °C, cryst)	$HOCH_2$—Resin(manual)[b]	5 days	61.5
Z-Gly-Phe-Phe-Tyr-Thr-$HNNH_2$ (III) (mp 215–218 °C, cryst)	$ClCH_2$—Resin	6 days	34.0
Z-Gly-Phe-Phe-Tyr-Thr-OH (IV) (mp 205–208 °C, cryst)	$HOCH_2$—OCH_2—Resin	4 days	61.2
Fmoc-Gly-Phe-Phe-Tyr-Thr-$HNNH_2$ (V) (mp 196–198 °C, cryst)	H_2NNH—COO—C(CH_3)(CH_3)—CH_2—CH_2—OCH_2—Resin[b]	4 days	36.1
Z-Gly-Phe-Phe-Tyr-Thr-$HNNH_2$ (VI) (mp 241–243 °C, cryst)	Classical synthesis (3 + 2)	40 days[c]	33.0

[a] Average of five synthetic runs. [b] For experimental details, see ref 8. [c] The time consumed includes purification and characterization of intermediates. The actual time spent on the synthetic operations was about 15 days.

resin as well as the preparation of Fmoc-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-$HNNH_2$ (V) on 3-(*p*-benzyloxyphenyl)-1,1-dimethylpropyloxycarbonylhydrazide resin have already been described previously.[8] Preparation of Z-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-$HNNH_2$ (III) by the standard Merrifield technique[14] on chloromethyl resin gave the desired compound in 34% overall yield. This synthesis was started by refluxing Boc-Thr(Bzl)-OH triethylamine salt with $ClCH_2$-C_6H_4-resin. The pentapeptide chain was subsequently built up in the usual manner[3,14] with Boc-Tyr(Bzl)-OH, Boc-Phe-OH, Boc-Phe-OH, and Z-Gly-OH. The low yield of this process probably is attributable to the fact that the clevage product is heavily contaminated with hydrazine hydrochloride which tends to reduce the recovery of the desired compound by crystallization.

For the synthesis of Z-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-OH (IV), Bpoc-Thr(Bzl)-OH was esterified to *p*-alkoxybenzyl alcohol resin[15] through the 4-dimethylaminopyridine catalyzed DCC method.[8] The synthesis was then continued by sequential incorporation of Bpoc-Tyr(Bzl)-OH, Bpoc-Phe-OH, Bpoc-Phe-OH, and Z-Gly-OH into the resin under the conditions identical with those described above except that the deblocking of the Bpoc groups was effected by 0.5% TFA in CH_2Cl_2 (10 min). Product IV was obtained in 61.2% overall yield as a pure, crystalline solid after cleavage from the polymer support by 50% TFA (30 min) and crystallization.

For a classical synthesis of Z-Gly-Phe-Phe-Tyr(Bzl)-Thr-$HNNH_2$ (VI), a 3 + 2 fragment condensation approach was chosen. Boc-Tyr(Bzl)-OH was coupled to H-Thr-OCH_3 by the DCC procedure[16] to provide Boc-Tyr(Bzl)-Thr-OCH_3 which on treatment with HCl–THF gave the dipeptide ester salt HCl·H-Tyr(Bzl)-Thr-OCH_3. Reaction of phenylalanine with Boc-Phe-OSu yielded Boc-Phe-Phe-OH, which was treated with TFA and the resulting dipeptide H-Phe-Phe-OH was subsequently acylated with Z-Gly-OSu to give Z-Gly-Phe-Phe-OH. This tripeptide was then condensed with the dipeptide ester HCl·Tyr(Bzl)-Thr-OCH_3 obtained above by the DCC–HOBT procedure[17] to afford the pentapeptide methyl ester Z-Gly-Phe-Phe-Tyr(Bzl)-Thr-OCH_3. On hydrazinolysis, the desired product VI was obtained in 33% overall yield. A total of 40 days were required for completing this synthesis, including the time spent on purification, crystallization, and analytical characterization of the intermediates and the product. It is obvious that the time requirement would be appreciably reduced if the classical synthesis were to be repeated, and it could readily be scaled up. However, the method is far less adaptable to automation than solid phase synthesis.

Reuse of the same hydroxymethyl resin (II) after synthesis of one compound for he preparation of another is also demonstrated. The resin II that had been used as the polymer support for synthesis I was utilized in solid phase synthesis of Z-Gly-His(Tos)-Lys(Z)-OCH_2-C_6H_4-resin. Ammonolysis of this material produced crystalline pure Z-Gly-His-Lys(Z)-

NH_2 in 64.2% overall yield. The *p*-toluenesulfonyl protecting group of the histidine side chain was cleanly removed at the same time during ammonolytic cleavage.

Experimental Section

Melting points are uncorrected. Thin layer chromatography was carried out on precoated silica gel plates (Merck, F-254) using the solvent system *n*-BuOH–HOAc–H_2O (4:1:1), *n*-BuOH–pyridine–HOAc–H_2O (15:10:3:12), and *n*-BuOH–EtOAc–HOAc–H_2O (1:1:1:1). Elemental analyses, amino acid analyses, and other physicochemical measurements (uv, ir, NMR, specific rotation) were performed by the Physical Chemistry Department.

Merrifield resin (chloromethylated copolystyrene–1% divinylbenzene beads, 200–400 mesh, 0.70 mmol Cl/g) was purchased from Lab Systems, Inc., San Mateo, Calif. Hydroxymethyl resin was prepared from Merrifield resin as described previously.[8] Boc-amino acids were obtained from Bachem Inc., Marina Del Ray, Calif., or from Beckman Instruments, Inc. Bpoc-amino acids were prepared according to the literature.[18,19] Other chemicals and solvents used were all of reagent grade materials available form commercial sources.

Boc-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-HNNH$_2$ (I). Hydroxymethyl resin II (6.0 g, 4.2 mmol) was placed in the reaction vessel of a Beckman Model 990 peptide synthesizer and the machine was programmed to perform the following steps automatically with 100-ml portions of solvents or reagents: (1) three washings with CH_2Cl_2, (2) stir 120 min with 10 mmol each of 4-dimethylaminopyridine, Boc-Thr(Bzl)-OH, and DCC in CH_2Cl_2, (3) three washings with CH_2Cl_2,[20] (4) stir 15 min with 4.5 mmol each of pyridine and benzoyl chloride in CH_2Cl_2, (5) three washings with CH_2Cl_2, (6) prewash with 33% TFA in CH_2Cl_2, (7) stir 20 min with 33% TFA in CH_2Cl_2, (8) three washings each with 33% dioxane in CH_2Cl_2, CH_2Cl_2 (9) prewash with 10% Et_3N in CH_2Cl_2, (10) stir 10 min with 10% Et_3N in CH_2Cl_2, (11) three washings with CH_2Cl_2, (12) stir 120 min with 10 mmol each of Boc-Tyr(Bzl)-OH and DCC in CH_2Cl_2, (13) three washings each with CH_2Cl_2, DMF, MeOH, (14) repeat steps 5–13 using Boc-Phe-OH (10 mmol) in step 12 instead of Boc-Tyr(Bzl)-OH, (15) repeat steps 5–13 with Boc-Phe-OH (10 mmol) in 12th step, (16) repeat steps 5–13 with Boc-Gly-OH (10 mmol) in 12th step, (17) three washings with CH_2Cl_2, (18) stir 990 min in 10% anhydrous H_2NNH_2 in DMF, collect the filtrate, (19) rinse with DMF, collect the filtrate, (20) rerun steps 1–19 four more times.

The filtrates from steps 18 and 19 in each run wer separately evaporated to dryness and the residue treated with ether. The crude solid material obtained was triturated with boiling MeOH and crystallized from DMF (60 ml) and EtOH (120 ml). The materials obtained from five runs were analyzed and then results listed in Table I.

Z-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-HNNH$_2$ (III). Boc-Thr(Bzl)-OCH$_2$-C$_6$H$_4$-resin (25 g, 3.5 mmol) prepared from chloromethyl resin (0.70 mmol Cl/g, 1% DVB) and Boc-Thr(Bzl)-OH (4.7 g) according to the literature procedure[3] was deprotected (50% TFA, 30 min), neutralized (10% Et_3N, 10 min) and coupled with Boc-Tyr(Bzl)-OH (2.7 g, 8.7 mmol) in the presence of DCC (1.81 g) in CH_2Cl_2 (120 min). The synthetic cycle was repeated with 8.7 mmol each of Boc-Phe-OH (2.3 g), Boc-Phe-OH, and Z-Gly-OH (1.83 g) to give Z-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-OCH$_2$C$_6$H$_4$-resin (26.2 g). It was suspended in DMF and stirred with H_2NNH_2 (8 ml) for 66 h. The peptide in the filtrate was then concentrated to near dryness and treated with ether, whereupon 5.7 g of solid precipitated. The crude material was triturated in MeOH and crystallized from DMF and EtOH: yield, 1.15 g (34%); mp 215–218 °C; $[\alpha]^{25}D$ −3.94 ° (c 1, DMF); NMR spectrum agreed with the structure.

Anal. Calcd for $C_{55}H_{59}N_7O_9$ (962.1): C, 68.66; H, 6.18; N, 10.19. Found: C, 68.67; H, 6.16; N, 9.91.

Z-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-OH (IV). Bpoc-Thr(Bzl)-OCH$_2$-C$_6$H$_4$-OCH$_2$-C$_6$H$_4$-resin (1.1 g, 0.43 mmol) prepared from Bpoc-Thr(Bzl)-OH, HOCH$_2$-C$_6$H$_4$-OCH$_2$-C$_6$H$_4$-resin[15] by the dimethylaninopyridine catalyzed DCC procedure[8] was deprotected (0.5% TFA in CH_2Cl_2, 10 min), neutralized (10% Et_3N in CH_2Cl_2), and coupled (120 min) with Bpoc-Try(Bzl)-OH (0.55 g, 1.08 mmol) in the presence of DCC (0.277 g). The coupling cycle was repeated with 1.08 mmol each of Bpoc-Phe-OH (0.44 g), Bpoc-Phe-OH, and Z-Gly-OH (0.26 g) to give Z-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-OCH$_2$-C$_6$H$_4$-OCH$_2$-C$_6$H$_4$-resin (1.21 g). During the synthesis, 0.5% TFA in CH_2Cl_2 (10 min) was utilized as deprotecting agent for Bpoc group. The peptide was released from the resin with 50% TFA in CH_2Cl_2 (30 min) and isolated as an amorphous solid when the solvents were removed and the residue was treated with ether. The compound was crystallized from MeOH: yield, 0.25 g (61.2%); mp 205–208 °C; $[\alpha]^{25}D$ +13.97° (c 1, HOAc); NMR spectrum agreed with the structure.

Anal. Calcd for $C_{55}H_{57}N_5O_{10}$ (948.0): C, 69.68; H, 6.06; N, 7.39. Found: C, 69.39; H, 5.90; N, 7.35.

H-Thr-OCH$_3$. A suspension of L-threonine (50 g) in 500 ml of MeOH was nearly saturated with HCl gas. The mixture was then refluxed at 85 °C for 30 min. The solvent was evaporated at 40 °C and the residue taken up in 300 ml of fresh MeOH which was again evaporated. After two repetitions of the entire process, 85 g of a clear oil was obtained. It was dispersed in $CHCl_3$ (280 ml) and treated with an equal volume of NH_3 saturated $CHCl_3$ at 0 °C. A white precipitate of NH_4Cl formed which was filtered off. Concentration at 15 °C provided a heavy oil which solidified on standing. Crystalization from ether and petroleum ether yielded 44.4 g (79%) of the desired compound: mp 68–70 °C (lit.[21] mp 70–72 °C); $[\alpha]^{25}D$ +14.61° (c 1, MeOH).

Anal. Calcd for $C_5H_{11}NO_3$ (133.15): C, 45.11; H, 8.33; N, 10.52. Found: C, 45.01; H, 8.40; N, 10.46.

Boc-Tyr(Bzl)-Thr-OCH$_3$. Boc-Tyr(Bzl)-OH (15.8 g) was stirred with H-Thr-OCH$_3$ (5.67 g) and DCC (9.65 g) at 0 °C for 1 h and at 25 °C for 2 h. After removal of the insoluble by-products the solvent was evaporated to form a syrup. It was taken up in 200 ml of ethyl acetate, filtered, and evaporated again to an oil. The compound crystallized when stored under petroleum ether. Recrystallized from THF and petroleum ether: yield 17.2 g (83%); mp 110–112 °C; $[\alpha]^{25}D$ −2.72° (c 1, MeOH).

Anal. Calcd for $C_{26}H_{34}N_2O_7$ (486.6); C, 64.18; H, 7.04; N, 5.76. Found: C, 64.40; H, 7.08; N, 5.71.

H-Tyr(Bzl)-Thr-OCH$_3$·HCl. The above compound (11.4 g) was dissolved in 500 ml of freshly prepared 2.6 N HCl in THF. After standing for 90 min with occasional shaking, the accumulated solid product was collected and washed with ether. The crude product was recrystallized from MeOH and ether: yield 7.0 g (71%); mp 232–234 °C; $[\alpha]^{25}D$ +2.09° (c 1, MeOH).

Anal. Calcd for $C_{21}H_{26}N_2O_5$·HCl (422.9): C, 59.64; H, 6.44; N, 6.62. Found: C, 59.43; H, 6.42; N, 6.54.

Boc-Phe-Phe-OH. L-Phenylalanine (13.2 g) was ground in a motar and pestle and suspended in 250 ml of DMF. It was stirred with 29 g of Boc-Phe-OSu for 24 h in the presence of 9.5 g of tetramethylguanidine. The reaction mixture was then partitioned between 600 ml of 2% citric acid and 800 ml of ethyl acetate. The organic layer was washed with 2% citric acid followed by three washings with water, dried (Na_2SO_4), and evaporated to an oil which solidified gradually. The compound was crystallized from ethyl acetate by addition of petroleum ether: yield 17.5 g (53%); mp 145–146 °C; $[\alpha]^{25}D$ −2.67° (c 1, MeOH).

Anal. Calcd for $C_{23}H_{28}N_2O_5$ (412.5): C, 66.98; H, 6.84; N, 6.79. Found: C, 66.93; H, 6.81; N, 6.79.

Z-Gly-Phe-Phe-OH. Boc-Phe-Phe-OH (12.5 g) was dissolved in 120 ml of TFA and left standing for 15 min. After evaporation of the solvents, the residue was treated with ether upon which the dipeptide salt precipitated as white solid. It was collected and washed with ether and then stirred with 9.5 g of Z-Gly-OSu for 24 h in the presence of 6.5 ml of Et_3N. The product was worked up as usual ad crystallized from ethyl acetate: yield 12.2 g (80%); mp 180–182 °C; $[\alpha]^{25}D$ +16.74° (c 1, HOAc).

Anal. Calcd for $C_{28}H_{29}N_3O_6$ (503.6): C, 66.79; H, 5.81; N, 8.34. Found: C, 66.72; H, 5.69; N, 8.34.

Z-Gly-Phe-Phe-Tyr(Bzl)-Thr-OCH$_3$. The dipeptide salt H-Tyr(Bzl)-Thr-OCH$_3$·HCl (6.25 g) and the tripeptide Z-Gly-Phe-Phe-OH (7.43 g) were dissolved in 120 ml of DMF and cooled to −10 °C when 1.66 ml of *N*-methylmorpholine, 4.0 g of HOBT, and 3.7 g of DCC were added. The mixture was stirred at −10 °C for 4 h and then at 25 °C for 48 h. Removal of the insoluble by-product and evaporation of the solvent (40 °C) left a solid mass. It was triturated with ethyl acetate and crystallized from MeOH: yield 8.5 g (66%); mp 181–184 °C; $[\alpha]^{25}D$ −16.58° (c 1, DMF).

Anal. Calcd for $C_{49}H_{53}N_5O_{10}$ (871.99): C, 67.49; H, 6.13; N, 8.03. Found: C, 66.97; H, 6.11; N, 8.08.

Z-Gly-Phe-Phe-Tyr(Bzl)-Thr-HNNH$_2$ (VI). The pentapeptide methyl ester above (8.5 g) was stirred in 10% H_2NNH_2 in DMF (140 ml) for 24 h. Upon dilution with 1500 ml of MeOH a heavy white precipitate formed. The product was crystallized from DMF (115 ml) and MeOH (250 ml): yield 6.8 g (78%); mp 241–243 °C; $[\alpha]^{25}D$ −16.73° (c 1, DMF); NMR spectrum agreed with the structure. Amino acid analysis after hydrogenation and digestion with leucine amino peptidase: Gly, 1.02, Thr, 1.01; Tyr, 0.97; Phe, 2.11.

Anal. Calcd for $C_{48}H_{53}N_7O_9$ (871.96): C, 66.11; H, 6.12; N, 11.24. Found: C, 65.95; H, 6.19; N, 11.09.

Z-Gly-His-Lys(Z)-nh$_2$ Resin II (5 g) that had been used for the

synthesis of I as described[8] was allowed to react with Boc-Lys(Z)-OH (1.95 g), pyridine (0.4 ml), and DCC (1.1 g) in CH_2Cl_2 for 2 h to give 6.0 g of Boc-Lys(Z)-OCH_2-C_6H_4-resin (3.24 mmol). After benzoylation[15] at 0 °C for 15 min with 0.83 ml of pyridine and 0.98 ml of benzoyl chloride in 60 ml of CH_2Cl_2 the resin was deprotected (50% TFA in CH_2Cl_2, 30 min), neutralized (10% Et_3N in CH_2Cl_2, 10 min), and coupled (120 min) with Boc-His(Tos)-OH·DCHA (5.4 g, 8.1 mmol)[22] in the presence of DCC (1.69 g). The synthetic cycle was repeated again with 8.1 mmol each of Z-Gly-OH (1.7 g) and DCC (1.69 g) to give 6.9 g of Z-Gly-His(Tos)-Lys(Z)-OCH_2-C_6H_4-resin. Ammonolysis in 450 ml of NH_3-saturated MeOH for 70 h provided a partially crystalline precipitate. It was concentrated to a smaller volume, diluted with an equal volume of DMF, filtered to remove the resin particles, and evaporated to a solid mass. Crystallization from DMF with MeOH gave 1.31 g (64%) of the desired compound: mp 210–212 °C; $[\alpha]^{25}D$ −8.51° (*c* 1, DMF); the NMR spectrum agreed with the structure.

Anal. Calcd for $C_{30}H_{37}N_7O_7$ (607.6): C, 59.30; H, 6.14; N, 16.14. Found: C, 59.24; H, 6.09; N, 16.16.

Acknowledgments. The authors thank Dr. R. B. Merrifield and Dr. J. Meienhofer for discussions, and Dr. F. Scheidl, Dr. T. Williams, Dr. V. Toome, Mr. Traiman, and their colleagues for physicochemical measurements.

Registry No.—I, 54276-64-1; III, 59790-71-5; IV, 54647-58-4; V, 54276-67-4; VI, 57471-75-7; Boc-Thr(Bzl)-OH, 15260-10-3; Boc-Tyr(Bzl)-OH, 2130-96-3; Boc-Phe-OH, 13734-34-4; Boc-Gly-OH, 4530-20-5; Z-Gly-OH, 1138-80-3; Bpoc-Tyr(Bzl)-OH, 25692-91-5; Bpoc-Phe-OH, 40099-50-1; H-Thr-OCH_3, 59790-72-6; H-Thr-OH, 72-19-5; Boc-Tyr(Bzl)-Thr-OCH_3, 3373-59-9; H-Tyr(Bzl)-Thr-OCH_3·HCl, 57471-73-5; Boc-Phe-Phe-OH, 13122-90-2; H-Phe-OH, 63-91-2; Boc-Phe-OSu, 3674-06-4; Z-Gly-Phe-Ph-OH, 57471-71-3; Z-Gly-OSu, 2899-60-7; Z-Gly-Phe-Phe-Tyr(Bzl)-Thr(Bzl)-Thr-OCH_3, 57471-74-6; Z-Gly-His-Lys(Z)-NH_2, 59790-73-7; Boc-Lys(Z)-OH, 2389-45-9; copolystyrene–divinylbenzene, 9003-70-7.

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(6) Abbreviations used are those recommended by IUPAC–IUB Commission on Biological Nomenclature: *J. Biol. Chem.*, **247**, 977 (1972). Others are: dcc, dicyclohexylcarbodiimide; DMF, dimethylformamide; DVB, divinylbenzene; HOBT, 1-hydroxybenzotriazole; HOSu, *N*-hydroxysuccinimide; Et_3N, triethylamine; TFA, trifluoroacetic acid; THF, tetrahydrofuran.
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Solid Phase Synthesis of Protected Peptides via Photolytic Cleavage of the α-Methylphenacyl Ester Anchoring Linkage

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Photolysis of α-methylphenacyl esters was adapted to solid phase peptide synthesis. Cleavage of the peptide to resin α-methylphenacyl ester anchoring bond by irradiation at 350 nm provided protected peptides in good yields. The process is examplified by the synthesis of Z-Lys(Z)-Phe-Phe-Gly-OH. For comparison, the same peptide was also prepared through photolytic cleavage of the *o*-nitrobenzyl ester anchoring linkage.

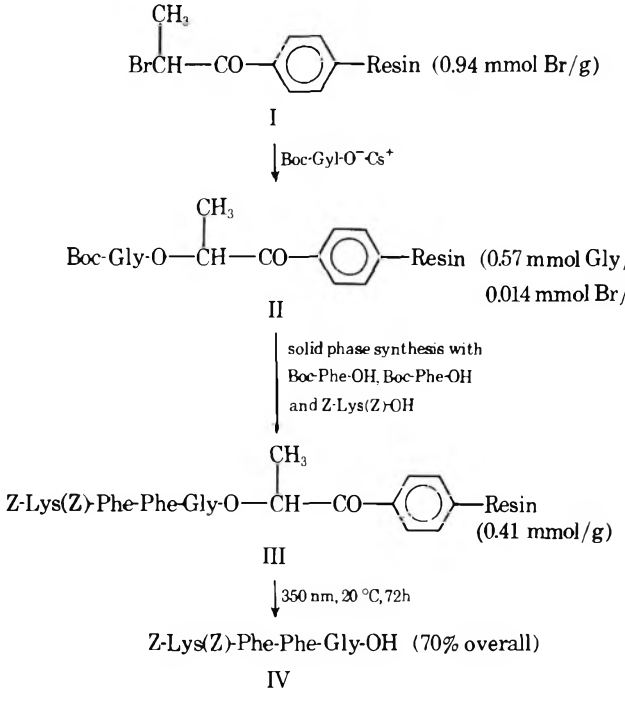
Studies on several photolyzable protecting groups that are potentially useful in peptide chemistry have recently been described in the literature.[1-11] Among these, the α-methylphenacyl ester[8] is of particular interest since it can readily be introduced into polymer matrices[12] and thus serve as an anchoring linkage between peptide chain and polymer support in solid phase synthesis.[13-17] Photolytic cleavage of this bond would therefore provide protected peptide intermediates that could subsequently be utilized in the synthesis of polypeptides by fragment condensation.[18-21]

In this report, the development of an efficient and convenient procedure for the preparation of protected peptides based on photolysis of the polymer linked α-methylphenacyl ester bond is described. A similar process involving photolytic cleavage of peptides from the o-nitrobenzyl ester resin[13] has recently been outlined.[10]

2-Bromopropionyl chloride was allowed to react with copolystyrene–2% divinylbenzene beads (200–400 mesh) in the presence of $AlCl_3$ as catalyst to form 2-bromopropionyl resin $BrCH(CH_3)CO$-C_6H_4-resin (I). The product contained 0.94 mmol of Br per gram of resin according to microanalysis. It showed an intense absorption band at 1685 cm^{-1} in the ir spectrum. The incorporation of Boc amino acids[22] into the resin was achieved by stirring I with a slight excess of Boc amino acid cesium salt[23] in dimethylformamide. The resultant Boc-HN-CHR-COO-CH-(CH_3)-CO-C_6H_4-resin (II) showed strong absorption bands at 1750 and 1725 cm^{-1} in addition to that at 1685 cm^{-1} in the ir spectrum. The degree of substitution is normally in the range of 0.5–0.7 mmol/g. There was practically no residual Br remaining after this treatment.

As outlined in Scheme I, Boc-Gly-$OCH(CH_3)$-CO-C_6H_4-resin (II) was deprotected, neutralized, and coupled with Boc-Phe-OH. The synthetic cycle was repeated with Boc-Phe-OH and then again with Z-Lys(Z)-OH. The

Scheme I. Preparation of Z-Lys(Z)-Phe-Phe-Gly-OH (IV) via Photolysis of the α-Methylphenacyl Ester Anchoring Bond



protected tetrapeptide resin Z-Lys(Z)-Phe-Phe-Gly-$OCH(CH_3)$-CO-C_6H_4-resin (III) thus obtained was then suspended in dimethylformamide and irradiated at 350 nm in a Rayonet photochemical reaction chamber for 72 h at 20 °C. The product Z-Lys(Z)-Phe-Phe-Gly-OH (IV) released from the resin was crystallized to give an analytically pure material in 70% overall yield. It was shown to be identical with a reference compound prepared by an alternate route.[24] The residual resin after photolysis retained 0.047 mmol/g of peptide according to amino acid analysis which indicated 92% photolytic cleavage under these conditions.

The stability of the α-methylphenacyl ester anchoring linkage of III under various conditions was studied. Rates of photolysis, hydrazinolysis, and acidolysis are shown in Figure 1. Photolysis proceeded rapidly with a half-life of approximately 5 h. The anchoring bond was completely stable against 50% trifluoroacetic acid in CH_2Cl_2 but surprisingly labile toward hydrazinolysis. For comparison, similar experiments were conducted with Z-Lys(Z)-Phe-Phe-Gly-OCH_2-C_6H_3(3-NO_2)-CO-N($CH_2CH_2CH_3$)-CH_2-C_6H_4-resin (VII) and also with Z-Lys(Z)-Phe-Phe-Gly-OCH_2-C_6H_4-resin (VIII), Figure 1. As expected, the polymer-bound benzyl ester linkage was completely stable to photolysis (350 mm) but rapidly cleaved by hydrazinolysis (10% H_2NNH_2 in dimethylformamide). In agreement with observations made by several investigators,[14,25] the benzyl ester anchoring linkage was cleaved slowly by 50% trifluoroacetic acid in CH_2Cl_2. The polymer bound o-nitrobenzyl ester in VII was photolyzed sluggishly under the conditions used. However, this bond is extremely sensitive to hydrazinolysis and completely inert toward 50% trifluoroacetic acid.

For preparation of Z-Lys(Z)-Phe-Phe-Gly-OH (IV) using $BrCH_2$-C_6H_3(3-NO_2)-CO-N($CH_2CH_2CH_3$)-$CH_2C_6H_4$-resin (V), Merrifield resin (0.7 mmol Cl/g, 1% cross-linked, 200–400 mesh) was allowed to react with n-propylamine (see Scheme II). The amine resin was then acylated with 3-nitro-4-bromomethylbenzoic acid[10] to form V. Reaction of this material with the cesium salt[23] of Boc-Gly-OH afforded Boc-Gly-OCH_2-C_6H_3(3-NO_2)-CO-N($CH_2CH_2CH_3$)-CH_2-C_6H_4-resin (VI). Solid phase synthesis was then continued by sequential incorporation of Boc-Phe-OH, Boc-Phe-OH, and Z-Lys(Z)-OH into the resin. The ensuing protected tetrapeptide resin VII was photolyzed at 350 nm to produce the desired compound IV in 40% overall yield. The lower yield of this process is due primarily to the slower rate of photolysis of this anchoring bond.

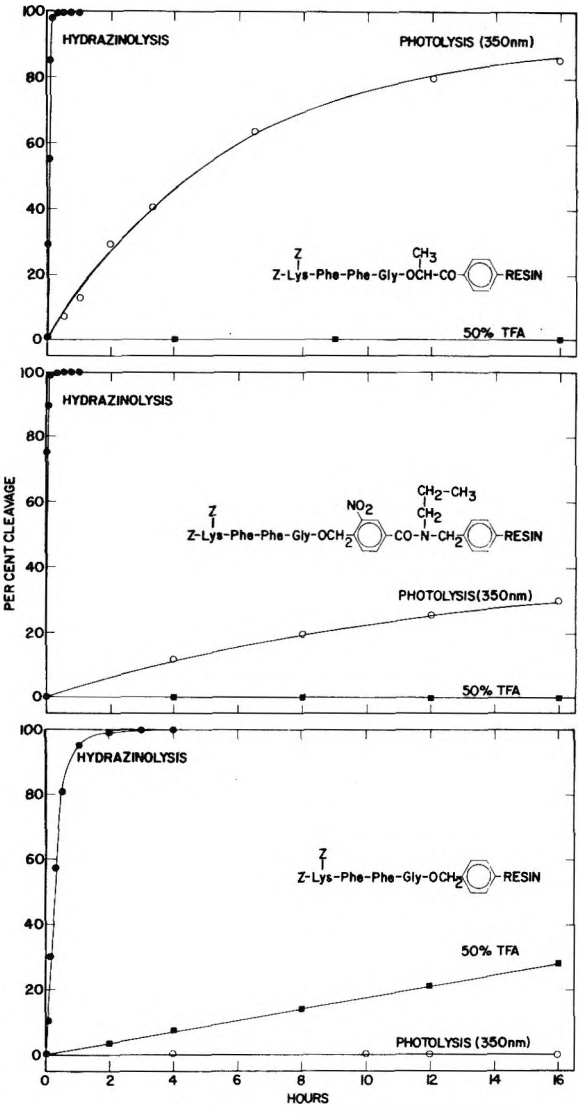


Figure 1. Cleavage of peptide resin α-methylphenacyl, o-nitrobenzyl, and benzyl ester anchoring bonds by photolysis, acidolysis, and hydrazinolysis (10% H_2NNH_2 in DMF). The rate of decrease in the peptide content (by amino acid analyses) of a resin was taken as the rate of cleavage of an anchoring bond.

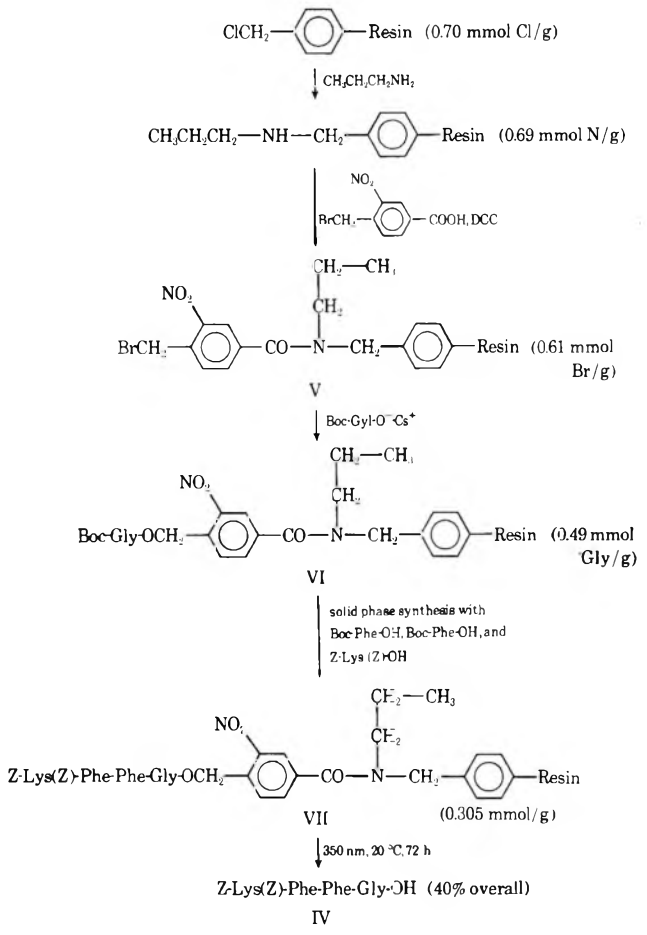
Preliminary experiments indicated that photolysis of the α-methylphenacyl ester anchoring linkage involving peptides with carboxyl terminal amino acids other than glycine (Ala, Leu, Thr(Bzl), Ile) was two to five times slower under similar conditions. Thus the process utilizing resin I as solid support would appear best suited for the synthesis of protected peptide fragments posessing carboxyl-terminal glycine residues.

Experimental Section

Melting points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 137 spectrophotometer using KBr pellets. Thin layer chromatography was carried out on precoated silica gel plates (Merck F254) using solvent systems described previously.[26] Microanalyses, amino acid analyses, and other physicochemical measurements were performed by the Physical Chemistry Department.

Copolystyrene–2% divinylbenzene beads (200–400 mesh, Bio-Beads S-X2) was purchased from Bio-Rad Laboratories, Richmond, Calif. Amino acid derivatives were obtained from Bachem, Inc., Marina Del

Scheme II. Preparation of Z-Lys(Z)-Phe-Phe-Gly-OH (IV) via Photolysis of the *o*-Nitrobenzyl Ester Anchoring Bond



Ray, Calif., or prepared in this laboratory and were of L configuration. 2-Bromopropionyl chloride was bought from Aldrich Chemical Company, Milwaukee, Wis., and Cs_2CO_3 was from Gallard-Schlesinger Corp., N.Y. Other chemicals and solvents were reagent grade products from various commercial sources.

$BrCH(CH_3)$-CO-C_6H_4-Resin (I). 2-Bromopropionyl chloride (50 g, 243 mmol) was added slowly to a suspension of $AlCl_3$ (39 g) in 250 ml of CH_2Cl_2 with gentle stirring. The solid dissolved after a brief period of time, forming a light brown solution. It was cautiously added to a suspension of Bio-Beads S-X2 (216 g, 200–400 mesh) in 2200 ml of CH_2Cl_2 during a period of approximately 30 min. The mixture was stirred for an additional 17 h. The acylated resin thus obtained was collected and washed successively with CH_2Cl_2, nitrobenzene, and THF. The slightly brownish resin was stirred in a mixture of THF–H_2O (6000 ml, 2:1) for 30 min and collected by filtration. The operation was repeated twice more and the resin again washed with H_2O, THF, and then MeOH to give 248,3 g of light buff colored material: ir (KBr) 1685 cm^{-1}; Br, 7.50 (0.94 mmol/g); Cl, 0.06.

Boc-Gly-OCH(CH_3)-CO-C_6H_4-Resin (II). Boc-Gly-OH (4.38 g, 25 mmol) was dissolved in a mixture of 40 ml of EtOH and 10 ml of H_2O. The solution was titrated to pH 7.0 with 20% Cs_2CO_3. The mixture was evaporated to dryness (35 °C) and the residual solid was evaporated twice with fresh DMF. Boc-Gly-O^--Cs^+ thus obtained was stirred with 20 g of I (18.8 mmol) in 80 ml of DMF for 17 h. The esterified resin was then collected and washed successively with DMF, DMF–H_2O, H_2O, THF–H_2O, THF, and MeOH to give 20.5 g of the desired product II. Amino acid analysis indicated the presence of 0.57 mmol Gly/g; Br, 0.11% (0.014 mmol/g); ir (KBr) 1750, 1725, 1685 cm^{-1}.

Similarly prepared were the resin analogues of Boc-Ala-OH (0.60 mmol Ala/g; 0.08% Br); Boc-Leu-OH (0.58 mmol Leu/g; 0.13% Br) and Boc-Thr(Bzl)-OH (0.62 mmol Thr/g; 0.07% Br).

Z-Lys(Z)-Phe-Phe-Gly-OH (IV). A. Ten grams of II (5.7 mmol) was deprotected (50% TFA, 30 min), neutralized (10% Et_3N, 10 min), and coupled with Boc-Phe-OH (4.77 g, 18 mmol) for 120 min in CH_2Cl_2 using DCC (3.7 g, 18 mmol) as coupling reagent. Solid phase synthesis was continued by sequential incorporation of Boc-Phe-OH (4.77 g) and Z-Lys(Z)-OH (7.5 g, 18 mmol) to produce tetrapeptide resin III (12.7 g). Amino acid analysis indicated that this product contained 0.41 mmol of peptide per gram of resin. Amino acid composition Gly, 1.11; Phe, 1.94; Lys, 0.95. Nitrogen analysis, 3.04% (0.44 mmol peptide/g).

The protected tetrapeptide resin III (10 g, 4.1 mmol) was suspended in 250 ml of DMF that had been treated with argon gas (2 ml/s) for 15 min inside a jacketed Pyrex tube (3.5 × 30 cm). The suspension was further flushed with argon for an additional 60 min with gentle magnetic stirring. The reaction mixture was then tightly stoppered and irradiated at 350 nm (16 × 24 W) in a Rayonet photochemical reaction chamber for 72 h with efficient water cooling (20 °C). The released peptide was separated by suction filtration and the solvent removed at 40 °C under reduced pressure to give 3.5 g of clear oil which solidified immediately on treatment with ethyl acetate. It was crystallized from THF and water: yield 2.42 g (77%); mp 218–220 °C; $[\alpha]^{25}D$ −25.12° (c 1, DMF) [lit.[24] mp 220–222 °C; $[\alpha]^{25}D$ −25.55° (c 1, DMF)]; NMR and ir spectra identical with those of the reference compound.[24] No depression in mixture melting point.

Anal. Calcd for $C_{42}H_{47}N_5O_9$ (765.9): C, 65.87; H, 6.19; N, 9.14. Found: C, 65.82; H, 6.16; N, 9.24.

Amino Acid Anal. Gly, 0.96; Phe, 2.00; Lys, 1.03. Average recovery, 98%.

The residual resin (7.3 g) after photolytic cleavage contained 0.047 mmol of peptide according to amino acid analysis. It had amino acid composition of Gly, 0.88; Phe, 2.00; Lys 1.07. Thus, the photolysis can be calculated as 92% complete.

B. Resin VI (6.0 g, 2.94 mmol) was deprotected (50% TFA, 30 min), neutralized (10% Et_3N, 10 min), and coupled with Boc-Phe-OH (1.93 g, 7.3 mmol) in the presence of DCC (1.54 g, 7.5 mmol) for 120 min. Solid phase synthesis was then continued with Boc-Phe-OH (1.93 g), followed by Z-Lys(Z)-OH (3.11, 7.5 mmol) in the next two cycles to give protected tetrapeptide resin VII (7.9 g). Amino acid analysis indicated that there was 0.305 mmol of peptide per gram of resin. Resin VII (7.0 g, 2.14 mmol) was photolyzed as described in A at 350 nm for 72 h. The released peptide was worked up as above: yield 0.80 g (48.7%); mp 211–215 °C; $[\alpha]^{25}D$ −25.32° (c 1, DMF); NMR and ir spectra identical with those of the reference.[24]

Anal. Found: C, 65.94; H, 6.28; N, 9.04.

$BrCH_2$-C_6H_3(3-NO_2)-CO-N($CH_2CH_2CH_3$)-$CH_2C_6H_4$-Resin (V). Chloromethyl resin (10 g, 7 mmol) was suspended in DMF (100 ml) and stirred with 11 ml of *n*-propylamine for 70 h. The resin was washed with DMF, THF, and MeOH to provide 10.1 g of $CH_3CH_2CH_2$-NH-CH_2-C_6H_4-resin (N, 0.97; Cl, 0.09). It was washed several times with CH_2Cl_2 and suspended in 150 ml of CH_2Cl_2 when 2.35 g of 3-nitro-4-bromomethylbenzoic acid[10] (9 mmol) and 2.0 g of DCC (9.7 mmol) were added. After stirring for 2 h the resin was collected and washed as usual yielding 11.5 g of desired product V (N, 0.86; Br, 4.88). The resin absorbed strongly at 1600 cm^{-1} in the ir spectrum.

Boc-Gly-OCH_2-C_6H_3(3-NO_2)-CO-N($CH_2CH_2CH_3$)-CH_2-C_6H_4-Resin (VI). Boc-Gly-OH (0.7 g, 4 mmol) was dissolved in 8 ml of *i*-PrOH plus 2 ml of H_2O and the mixture titrated to pH 7.0 with 20% Cs_2CO_3. The solution was evaporated to dryness, reevaporated twice with DMF (40 °C), and then stirred in DMF (25 ml) with 6 g of V (3.68 mmol) for 24 h. The resin was then washed as usual and dried to give 6.2 g of material. Amino acid analysis indicated that there was 0.49 mmol of glycine per gram of resin. There was virtually no residual bromide left (0.13%). There were strong absorption bands at 1750, 1710, and 1600 cm^{-1}.

Z-Lys(Z)-Phe-Phe-Gly-OCH_2-C_6H_4-Resin (VIII). Hydroxymethyl resin (4 g, 2.8 mmol), prepared as described before,[26] was allowed to react with Boc-Gly-OH (0.98 g, 5.6 mmol), 4-dimethylaminopyridine (0.69 g, 5.6 mmol), and DCC (1.2 g, 5.9 mmol) in CH_2Cl_2 (55 ml) for 120 min. The resin was collected and washed to give 4.32 g of material. Amino acid analysis indicated that the product, Boc-Gly-OCH_2-C_6H_4-resin, contained 0.58 mmol Gly/g. After benzoylation,[26] the resin was deprotected (50% TFA, 30 min), neutralized (10% Et_3N, 10 min), and coupled (120 min) with Boc-Phe-OH (1.32 g, 5 mmol) in the presence of DCC (1.03 g, 5 mmol). Continuation of solid phase synthesis with Boc-Phe-OH (1.32 g) in the next cycle followed by Z-Lys(Z)-OH (2.07 g, 5 mmol) in another cycle gave Z-Lys(Z)-Phe-Phe-Gly-OCH_2-C_6H_4-resin (4.9 g). Amino acid analysis showed that the resin contained 0.51 mmol peptide/g with an amino acid composition of Gly, 1.02; Phe, 1.98; Lys, 1.00.

Rates of Cleavage of Peptide α-Methylphenacyl, o-Nitrobenzyl, and Benzyl Ester Anchoring Bonds by Photolysis, Acidolysis, and Hydrazinolysis. The protected tetrapeptide resin III (2.0 g) was suspended in 50 ml of argon-saturated DMF and irradiated at 350 nm in the manner described for the preparation of IV. At dif-

ferent time intervals aliquots (4 ml) were withdrawn (under argon) and the resin separated immediately by suction filtration, washed thoroughly with DMF, CH_2Cl_2, and MeOH, and then subjected to amino acid analysis. The rate of decrease in amino acid content was taken as the rate of photolysis of the α-methylphenacyl ester anchoring bond. Exactly the same experiments were performed on tetrapeptide resins VII and VIII to determine the rate of photolytic cleavage of the o-nitrobenzyl and benzyl ester linkages. The results are summarized in Figure 1. For the studies of the rates of acidolysis or hydrazinolysis of the resins III, VII, and VIII, 0.5 g each of the samples were stirred individually in 20 volumes each of TFA–CH_2Cl_2 (1:1) or 10% H_2NNH_2 (DMF) in six separate flasks. Aliquots (1 ml) from each reaction were taken at different times and treated as described above for the photolysis experiments. The results are also shown in Figure 1.

Acknowledgment. The author wishes to thank Dr. R. B. Merrifield and Dr. J. Meienhofer for suggestions and discussions; Dr. F. Scheidl, Dr. T. Williams, Dr. V. Toome, Mr. S. Traiman, and their colleagues for physicochemical measurements and determinations; and Dr. C. C. Wei for discussions concerning some of the photochemical techniques.

Registry No.—IV, 40099-54-5; copolystyrene divinylbenzene, 9003-70-7; 2-bromopropionyl chloride, 7148-74-5; Boc-Gly-OH, 4530-20-5; Boc-Phe-OH, 13734-34-4; Z-Lys(Z)-OH, 405-39-0.

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(22) Abbreviations used: Boc, *tert*-butyloxycarbonyl; Bzl, benzyl; DCC, dicyclohexylcarbodiimide; DMF, dimethylformamide; THF, tetrahydrofuran; TFA, trifluoroacetic acid; Z, benzyloxycarbonyl.
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Total Synthesis of Sativene and Copacamphene via a Free Radical Cyclization

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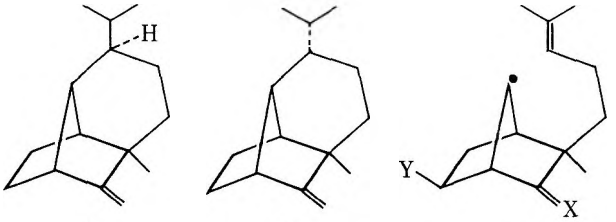
A synthesis of the tricyclic sesquiterpenes sativene (1) and copacamphene (2) is described, the key carbon–carbon bond formation being effected via a free-radical cyclization of the bicyclic compound 3 (X = O; Y = H). A new method for transforming a terminal olefin to an aldehyde via the corresponding alkyl phenyl sulfide followed by oxidation with *N*-chlorosuccinimide and hydrolysis of the resulting chloroalkyl phenyl sulfide is used to prepare the aldehyde precursor of 3.

The tricyclic sesquiterpenes sativene (1) and copacamphene (2) possess five chiral centers and thus offer interesting substrates to test and develop synthetic methodology.[1] While schemes based on heterolytic processes leading to carbon–carbon bond formation have been responsible for all but a handful of synthesis, one can expect[2] that homolytical processes, at least in isolated steps, will become more and more common as traditional prejudices against free-radical intermediates are removed.[3] Accordingly, we sought to develop a synthetic scheme based on free-radical intermediates which might be used to synthetize not only sativene and copacamphene, but also structurally related compounds such as cyclosativene, isosativene, and longifolene.

The key intermediate of our projected synthesis was the free radical 3, which could be expected[4] to cyclize to the tricyclic skeleton found in 1 and 2. Unfortunately, the factors controlling stereoselectivity of free-radical cyclizations are not understood, but because of the strained nature of the 7-norbornyl radical[5] and the expected stability of the tertiary radical produced, the product ratio should reflect kinetic and



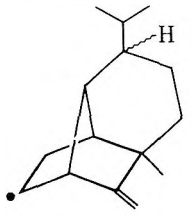
1 2 3

not thermodynamic factors. However, no clear prediction of the stereoselectivity expected could be made by consulting Dreiding models of radical 3. This steric ambiguity was offset by the choice of the norbornanone skeleton as the starting point of the synthesis, the other four asymmetric centers being controlled by the topological and steric restraints of the bicyclic ring structure.

Of the variety of methods that could be used to synthesize the desired radical 3, the Barton reaction appeared to have several advantages since the desired precursors should be

readily prepared and, additionally, the cyclized product from **3** (Y = CH_2OH) should be convertible into the tetracyclic sesquiterpenoids cyclosativine and cyclocopacamphene by an additional free-radical cyclization of radical **4**.

As a model system, we examined the Barton reaction on compound **5**, but found no evidence of functionalization at



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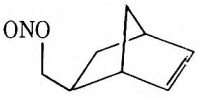

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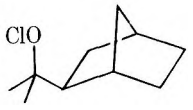

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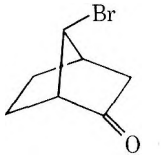
C-7. This result is consistent with that obtained with compound **6**,[6] although the alkoxy radical derived from the latter system is expected to be more prone to fragmentation reactions. Accordingly, we decided to prepare the desired radical in a less ambigouous manner from the corresponding 7-bromo compound.

The readily available[7] *syn*-7-bromcnorbornanone (**7**) was methylated in DME using the conditions developed by House[8] to give a 3:1 mixture of **8a** and **8b**, the stereochemistry being assigned on the basis of H NMR data as follows. The chemical shifts of the methyl groups in *exo*- and *endo*-3-methylbicyclo[2.2.1]heptan-2-one are nearly identical[9] and substitution



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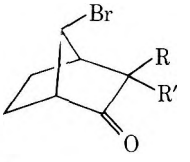
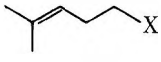
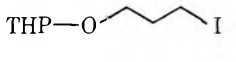


8a, R = CH_3; R′ = H
b, R = H; R′ = CH_3
c, R = $CH_2CH_2CH{=}C(CH_3)_2$; R′ = CH_3
d, R = $CH_2CH{=}CH_2$; R′ = CH_3
e, R = CH_3; R′ = $CH_2CH{=}CH_2$



9, X = Br, I, OTs



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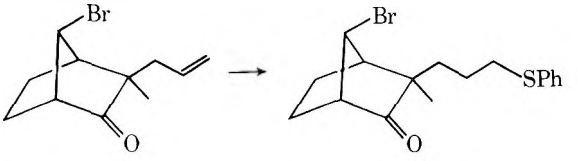
of the syn hydrogen at C-7 by a bromine atom would be expected[10] to deshield an exo methyl group more than the endo methyl substituent. The observed difference, 0.31 ppm, of the chemical shifts of the methyl groups in compounds **8a** and **8b** permits assignment of the stereochemistry. Collaboration for this assignment comes from the multiplicies of the bromomethine peaks, compound **8a**, capable of a "W"-type coupling between the hydrogens at C-3 and C-7, presenting a multiplet while in **8b** the peak appears as an apparent triplet.[11]

The relatively low stereoselectivity in the alkylation step is in contrast to the stereospecific methylation of norbornanone,[9] although we cannot be certain that our ratio does not reflect some postalkylation equilibration.[12] In the event, while the isomers could be separated, this is not necessary since the synthetically important stereoselectivity is determined in the subsequent alkylation step.

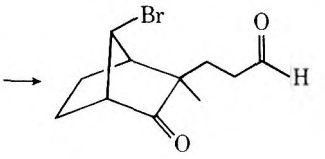
Unfortunately, the alkylation of **8a** and **8b** with **9** (X = Br, I, or OTS) failed under a great variety of conditions, in sharp contrast to the success in the debromo case.[9] Conditions that were examined included bases such as potassium *tert*-butoxide and *tert*-amyl oxide, in various solvents, NaH in benzene, DMF, or Me_2SO, lithium diisopropylamide in DME, and butylmagnesium bromide in HMPA. In all cases, only the endo starting material **8b**, or products that indicated ring cleavage and elimination, were isolated. Equally disappointing were attempts to alkylate **8a** and **8b** with the three-carbon synthon **10** or effect Michael reaction with acrolein.[13]

Successful alkylation was affected by allylation of the magnesium enolate[15] of **8a** and **8b** in HMPA at 60 °C. ^1H NMR analysis of the crude product mixture indicated a ca. 3:5 ratio of O- and C-alkylated products, the alkylated compounds **8d** and **8e** being formed in a 4:1 ratio, respectively. Use of higher temperatures to effect a postalkylation Claisen rearrangement increased the amount of C-alkylated product, but the exo to endo ratio decreased and with prolonged reaction times, the syn bromo substituent suffered SN2 attack by magnesium bromide (see Experimental Section).

Hydroboration followed by oxidation of the exo allyl compound **8d** and subsequent oxidation of the resulting alcohol by CrO_3–pyridine in CH_2Cl_2[16] gave the unstable aldehyde **12**



8d **11**

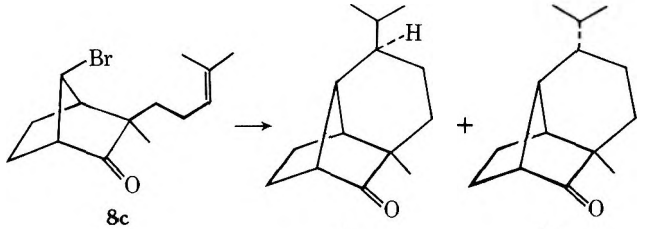


12

in 35% overall yield. The yield for the hydroboration–oxidation steps was not improved by use of other hydroboration reagents such as 9-BBN or diborane in dimethyl sulfide. Equally disappointing were other olefin to aldehyde transformations via the corresponding epoxides,[17] thus forcing us to develop an alternate sequence of reactions.[18]

Treatment of **8d** with thiophenol at 80 °C in the presence of AIBN (azobisisobutyronitrile) led to sulfide **11**, which was oxidized with *N*-chlorosuccinimide by refluxing in carbon tetrachloride for 20 min. The crude chloro sulfide was hydrolized in the presence of Cu^{II} (to oxidize the thiophenol formed)[19] to give the aldehyde **12** in 60% isolated yield (87% yield by NMR).[20] Treatment of the crude aldehyde **12** with $Ph_3P{=}C(CH_3)_2$ in Me_2SO at 60 °C led to a nearly quantitative retro-Michael reaction, the major product being **8b**. However, reaction of the Wittig reagent at −65 °C and in ether as solvent gave the desired isopropylidene compound **8c** in 64% yield, shown to be free of its epimer at C-3 by the absence of a low-field methyl group.

The key carbon–carbon bond formation reaction, cyclization via the intermediate **3** (X = O; Y = H), was conveniently carried out in 62% yield by the catalyzed reaction of **8c** and tributyl stannane in benzene at 36 °C. The resulting products, norsativone (**13**)[21] and copacamphenilone (**14**),[22] formed in a 3:2 ratio, respectively, were separated by careful chromatography on silica gel. The separated ketones **13** and **14** were



8c **13** **14**

transformed into sativene (**1**) and copacamphene (**2**) by published[21,22] procedures and found to be identical in all respects examined with the authentic natural products.

Experimental Section

***syn*-7-Bromo-3-methylbicyclo[2.2.1]heptan-2-ones (8a and 8b).** To a solution of excess lithium diisopropylamide in 350 ml of dry DME[8] at 0 °C, under N_2, containing 200 mg of triphenylmethane as indicator, was added 8.9 g of *syn*-7-bromobicyclo[2.2.1]heptan-2-one (7) in 15 ml of DME over a 15-min period. To the resulting pink solution was added 15 ml of methyl iodide and the mixture allowed to come to room temperature. After standing overnight, the mixture was poured into water, extracted with ether, dried over Na_2SO_4, and filtered, and solvent was removed to give 7.6 g of crude product, shown by GLC (DC 550 column at 170 °C) to be a mixture of starting material and exo and endo methylated ketones **8a** and **8b** (3:1 exo:endo ratio). Chromatography on 250 g of silica with 1:5 benzene–petroleum ether gave 4.37 g of monomethylated ketones **8a** and **8b** (56% yield based on unrecovered starting material) and 1.60 g of starting material. Rechromatography of the methylated ketones separated the two isomers, the endo isomer **8b** eluting first. Analytical samples of **8a** and **8b** were prepared by bulb to bulb distillation at 0.05 mm (75 °C bath temperature). **8a:** ir (neat) 5.70 μ; ^{1}H NMR (CCl_4) δ 4.04 (m, 1 H, CHBr), 2.67 (m, 2 H, C-1 and C-4 methines), 1.38 (d, J = 7 Hz, CH_3). **8b:** ir (neat) 5.70 μ; ^{1}H NMR (CCl_4) δ 4.25 (t, 1 H, J = 1.5 Hz, CHBr), 2.68 (m, 2 H, C-1 and C-4 methines), 1.07 (d, 3 H, J = 7 Hz, CH_3).

Anal. Calcd for $C_8H_{11}BrO$ (**8a**): C, 47.31; H, 5.46. Found: C, 47.43; H, 5.55.

Anal. Calcd for $C_8H_{11}BrO$ (**8b**): C, 47.31; H, 5.46. Found: C, 47.35; H, 5.45.

Allylation of *syn*-7-Bromo-3-methylbicyclo[2.2.1]heptan-2-ones (8a and 8b). A solution of 6.25 g of butyl bromide in 50 ml of ether was added to 1.13 g of Mg, under N_2. Ether was removed from the resulting Grignard solution at 60 °C, under vacuum, replaced with 50 ml of freshly distilled (from Na) HMPA, and stirred at 80 °C for 10 min. To this solution was added 8.66 g of ketone **8a** or **8b** in 10 ml of HMPA, dropwise, over 5 min. After stirring for an additional 30 min, the mixture was cooled to 60 °C; to it was added 11 ml of allyl bromide and the mixture was stirred overnight at 60 °C. The cooled mixture was diluted with water and extracted with ether; the extract was washed several times with water and dried over Na_2SO_4 and solvent was removed to give 9.00 g of crude product, shown by ^{1}H NMR to be a mixture of C- and O-allylated compounds. Chromatography on 250 g of silica gel with 2:1 petroleum ether–benzene gave 1.50 g of starting material and 4.85 g of a 4:1 mixture of exo and endo allylated product (57% yield, based on unrecovered starting material). The isomers were separated upon careful rechromatography, the endo allyl compound **8e** eluting first. Analytical samples were prepared by bulb to bulb distillation. Exo allyl compound **8d:** ir (neat) 5.72, 6.09 μ; ^{1}H NMR (CCl_4) δ 4.15 (t, 1 H, J = 1.0 Hz, CHBr), 1.07 (s, 3 H, CH_3). Endo allyl compound **8e:** ir (neat) 5.72, 6.09 μ; ^{1}H NMR (CCl_4) δ 4.14 (t, 1 H, J = 1.0 Hz, CHBr), 1.44 (s, 3 H, CH_3).

Anal. Calcd for $C_{11}H_{15}BrO$ (**8d**): C, 54.33; H, 6.22. Found: C, 54.48; H, 6.25.

Anal. Calcd for $C_{11}H_{15}BrO$ (**8e**): C, 54.33; H, 6.22. Found: C, 54.23; H, 6.15.

The alkylation could be forced to completion by heating the crude reaction mixture at 130–150 °C for 3–6 h. However, the exo to endo allylation ratio decreased to about 2:1, and after prolonged reaction times *anti*-7-bromo-*exo*-3-allyl-*endo*-3-methylbicyclo-[2.2.1]heptan-2-one became an important by-product. It was isolated and purified as above, bulb to bulb distillation providing an analytical sample: ir (neat) 5.70, 6.08 μ; ^{1}H NMR (CCl_4) δ 4.58 (m, 1 H, CHBr), 1.06 (s, 3 H, CH_3).

Anal. Calcd for $C_{11}H_{15}BrO$: C, 54.33; H, 6.22. Found: C, 54.49; H, 6.26.

Addition of Thiophenol to *syn*-7-Bromo-exo-3-allyl-*endo*-3-methylbicyclo[2.2.1]heptan-2-one (8d). A mixture of 750 mg of olefin **8d**, 225 mg of AIBN, and 5 ml of thiophenol was stirred at 77 °C under N_2 for 2.5 h, cooled, poured into 10% KOH solution, and extracted with ether. The extract was washed three times with water and dried over Na_2SO_4, and solvent was removed to give 1.275 g of crude product. Two chromatographies on 65 g of alumina neutral, activity 2–3, elution with 2:1 petroleum ether–benzene to 1:1 petroleum ether–benzene separated, in order of elution, 210 mg of diphenyl disulfide, 120 mg of starting material **8d**, and 783 mg of sulfide **11** (86% yield, based on unrecovered starting material). An analytical sample was prepared by bulb to bulb distillation at 0.1 mm (165 °C pot temperature): ir (neat) 5.70, 6.27, 13.5, and 14.45 μ; ^{1}H NMR (CCl_4) δ 7.22 (m, 6 H, aromatic), 4.06 (t, 1 H, J = 1.5 Hz, CHBr), 2.84 (t, 2 H, J = 7 Hz, CH_2SPh), 1.03 (s, 3 H, CH_3).

Anal. Calcd for $C_{17}H_{21}BrOS$: C, 57.79; H, 5.99. Found: C, 57.67; H, 5.91.

Preparation of *syn*-7-Bromo-*endo*-3-methyl-*exo*-3-(4-methyl-3-pentenyl)bicyclo[2.2.1]heptan-2-one (8c). A mixture of 164 mg of sulfide **11**, 70 mg of *N*-chlorosuccinimide, and 5 ml of CCl_4 was refluxed under N_2 for 20 min, cooled and filtered and solvent was removed. To the residue was added 170 mg of CuO, 170 mg of $CuCl_2 \cdot 2H_2O$, 5 ml of acetone, and 0.1 ml of H_2O and the mixture was refluxed under N_2 for 15 min, cooled, poured into water, and extracted with ether. The extract was washed with 10% KOH, three times with water, and dried over Na_2SO_4 and solvent was removed to give 146 mg of crude aldehyde **12** (see below), used without purification in the next step.

The above aldehyde, in 3 ml of ether, was added over 6.5 min to a Wittig solution at −65 °C (prepared at room tmperature by treating a suspension of 430 mg of triphenylisopropylphosphonium iodide in 10 ml of Et_2O, under N_2, with 490 μl of 1.9 M *n*-BuLi in hexane). After the mixture was stirred at −65 °C for an additional 0.5 h, it was allowed to come to room temperature over 1 h and then poured into water and extracted with ether. The extract was washed with water and dried over Na_2SO_4 and solvent was removed to give 187 mg of crude product, purified by chromatography on 15 g of silica gel by eluting with 1:1 petroleum ether–benzene to 1:2 petroleum ether–benzene. The resulting oil, 64 mg (48% overall yield from **11**), was distilled at 0.2 mm (100 °C pot temperature) to give an analytical sample of **8c**: ir (neat) 5.71 μ; ^{1}H NMR (CCl_4) δ 5.08 (m, 1 H, vinyl), 4.13 (t, 1 H, J = 1.6 Hz, CHBr), 1.67 and 1.61 (s, 6 H, isopropylidine), 1.07 (s, 3 H, CH_3).

Anal. Calcd for $C_{14}H_{21}BrO$: C, 58.95; H, 7.42. Found: C, 58.85; H, 7.44.

Purification of the aldehyde **12** used above resulted in lower overall yields for the three steps, presumably because of the instability of the aldehyde for which acceptable C, H analyses were not obtained. ^{1}H NMR analysis of the products of the oxidation and hydrolysis steps indicated yields of aldehyde up to 87% but isolated yields never exceeded 60%, while the maximum yield for the Wittig reaction on purified aldehyde was 64%. For **12**: ir (neat) 3.65, 5.72, 5.78 μ; ^{1}H NMR (CCl_4) δ 9.71 (broad s, 1 H, aldehyde), 4.19 (t, 1 H, J = 1.5 Hz, CHBr), 1.07 (s, 3 H, CH_3).

Free-Radical Cyclization of 8c to Norsativone (13) and Copacamphenenilone (14). A mixture of 235 mg of the olefin **8c**, 220 mg of freshly distilled tributylstannane, and 10 mg of *tert*-butyl perbenzoate in 20 ml of benzene was irradiated at 36 °C in a Merry-Go-Round apparatus with the 257-mm source for 1.5 h (quartz tube). Removal of solvent left 530 mg of residue, which was chromatographed on 60 g of silica gel using 1:1 petroleum ether–benzene as eluent to give, in order of elution, 340 mg of tributyltin bromide, 9 mg of starting olefin **8c**, 47 mg of a mixture of norsativone and copacamphenilone enriched in norsativone, and 53 mg of a mixture favoring copacamphenilone (62% yield of cyclized material). Chromatography of the latter fraction on 45 g of silica gel gave 20 mg of a mixture of **13** and **14** and 29 mg of copacamphenilone[1b] (**14**). The above two mixtures were combined and rechromatographed on 45 g of silica gel to give 58 mg of norsativone[1a] (**13**) and 5 mg of copacamphenilone (**14**). The separated ketones **13** and **14** were transformed into sativene and copacamphene, respectively, by published procedures.[1a,1c] Sativene was identified by comparison of ir, ^{1}H NMR, mass spectrum, and TLC behavior with an authentic sample, while copacamphene was identified by spectral comparison (ir, ^{1}H NMR, mass spectrum).

Acknowledgment. We thank Professor Piers for a generous sample of sativene, Professors McMurry and Dalton for spectral data, Professor Moriatity for unpublished experimental details, and Professor Baker of the Centro de Pesquisas de Produtos Naturais for mass spectra determination. The partial support of this work by the Conselho Nacional de Pesquisas is gratefully acknowledged.

Registry No.—**3**, 59796-80-4; **7**, 7176-91-2; **8a**, 59796-81-5; **8b**, 59796-82-6; **8c**, 59796-83-7; **8d**, 59796-84-8; **8e**, 59796-85-9; **11**, 59796-86-0; **12**, 59796-87-1; allyl bromide, 106-95-6; *anti*-7-bromo-*exo*-3-allyl-*endo*-3-methylbicyclo[2.2.1]heptan-2-one, 59796-88-2; thiophenol, 108-98-5: sativene, 6813-05-4; copacamphene, 16641-59-1.

References and Notes

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(12) In some of our alkylations we isolated a compound whose ^{1}H NMR spectra was consistent with dialkylated material; thus postalkylation equilibration is a definite possibility. The results of our allylation experiments (vide infra) are equally ambiguous, since we cannot be sure that the endo to exo product ratio does not reflect a Claisen rearrangement contribution.
(13) The simplest rationale to explain the failures of these alkylations is the steric hindrance offered by the syn bromo substituent. This would presumably increase O-alkylation, but should also have resulted in endo alkylation, which was not observed. The anti bromo compound corresponding to **8a** or **8b** is not expected to be more useful, since it could be expected[14] to undergo intramolecular alkylation.
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(21) References 1a, c, and d.
(22) References 1b-d.

Celorbicol, Isocelorbicol, and Their Esters: New Sesquiterpenoids from *Celastrus orbiculatus*

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Esters of two new sesquiterpenoid polyalcohols—celorbicol (**1a**) and isocelorbicol (**2a**)—have been isolated from *Celastrus orbiculatus*. Structures of the parent alcohols have been established by x-ray crystallography, and those of the derived esters have been assigned by NMR spectroscopy. These compounds are structurally related to other polyesters and ester alkaloids from the Celastraceae, all of which are based on the dihydroagarofuran ring system.

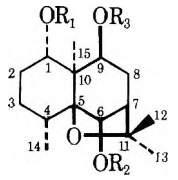
In a previous paper,[1a] we reported the isolation of a series of sesquiterpenoid polyol esters from seeds of *Celastrus orbiculatus* (Celastraceae). In this present paper, we report the complete structural elucidation of the parent alcohols and present evidence for the structures of three of their naturally occurring esters.

The occurrence of sesquiterpenoid esters in the seed oil of *Celastrus paniculatus* was first suggested by Gunde and Hilditch in 1938.[2] Recently, several esters of this sesquiterpenoid group from various celastraceous genera have been characterized, including examples from *Celastrus*,[3,4] *Euonymus*,[5-10] *Maytenus*,[11] and *Catha*.[12,13] The parent alcohols of several of these esters have been characterized, including malkanguniol,[3,4] celapanol,[4] euonyminol,[5] isoeuonyminol,[5] evoninol,[5,7-9] alatol,[5e] maytol,[11] deoxymaytol,[11a] 8-epideoxymaytol,[8] 3,4-dideoxy-7β-hydroxymaytol,[8] and cathol.[12,13] Apparently, all of these alcohols have the same ring system, but they vary in the number, position, and configuration of hydroxyl substituents. This ring system[14] has been considered to be identical with that of β-dihydroagarofuran; however, the widely accepted stereochemistry of β-dihydroagarofuran has been questioned recently.[15] As isolated from their natural sources, the hydroxyl groups of these polyalcohols are acylated with acetic acid and various other carboxylic acids.[3-13] Since certain of these acyl groups contain nitrogen, some of the esters of this series are classed as alkaloids.[4-13]

Isolation of Polyalcohols. After alkaline hydrolysis of *Celastrus orbiculatus* seed oil, a neutral fraction was isolated which provided two isomeric polyalcohols—celorbicol (**1a**) and isocelorbicol (**2a**)[16]—when subjected to preparative TLC. Alcohols **1a** and **2a** are high-melting, crystalline solids with the empirical formula $C_{15}H_{26}O_4$, as shown by high-resolution mass spectra. Their ir spectra showed strong hydroxyl absorptions, but none for carbonyl groups. General features of the NMR and mass spectra of **1a, 2a,** and their various esters (vide infra) led us to infer that **1a** and **2a** are closely related to malkanguniol,[3] and that **1a** is a 1,6,9-trihydroxy derivative of the dihydroagarofuran system.[1a] The complete structure and stereochemistry of **1a** and **2a** were established subsequently by single crystal x-ray crystallography.

X-Ray Crystallographic Analysis. Celorbicol was converted to a mono-*p*-bromobenzoate derivative (**1f**) which was used to elucidate its absolute stereostructure by x-ray diffraction experiments. A computer-generated drawing of the final x-ray model is presented in Figure 1. Table I lists fractional coordinates for **1f.** Figure 1 clearly shows both of the cyclohexane rings in the chair conformation. The hydroxyl at C-1 is equatorial while the one at C-9 is axial. The C-14 and C-15 methyl groups are both axial. The absolute configuration we assign to this structure is the same as that previously reported by Sasaki and Hirata[6,17] for neoevonine. Bond distances and angles agree with generally accepted values and

Scheme I



1a, $R_1 = R_2 = R_3 = H$

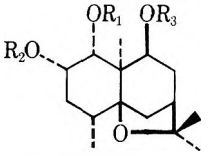
b, $R_1 = C_6H_5C(=O); R_2 = R_3 = Ac$

c, $R_1 = R_2 = C_6H_5C(=O); R_3 = Ac$

d, $R_1 = Ac; R_2 = R_3 = H$

e, $R_1 = R_2 = Ac; R_3 = H$

f, R_1 = *p*-bromobenzoyl; $R_2 = R_3 = H$



2a, $R_1 = R_2 = R_3 = H$

b, $R_1 = C_6H_5CH{=}CHC(=O); R_2 = R_3 = Ac$

c, $R_1 = Ac; R_2 = R_3 = H$

d, $R_1 = R_2 = Ac; R_3 = H$

e, R_1 = *p*-bromobenzoyl; $R_2 = R_3 = H$.

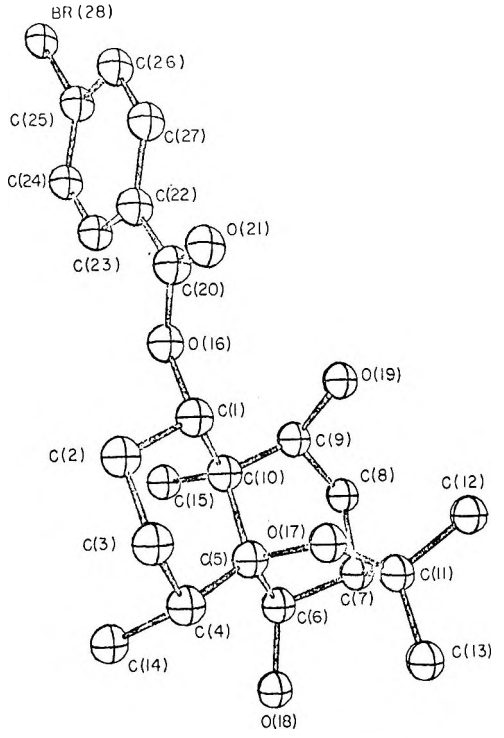


Figure 1. Computer-generated drawing of celorbicol mono-*p*-bromobenzoate (**1f**). Hydrogens are omitted for clarity.

there are no abnormally short intermolecular contacts.[18]

The structure of isocelorbicol was similarly solved by x-ray diffraction. Use of underivatized **2a** proved advantageous, even though its mono-*p*-bromobenzoate (**2e**) was available. A computer-generated drawing of **2a** is given in Figure 2, and Table II gives the final fractional coordinates.[18] The overall molecular conformation of isocelorbicol (**2a**) is identical with that of celorbicol. The hydroxyl groups are located at C-1, C-2, and C-9, and they are equatorial, axial, and axial, respectively. The molecular geometry agrees well with generally accepted values, and there are no abnormally short intermolecular contacts.[18] We have assumed the same absolute configuration for **2a** as we have determined for **1a**.

Table I. Final Fractional Coordinates for the *p*-Bromobenzoate of Celorbicol (1f) [a]

C(1)	1.065 (2)	0.066 (2)	0.2294 (9)
C(2)	1.083 (2)	0.109 (2)	0.118 (1)
C(3)	1.206 (2)	0.205 (2)	0.1368 (9)
C(4)	1.110 (2)	0.285 (2)	0.2009 (9)
C(5)	1.073 (1)	0.241 (2)	0.3109 (9)
C(6)	0.976 (2)	0.314 (2)	0.383 (1)
C(7)	1.068 (1)	0.276 (2)	0.4990 (9)
C(8)	0.964 (2)	0.174 (2)	0.511 (1)
C(9)	0.969 (1)	0.095 (2)	0.420 (1)
C(10)	0.956 (1)	0.135 (2)	0.3002 (9)
C(11)	1.294 (1)	0.264 (2)	0.4902 (9)
C(12)	1.414 (2)	0.191 (2)	0.580 (1)
C(13)	1.405 (2)	0.363 (3)	0.494 (1)
C(14)	0.930 (2)	0.335 (2)	0.119 (1)
C(15)	0.731 (2)	0.148 (2)	0.245 (1)
O(16)	0.944 (1)	−0.029 (2)	0.2128 (7)
O(17)	1.2712 (8)	0.218 (2)	0.3810 (6)
O(18)	1.011 (1)	0.419 (2)	0.3628 (7)
O(19)	1.131 (1)	0.021 (2)	0.4550 (6)
C(20)	1.039 (2)	−0.117 (2)	0.206 (1)
O(21)	1.218 (1)	−0.125 (2)	0.2169 (9)
C(22)	0.892 (1)	−0.201 (2)	0.1801 (9)
C(23)	0.684 (2)	−0.186 (2)	0.1516 (9)
C(24)	0.55 (2)	−0.266 (2)	0.126 (1)
C(25)	0.636 (2)	−0.363 (2)	0.136 (1)
C(26)	0.835 (2)	−0.383 (2)	0.165 (1)
C(27)	0.959 (2)	−0.299 (2)	0.187 (1)
Br(28)	0.4520 (2)	−0.476 (2)	0.1045 (2)
H(1)	1.207 [b]	0.054	0.268
H(2A)	0.948	0.124	0.077
H(2B)	1.149	0.056	0.080
H(3A)	1.220	0.229	0.063
H(3B)	1.344	0.185	0.183
H(4)	1.203	0.342	0.226
H(6)	0.828	0.313	0.366
H(7)	1.054	0.316	0.565
H(8A)	0.822	0.188	0.513
H(8B)	1.033	0.143	0.586
H(9)	0.839	0.055	0.412
H(12A)	1.428	0.219	0.657
H(12B)	1.551	0.175	0.566
H(12C)	1.341	0.121	0.580
H(13A)	1.543	0.347	0.478
H(13B)	1.421	0.392	0.571
H(13C)	1.332	0.409	0.436
H(14A)	0.874	0.389	0.157
H(14B)	0.823	0.278	0.095
H(14C)	0.973	0.358	0.050
H(15A)	0.665	0.077	0.239
H(15B)	0.716	0.177	0.170
H(15C)	0.663	0.190	0.294
H(18A) [c]	0.963	0.430	0.299
H(18B)	0.957	0.451	0.404
H(19)	1.129	0.000	0.518
H(23)	0.629	−0.117	0.149
H(24)	0.406	−0.259	0.100
H(26)	0.890	−0.455	0.167
H(27)	1.107	−0.314	0.211

[a] Hydrogen atoms are given the same number as the heavy atom to which they are attached. The estimated standard deviation of the least significant figure is given in parentheses. [b] The hydrogen positions were not varied in refinement. [c] Since this hydrogen appeared twice in the difference map, both positions were included, each with an occupancy factor of one-half.

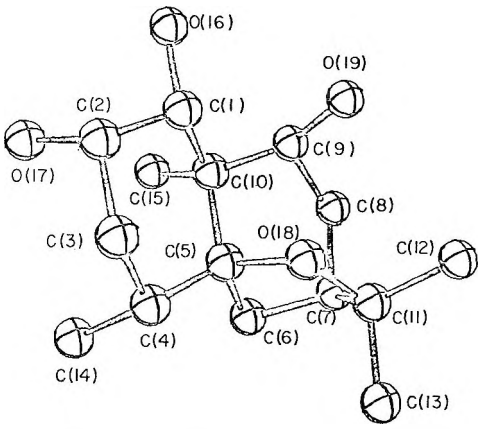


Figure 2. Computer-generated drawing of isocelorbicol (**2a**). Hydrogens are omitted for clarity.

Celoribicol can now be described as a 1α,6β,9β-trihydroxy derivative of β-dihydroagarofuran while isocelorbicol is the corresponding 1α,2α,9β-triol.

Esters of Celorbicol and Isocelorbicol. The most polar fractions from countercurrent distribution of *C. orbiculatus* seed oil contained esters of **1a** and **2a**.[1a] This mixture of esters was resolved into three discrete compounds by preparative TLC; traces of some related esters also were observed. Esters A (**1b**) and C (**1c**), partially characterized previously,[1a] yielded **1a** when subjected to alkaline hydrolysis, and ester B (**2b**) gave **2a** when treated similarly. The nature of the acyl groups of **1b**, **1c**, and **2b** was determined by GLC, mass spectra, and NMR.[1a]

When acetylated under mild conditions, **1a** afforded a monoacetate (**1d**) together with a diacetate (**1e**); monoacetate **2c** and diacetate **2d** were prepared similarly from **2a**. In both cases, one monoacetyl and one diacetyl derivative were the predominant products isolated by preparative TLC, although minor amounts of other isomers were apparent. Similarly, **1a** and **2a** each yielded mainly one mono-*p*-bromobenzoate (**1f** and **2e**) under mild acylating conditions.

NMR Spectra of Celorbicol and Its Esters. From inspection of their NMR spectra (Table III), it is obvious that compounds **1a–f** contain no hydroxymethylene function; no AB quartet corresponding to such a grouping is observed. Celorbicol and its various esters (**1a–f**) show three sets of signals which, within the framework of the dihydroagarofuran ring system, may be attributed to methine protons α to secondary hydroxyl groups. Each of these signals exhibits the expected downfield shift upon acylation of the corresponding hydroxyl group. Decoupling experiments revealed that none of these three methine protons is coupled to another of this group. These observations indicated that none of the hydroxyls has a vicinal relationship, and were consistent with a 1,6,9 arrangement of hydroxyl substituents.

One downfield methine proton appears as a slightly broadened singlet, only weakly coupled ($J < 1$ Hz) to any other proton. The axial proton at C-6 uniquely accommodates this observation with $\phi_{6,7} = 80°$, a dihedral angle corresponding to a value of $J < 1$ Hz.[19] Spectra of related esters from other sources exhibit comparable singlets for the corresponding C-6 protons.[3,4,8]

The axial proton at C-1 appears as a pair of doublets, the X portion of an ABX system, at δ 4.3 (**1a**) or 5.26–5.53 (**1b–f**). These multiplets have couplings appropriate for an axial–axial interaction (J = 10–12 Hz) together with one that is axial–equatorial (J = 4–6 Hz);[20] they are similar to those ascribed to the axial C-1 proton for esters of celapanol.[4] We assign the remaining methine-associated multiplet for **1b** and **1c** to the equatorial proton at C-9; this appears as a doublet of doublets with $J_{ae} = 6$ and $J_{ee} = 1$ Hz due to couplings with methylene protons at C-8 (compare with esters B-1 and B-4 from *Euonymus europaeus*.[8])

Upfield signals (Table III) include proton singlets for angular or geminal methyl groups—C-12, C-13, and C-15—and doublets (J = 7 Hz) for the secondary methyl group, C-14; singlets associated with the various acetyl functions also occur. The H-14 doublets are in accord with corresponding signals for esters of celapanol, as are the singlets generated by H-15.[3,4] In the spectra summarized in Table III (except that of **1e**), signals for C-12 and C-13 protons have the same chemical shift and appear as one six-proton singlet. The coincidence of these two peaks is not generally observed among spectra of related compounds; this overlap may result from a fortuitous balancing of shielding effects from axial oxygen functions at C-6 and C-9.

NMR proton integrals together with mass spectral data indicate that ester A (**1b**) contains two acetate and one benzoate groups, whereas ester C (**1c**) has one acetate and two

Table II. Final Fractional Coordinates for Isocelorbicol (2a)[a]

C(1)	0.3625 (2)	0.4618 (2)	0.3953 (2)
C(2)	0.3876 (2)	0.4697 (2)	0.5614 (2)
C(3)	0.5049 (2)	0.4557 (2)	0.5853 (2)
C(4)	0.5496 (2)	0.3516 (2)	0.5184 (2)
C(5)	0.5178 (1)	0.3395 (1)	0.3527 (2)
C(6)	0.5561 (2)	0.2345 (2)	0.2807 (3)
C(7)	0.5697 (2)	0.2725 (2)	0.1195 (3)
C(8)	0.4591 (2)	0.2894 (2)	0.0549 (3)
C(9)	0.3864 (2)	0.3667 (2)	0.1439 (2)
C(10)	0.3990 (1)	0.3567 (2)	0.3184 (2)
C(11)	0.5318 (2)	0.3763 (2)	0.1448 (2)
C(12)	0.6359 (2)	0.4539 (2)	0.0125 (3)
C(13)	0.7448 (2)	0.3556 (3)	0.1967 (3)
C(14)	0.5288 (2)	0.2524 (2)	0.5174 (3)
C(15)	0.3302 (2)	0.2605 (2)	0.3666 (3)
O(16)	0.2536 (1)	0.4810 (2)	0.3679 (2)
O(17)	0.3263 (1)	0.3940 (1)	0.6444 (2)
O(18)	0.5732 (1)	0.4253 (1)	0.2684 (2)
O(19)	0.3971 (1)	0.4754 (1)	0.0914 (2)
H(1)	0.400 (2)	0.523 (2)	0.350 (3)
H(2)	0.363 (2)	0.544 (2)	0.594 (3)
H(3A)	0.518 (2)	0.459 (2)	0.695 (3)
H(3B)	0.539 (2)	0.519 (2)	0.537 (3)
H(4)	0.631 (2)	0.365 (2)	0.513 (3)
H(6A)	0.504 (2)	0.176 (2)	0.291 (3)
H(6B)	0.624 (2)	0.212 (2)	0.329 (3)
H(7)	0.610 (2)	0.222 (2)	0.056 (3)
H(8A)	0.459 (2)	0.312 (2)	−0.054 (3)
H(8B)	0.425 (2)	0.213 (2)	0.057 (3)
H(9)	0.314 (2)	0.347 (2)	0.120 (3)
H(12A)	0.567 (3)	0.471 (3)	−0.040 (3)
H(12B)	0.673 (4)	0.518 (4)	0.045 (6)
H(12C)	0.682 (3)	0.428 (3)	−0.065 (5)
H(13A)	0.777 (3)	0.419 (4)	0.213 (5)
H(13B)	0.780 (4)	0.319 (4)	0.115 (6)
H(13C)	0.748 (3)	0.305 (3)	0.292 (5)
H(14A)	0.454 (3)	0.239 (3)	0.641 (4)
H(14B)	0.557 (3)	0.181 (3)	0.562 (4)
H(14C)	0.568 (3)	0.261 (3)	0.711 (4)
H(15A)	0.351 (3)	0.227 (3)	0.465 (4)
H(15B)	0.259 (3)	0.283 (3)	0.359 (5)
H(15C)	0.225 (3)	0.203 (3)	0.301 (4)
H(16)	0.216 (3)	0.469 (3)	0.447 (4)
H(17)	0.298 (2)	0.424 (2)	0.715 (4)
H(19)	0.453 (3)	0.504 (2)	0.131 (4)

[a] Hydrogen atoms are given the same number as the heavy atom to which they are attached. The estimated standard deviation of the least significant figure is given in parentheses.

Table III. Proton Chemical Shifts for Celorbicol (1a) and Derived Esters [a]

Protons	1a	1b	1c	1d	1e	1f
H-1	4.3, m	5.43, dd (J = 11, 4)	5.49 dd (J = 12, 4)	5.26, dd (J = 11, 6)	5.28, dd (J = 11, 6)	5.53, dd (J = 10, 5)
H-6	4.3, bs	5.28, bs	5.55, bs	4.34, bs	5.26, bs	4.37, bs
H-9	3.4 dd (?)	4.99, dd (J = 6, 1)	5.04, dd (J = 6, 1)	3.29, dd (J = 6, 1)	3.34, dd (J = 6, 1)	3.34, dd (J = 6, 1)
H-12	1.47, s	1.38, s	1.41, s	1.46, s	1.49, s[b]	1.46, s
H-13					1.35, s[b]	
H-14	1.11, d (J = 7)	0.98, d (J = 7)	1.00, d (J = 7)	1.14, d (J = 7)	0.95, d (J = 7)	1.17, d (J = 7)
H-15	1.04, s	1.30, s	1.36, s	1.13, s	1.16, s	1.28, s
1-*O*-Acyl		7.2–7.6, m 7.9–8.1, m	7.2–7.7, m 8.0–8.2, m	1.96, s	1.96, s[c]	7.50, 7.82, A_2B_2 system
6-*O*-Acyl		2.08, s			2.03, s[c]	
9-*O*-Acyl		1.58, s	1.59, s			

[a] Spectra were determined in $CDCl_3$. Chemical shifts (δ) are expressed in parts per million from tetramethylsilane. Letters following the shifts indicate the number and types of peaks observed before decoupling. [b,c] The assignment of these shifts is uncertain and possibly should be reversed.

Table IV. Proton Chemical Shifts for Isocelorbicol (2a) and Derived Esters [a]

Protons	2a	2b	2c	2d	2e
H-1	4.16, s (?)	5.52, bs	5.28, d (J = 3)	5.36, d (J = 3)	5.56, d (J = 3)
H-2	4.20, m	5.52, bs	4.32, ddd (J = 3, 3, 3)	5.50, ddd (J = 3, 3, 3)	4.47, ddd (J = 3, 3, 3)
H-9	3.2, m	4.73, dd (J = 6, 2)	3.25, m	3.27, m	3.33, m
H-12	1.18, s[b]	1.35, s[c]	1.27, s[d]	1.21, s[e]	1.40, s[f]
H-13	1.46, s[b]	1.38, s[c]	1.45, s[d]	1.45, s[e]	1.43, s[f]
H-14	1.23, d (J = 7)	1.28, d (J = 7)	1.19, d (J = 7)	1.18, d (J = 7)	1.30, d (J = 7)
H-15	1.18, s[b]	1.22, s	1.17, s[d]	1.18, s[e]	1.19, s
1-*O*-Acyl		6.33, 7.66, AB q (J = 16) 7.2–7.7, m	2.03, s	1.95, s	7.51, 7.87, A_2B_2 system
2-*O*-Acyl		1.82, s[g]		1.99, s	
9-*O*-Acyl		2.02, s[g]			

[a] See footnote *a*, Table III. [b-g] Assignments of these shifts are uncertain and possibly should be interchanged.

benzoate moieties.[1a] By comparing chemical shifts (Table III) for the various sets of three methine protons, the complete structures for esters **1b–f** may be assigned as depicted. Downfield shifts for H-1 signify that the corresponding hydroxyl is acylated in all five esters (**1b–f**); this conclusion is consistent with x-ray crystallographic analysis of **1f**. From similar considerations, the C-6 hydroxyl must be acylated in esters **1b, 1c,** and **1e** but not in **1d** and **1f**. Differences in downfield shifts for H-1 and H-6 indicate that **1c** has benzoate groups attached at both C-1 and C-6 hydroxyl functions, and that **1b** has its single benzoate moiety at C-1. Similarly, the C-9 hydroxyl is not acylated in **1d, 1e,** and **1f**.

Previous workers[4a,5b,11a] have drawn attention to the anomalous upfield shift of signals associated with acetate functions in certain polyalcohol esters of the dihydroagarofuran group. This shift has been attributed to the anisotropic shielding influence ofaromatic rings in neighboring acyl groups. One acetate resonance of **1b** and **1c** (δ 1.59) shows this effect, while other acetate signals recorded in Table I have more typical shifts in the range δ 1.96–2.08. Accordingly, the high-field acetate signals of **1b** and **1c** (δ 1.59) are considered to be generated by an acetoxy group at C-9 where it can be shielded by the benzoate moiety at C-1.

NMR Spectra of Isocelorbicol and Its Esters. The spectra (Table IV) of isocelorbicol and its esters (**2a–e**) indicate the absence of primary hydroxyl functions. As with celorbicol and its esters, there are three sets of signals due to methine protons which are shifted downfield when the adjacent secondary hydroxyl groups are acylated. Two of these resonances are coupled to each other, as revealed by irradiation experiments, but the third is coupled to neither of the other two; a 1,2,9-triol structure is consistent with these results. In the case of **2c,** for example, there was a doublet at δ 5.28 coupled to an apparent quartet at δ 4.32. The quartet collapsed to an apparent triplet when the spectrum was irradiated near δ 5.3, thus signifying three different couplings with adjacent protons, each with approximately the same coupling constant (J = 3 Hz). H-2 is coupled equally with the C-3 protons and also shows an axial–equatorial coupling with H-1; conversely, H-1 appears as a doublet, J = 3 Hz (compare with ddd for C-2 proton in euolalin[5d]). Overlap of signals for H-1 and H-2 obscured the multiplicity of both in the spectra of **2a** and **2b.**

The third methine proton, attached at C-9, appeared as a poorly defined multiplet near δ 3.2 except in the case of **2b,** where it formed a pair of doublets, J_{ae} = 6 and J_{ee} = 2 Hz, due to coupling with C-8 protons.

In contrast to those in the celorbicol series, singlets for C-12 and C-13 protons are well resolved. However, identification of upfield signals (Table IV) associated with methyl groups

of isocelorbicol and its derivatives is not as straightforward as with **1a–f** and assignments of the singlets for C-12, C-13, and C-15 protons are uncertain.

NMR and mass spectral data indicated that ester B contains two acetate and one *trans*-cinnamate groups.[1a] A comparison of the chemical shifts for the C-1 and C-2 methine protons leaves no doubt that the C-1 hydroxyl is acylated in **2b, 2c, 2d,** and **2e,** and that the C-2 hydroxyl likewise is acylated in **2b** and **2d.** From similar considerations, the C-9 hydroxyl must be acylated only in the case of **2b.** H-1 is shifted farther downfield in **2b** than in diacetate **2d,** and is displaced to about the same extent as in **2e** (the mono-*p*-bromobenzoate). From these comparisons, it seems likely that ester B has the structure that we have depicted as **2b.**

Mass Spectra of Celorbicol and Isocelorbicol. In their discussions of the mass spectra of malkanguniol and its esters, both den Hrtog et al.[3a] and Wagner et al.[4b] have stressed the importance of fragments at *m/e* 137 and 124 (or 125) which embrace the original furanoid ring. However, the *m/e* 137 ion is not prominent in the spectra of celapanol derivatives examined by Wagner and co-workers,[4b] nor in the polyalcohols investigated by Budzikiewicz and Römer.[8] In contrast, both the *m/e* 137–138 and 124–125 ions are conspicuous in spectra of **1a** and **2a,** despite the fact that **1a** carries an oxygen substituent at C-6 which must be eliminated. Apparently, the diagnostic value of the *m/e* 137 ion is limited.

Discussion

Celorbicol and isocelorbicol contain four oxygen atoms—fewer than any other of the series of polyalcohols from the Celastraceae. Others contain at least five and as many as ten oxygens. However, mono- and dihydroxy derivatives of dihydroagarofuran have been isolated from *Aquillaria agallocha* wood (family Thymeleaceae).[21] Isocelorbicol is the first of the series found to be acylated with *trans*-cinnamic acid.

ORD curves for **1a** and **2a** were recorded with both chloroform and methanol solutions to provide comparisons with optical rotations reported by den Hertog et al.[3b] and by Wagner et al.[4b] In all cases, values for $[\alpha]_D$ were negative; these results suggest that the sesquiterpenoid ring system of **1a** and **2a** has the same absolute configuration in *C. paniculatus* and *C. orbiculatus.*

Experimental Section

NMR spectra were recorded with a Varian[22] HA-100 instrument, and ir spectra with a Perkin-Elmer Model 137 instrument. Mass spectra were obtained with a Nuclide 12-90G spectrometer. A Beckman DK-2A spectrophotometer was used to measure uv spectra. ORD spectra were recorded with a Cary Model 60 spectropolarimeter. TLC, both preparative and analytical, was carried out on silica gel GF-254 plates (E. Merck, Darmstadt). Components were located under uv light after spraying with ethanolic dichlorofluroescein solution. Melting points were determined with a Fischer-Johns block and are uncorrected.

Isolation of Celorbicol (1a) and Isocelorbicol (2a). Extraction and hydrolysis of *C. orbiculatus* seed oil were described in a previous paper.[1a] A 0.514-g portion of the crude polyalcohol mixture isolated after hydrolysis with methanolic barium hydroxide was subjected to preparative TLC (five 20 × 20 × 0.2 cm plates) with the solvent system chloroform–acetone (3:1); **1a** appeared as a major component at R_f 0.5, and **2a** at R_f 0.3. In addition, three minor bands appeared which were not investigated.

Celorbicol. Elution of the R_f 0.5 bands with chloroform–methanol (3:1) provided 0.205 g of **1a:** mp 222–223 °C after recrystallization from chloroform–acetone; ir ($CHCl_3$) 3598, 3450 (OH), 2940, 1133, 1110, 1009, 965, 900, 855 (broad) cm^{-1}; ORD $[\alpha]^{26}D$ −24, $[\alpha]_{560}$ −27, $[\alpha]_{440}$ −46, $[\alpha]_{400}$ −59, $[\alpha]_{350}$ −83, $[\alpha]_{300}$ −126, $[\alpha]_{270}$ −177, $[\alpha]_{250}$ −236° (*c* 0.47, CH_3OH); $[\alpha]^{26}D$ −27, $[\alpha]_{\leq 80}$ −38, $[\alpha]_{400}$ −59, $[\alpha]_{320}$ −100, $[\alpha]_{280}$ −145, $[\alpha]_{260}$ −188° (c 0.37, $CHCl_3$); NMR, $CDCl_3$ shifts in Table III; Me_2SO-d_6, δ 0.90 (s, 3 H), 1.00 (d, 3 H, *J* = 7.5 Hz), 1.34 (s, 3 H), 1.41 (s, 3 H), 3.32 (dd, 1 H, *J* = 4, 1 Hz), 3.74 (d, 1 H on hydroxyl, *J* = 4 Hz), 4.0 (m, 3 H), 4.76 (d, 1 H on hydroxyl, *J* = 5 Hz); MS (70 eV) *m/e* (rel intensity) 270 (M^+, 12), 255 (M − CH_3, 100), 159 (50), 149 (35), 138 (36), 125 (34), 109 (38), 97 (23), 95 (25), 85 (28), 83 (29), 69 (27), 57 (22), 55 (35), 43 (61), 41 (24). Found: M^+, 270.182; $C_{15}H_{26}O_4$ requires 270.183.

Isocelorbicol. Elution of the R_f 0.3 band from TLC with chloroform–methanol (3:1) afforded 0.206 g of **2a:** mp 240–241 °C after recrystallization from chloroform–acetone; ir ($CHCl_3$) 3680, 3480 (OH), 2940, 1380, 1361, 1135, 1093, 1063, 1010, 980, 960, 862 (broad) cm^{-1}; ORD $[\alpha]^{26}D$ −8, $[\alpha]_{440}$ −14, $[\alpha]_{360}$ −21, $[\alpha]_{300}$ −25 (minimum), $[\alpha]_{260}$ −16, $[\alpha]_{250}$ −7, $[\alpha]_{245}$ 0, $[\alpha]_{240}$ +12, $[\alpha]_{235}$ +29° (*c* 0.54, MeOH); $[\alpha]^{26}D$ −18, $[\alpha]_{520}$ −22, $[\alpha]_{440}$ −31, $[\alpha]_{360}$ −43, $[\alpha]_{280}$ −69, $[\alpha]_{260}$ −78° (*c* 0.30, $CHCl_3$); NMR, $CDCl_3$ shifts in Table IV; Me_2SO-d_6, δ 1.03 (s, 3 H), 1.06 (s, 3 H), 1.16 (d, 3 H, *J* = 7.5 Hz), 1.41 (s, 3 H), 3.34 (dd, 1 H, *J* = 4,1 Hz), 3.63 (d, 1 H on hydroxyl, *J* = 6 Hz), 3.96 (bm, 4 H); MS (70 eV) *m/e* (rel intensity) 270 (M^+, 28), 255 (M − CH_3, 22), 252 (M − H_2O, 21), 237 (34), 219 (30), 208 (29), 183 (23), 168 (100), 154 (27), 151 (25), 137 (65), 135 (26), 125 (47), 124 (44), 123 (46), 121 (41), 119 (41), 109 (94), 97 (84), 95 (51), 93 (37), 85 (39), 83 (30), 71 (31), 69 (62), 57 (34), 55 (49), 43 (92), 41 (66), 18 (25). Found: M^+, 270.186; $C_{15}H_{26}O_4$ requires 270.183.

X-Ray Analyses. A. Celorbicol *p*-Bromobenzoate (1f). The unit cell of **1f** belonged to the monoclinic space group $P2_1$ with *a* = 6.818 (4), *b* = 13.111 (9), c = 12.147 (9) Å, and β = 101.91 (5)°. A calculated and measured density were interpreted to mean two molecules of $C_{22}H_{29}BrO_5$ in the unit cell or one molecule per asymmetric unit. All unique diffraction maxima with $\theta \leq 57°$ were collected using a fully automated four-circle diffractometer and monochromated Cu Kα radiation (1.54178 Å). A total of 1494 reflections were measured and after correction for Lorentz, polarization, and background effects, 1144 were judged observed [$F_o \geq 3\sigma(F_o)$, 77% observed].

Structure solution proceeded routinely. The bromine was located in the Patterson synthesis and careful inspection of the centrosymmetric Br-phased electron density synthesis revealed a plausible starting fragment.[23] The remaining nonhydrogen atoms were located in subsequent electron density syntheses. Hydrogen atoms were located on a difference synthesis after refinement. Full matrix least-squares refinement with nonhydrogen atoms anisotropic, hydrogens isotropic, and with anomalous scattering corrections for Br lowered the conventional discrepancy index to 0.074 for the structure and 0.076 for the enantiomorph.[18,24]

B. Isocelorbicol (2a). Crystals of **2a** are orthorhombic with *a* = 12.770 (1), *b* = 12.374 (3), and c = 8.9233 (9) Å and systematic extinctions indicating space groups $P2_12_12_1$. A calculated and measured density indicated one molecule of $C_{15}H_{26}O_4$ per asymmetric unit. Because of the excellent quality of the crystals, all reflections with $\theta \leq 78°$ were collected on a four-circle diffractometer using Cu Kα (1.54178 Å) radiation. After correction for Lorentz, polarization, and background effects, 1535 of the 1628 measured reflections were judged observed (94%).

A starting x-ray model was found by a multiple solution, weighted, tangent formula approach.[25] Refinement with anisotropic nonhydrogen atoms and isotropic hydrogens converged to a final *R* factor of 0.045 for the observed reflections.[18]

Isolation of Ester A (1b), Ester B (2b), and Ester C (1c). The countercurrent fractionation of *C. orbiculatus* seed oil was described in a previous paper.[1a] Material from combined transfers 1461–1469 (0.271 g) was applied to a preparative TLC plate, and was subjected to double development with the solvent system methylene chloride–ethyl ether (95:5); **1c** appeared as major component at R_f 0.65, **1b** at R_f 0.55, and **2b** at R_f 0.37.

Ester A (1b). Elution of the R_f 0.55 band with chloroform–methanol (3:1) yielded 0.116 g of **1b:** mp 179–180 °C after recrystallization from ethyl ether–hexane; ir ($CHCl_3$) 2940, 1730, 1710, 1390, 1375, 1285, 1136, 1107, 1087, 1023, 977, 967, 868 cm^{-1}; NMR, see Table III; MS (70 eV) *m/e* (rel intensity) 458 (M^+, 2) 443 (M − CH_3, 6), 416 (47), 206 (29), 159 (19), 138 (25), 105 (90), 77 (38), 43 (100). Found: M^+, 458.231; $C_{26}H_{34}O_7$ requires 458.230.

Ester B (2b). Elution of the R_f 0.37 band from preparative TLC with chloroform–methanol (3:1) gave 25 mg of **2b,** an amorphous solid which resisted efforts to crystallize it: ir ($CHCl_3$) 2970, 2930, 1740, 1710, 1640, 1450, 1370, 1163, 1135, 1110, 1092, 1070, 1046, 1020, 880 (broad) cm^{-1}; NMR, see Table IV; MS (70 eV) *m/e* (rel intensity) 484 (M^+, 9), 469 (M − CH_3, 2), 353 (79), 233 (30), 131 (100), 105 (23), 103 (24, 43 (56). Found: M^+, 484.246; $C_{28}H_{36}O_7$ requires 484.246.

Ester C (1c). The R_f 0.65 band from preparative TLC was eluted with chloroform–methanol (3:1) to give 23 mg of **1c,** a syrup: ir ($CHCl_3$) 2950, 2930, 1730, 1710, 1450, 1390, 1370, 1105, 1093, 1065, 1021, 980, 892, 875 cm^{-1}; NMR, see Table III; MS (70 eV) *m/e* (rel intensity) 520 (M^+, 11), 505 (M − CH_3, 4), 416 (7), 294 (11), 206 (14), 159 (11), 138 (9), 105 (100), 77 (18), 43 (17). Found: M^+, 520.247; $C_{31}H_{36}O_7$ requires 520.246.

Hydrolysis of Esters A, B, and C. A few milligrams each of **1b, 1c,** and **2a** were hydrolyzed by refluxing for 3 h with 0.2 M methanolic barium hydroxide. Alcohols, isolated by extracting the hydrolysates with chloroform, were examined by analytical TLC [solvent system, chloroform–acetone (75:25)]. The alcohol portion of the hydrolyzates from esters A (**1b**) and C (**1c**) were identical in R_f with **1a**, whereas that from ester B (**2b**) corresponded to **2a**.

Acetylation of Celorbicol (1a). A 0.100-g portion of **1a** was treated overnight at ambient temperature with acetic anhydride–pyridine (2:1). The resulting product was applied to a preparative TLC plate which was developed with chloroform–acetone (95:5). Elution of a band at R_f 0.40 provided a 53% yield of a monoacetate (**1d**), and an R_f 0.60 band gave 29% of a diacetate (**1e**); other minor bands were observed.

Monoacetate **1d** had mp 137–139 °C after recrystallization from chloroform–acetone; ir ($CHCl_3$) 3590, 3460, 2940, 1720, 1377, 1362, 1133, 1113, 1093, 1011, 961, 862 cm^{-1}; NMR, see Table III; MS (70 eV) *m/e* (rel intensity) 312 (M^+, 16), 297 ($M - CH_3$, 18), 252 (38), 243 (33), 237 (52), 219 (30), 210 (23), 206 (36), 194 (32), 191 (38), 177 (31), 176 (64), 159 (70), 155 (46), 140 (38), 138 (75), 137 (57), 125 (91), 109 (96), 97 (63), 95 (37), 85 (36), 83 (72), 72 (43), 69 (39), 55 (39), 43 (100), 41 (39), 28 (49), 18 (83). Found: M^+, 312.194; $C_{17}H_{28}O_5$ requires 312.194.

Diacetate **1e** had mp 154–157 °C after recrystallization from chloroform–hexane; ir ($CHCl_3$) 3590, 3470 (sh), 2940, 1720, 1358, 1135, 1087, 1013, 962, 866 cm^{-1}; NMR, see Table III; MS (70 eV) *m/e* (rel intensity) 354 (M^+, 4), 339 ($M - CH_3$, 3) 252 (21), 234 (23), 176 (51), 159 (27), 138 (32), 137 (21), 125 (21), 124 (12), 109 (27), 43 (100). Found: M^+, 354.204; $C_{19}H_{30}O_6$ requires 354.204.

Acetylation of Isocelorbicol (2a). A 0.100-g portion of **2a** was acetylated as described for **1a**, and the resulting product was similarly fractionated by TLC, except that the developing solvent was chloroform–acetone (90:10). Elution of a band at R_f 0.28 afforded a 72% yield of a monoacetate (**2c**), while an R_f 0.52 band gave 16% of a diacetate (**2d**); minor amounts of other components were noted.

Monoacetate **2c** had mp 176–178 °C after recrystallization from chloroform–hexane; ir ($CHCl_3$) 3570, 2940, 1725, 1360, 1135, 1065, 1013, 987, 957, 863 cm^{-1}; NMR, see Table IV; MS (70 eV) *m/e* (rel intensity) 312 (M^+, 1), 297 ($M - CH_3$, 3), 252 (24), 237 (23), 234 (15), 219 (21), 208 (18), 137 (41), 124 (21), 123 (23), 121 (22), 109 (48), 97 (27), 95 (24), 69 (27), 55 (24), 43 (100), 41 (37), 28 (20). Found: M^+, 312.194; $C_{17}H_{28}O_5$ requires 312.194.

Diacetate **2d** was isolated as a syrup that did not solidify; ir ($CHCl_3$) 3570, 2940, 1725, 1363, 1135, 1110, 1077, 1070, 1015, 978, 967, 855 cm^{-1}; NMR, see Table IV; MS (70 eV) *m/e* (rel intensity) 354 (M^+, 1), 339 ($M - CH_3$, 1), 234 (9), 137 (10), 120 (9), 109 (10), 87 (11), 85 (64), 83 (100), 48 (10), 47 (21), 43 (44), 36 (15). Found: M^+, 354.203; $C_{19}H_{30}O_6$ requires 354.204.

Preparation of Celorbicol *p*-Bromobenzoate (1f). Alcohol **1a** (37 mg) was treated with *p*-bromobenzoyl chloride in pyridine as described by Arora et al.[26] The crude product was applied to a preparative TLC plate which was developed with chloroform–acetone (90:10). Elution of a major component with R_f 0.47 provided 32 mg of **1f**: mp 223–226 °C after recrystallization from chloroform; ir ($CHCl_3$) 3590, 3450 (sh), 2920, 1710, 1585, 1402, 1225, 1100, 1013, 960, 864 cm^{-1}; NMR, see Table III; MS was not recorded because of thermolytic instability of the compound.

Anal. Calcd for $C_{22}H_{29}BrO_5$; c, 58.3; H, 6.5; Br, 17.6. Found: C, 58.1; H, 6.5; Br, 17.9.

Preparation of Isocelorbicol *p*-Bromobenzoate (2e). Alcohol **2a** (50 mg) was treated with *p*-bromobenzoyl chloride in pyridine as described by Arora et al.[26] and the crude product was fractionated by preparative TLC as described for **1f**. Elution of a band at R_f 0.56 yielded 70 mg of **2e**: mp 178–180 °C after recrystallization from ethyl ether–hexane; ir ($CHCl_3$) 3730, 3590, 2940, 1715, 1575, 1470, 1145, 1112, 1105, 1065, 1012, 1000, 990, 957, 863 cm^{-1}; NMR, see Table IV; MS was not recorded because of thermolytic instability of the compound.

Anal. Calcd for $C_{22}H_{29}BrO_5$: C, 58.3; H, 6.5. Found: C, 58.7, H, 6.4.

Registry No.—**1a,** 59812-41-8; **1b,** 59812-42-9; **1c,** 59812-43-0; **1d,** 59812-44-1; **1e,** 59812-45-2; **1f,** 59812-46-3; **2a,** 59812-47-4; **2b,** 59812-48-5; **2c,** 59812-49-6; **2d,** 59812-50-9; **2e,** 59812-51-0; *p*-bromobenzoyl chloride, 586-75-4.

Supplementary Material Available. A listing of bond distances, bond angles, and observed and calculated structure factors for the *p*-bromobenzoate of celorbicol (**1f**) and for isocelorbicol (**2a**) (16 pages). Ordering information is given on any current masthead page.

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Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. 43. Carbon-13 Nuclear Magnetic Resonance Analysis of Bis-Indoline Alkaloids of Two *Voacanga* Species[1-3]

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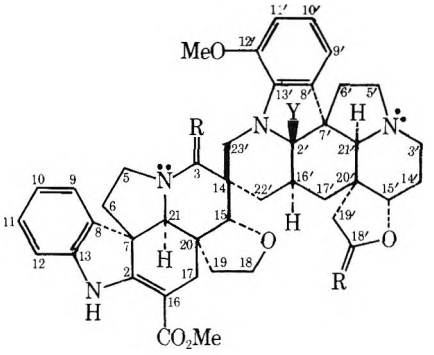
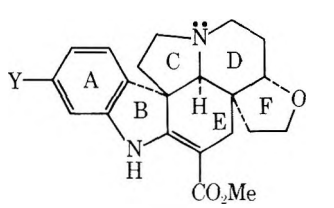
The ^{13}C NMR spectra of the bis-indoline alkaloids vobtusine, vobtusine lactone, and 2′-deoxyvobtusine lactone were recorded and their carbon shifts assigned. With the collected data and those of models the structures of the following natural bases were determined: vobtusine 3-lactam, vobtusine 3-lactam N_b′-oxide, voafolidine, voafoline, isovoafoline, folicangine, subsessiline, and subsessiline lactone.

Several indole alkaloids of high molecular weight were isolated recently from two *Voacanga* species[4,5] one of which proved to be vobtusine, a $C_{43}H_{50}O_6N_4$ alkaloid isolated earlier from *Callichilia subsessilis*[6] and *Hedranthera barteri*[7] and shown by x-ray analysis of its dibromo derivative[8] to possess structure 1a, a molecular framework composed of a spiro-

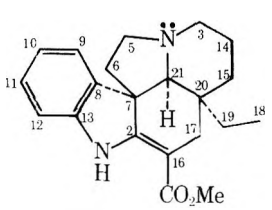


1a, R = R′ = H_2; Y = OH
b, R = H_2; R′ = O; Y = OH
c, R = H_2; R′ = O; Y = H
d, R = R′ = H_2; Y = OH; 2β,16β-dihydro
e, R = H_2; R′ = O; Y = OH; 2β,16β-dihydro
f, R = O; R′ = H_2; Y = OH
g, R = O; R′ = H_2; Y = OH; N_b′-oxide

fused combination of 11-demethoxyvandrikine-like (**2a**) skeleta and a C_1 unit. In order to facilitate the structure analysis of the congeners of vobtusine, all of which were suspected to be based on the same structure pattern, the study was initiated by the ^{13}C NMR analysis of the alkaloids of known constitution vobtusine (**1a**), vobtusine lactone (**1b**),[4] and 2′-deoxyvobtusine lactone (**1c**).[4] In this connection an earlier study of the Aspidosperma bases vandrikine (**2b**), tabersonine (**3a**), and related substances[9] proved very helpful.



2a, Y = H
b, Y = OMe



3a, $\Delta^{14,15}$
b, 14β,15β-oxide

* Rice University.

Since the three indole alkaloid "dimers" are 14,14-disubstituted 11-demethoxyvandrikines (**2a**), comparison of their ^{13}C NMR spectra with those of vandrikine (**2b**)[9] and tabersonine (**3a**)[9] allows direct signal matching for all carbons of ring A, B, C, and E. Whereas C(17) can be confused with C(14′) in vobtusine (**1a**), the ambiguity is relieved on comparison of the shifts of like carbons in the lactones. The identification of vobtusine's C(18) and C(19) shifts and their distinction from the similar C(18′) and C(19′) shifts rest on the δ values of like carbons in the monomer vandrikine (**2b**) and the modification of the latter pair on introduction of the lactone carbonyl group.

With the use of the aromatic carbon shifts of N_a-methyl-2β,16β-dihydrotabersonine[10] and methoxy substitution parameters[11] the methoxylated ring A′ carbon shifts can be assigned. Carbons 2′ and 16′ and the carbons of rings C′ and D′ can be recognized by the field position and multiplicity of their signals and relationship with like carbons of model **2b**. The C(3′) shift of vobtusine (**1a**) differs from that of other aminomethylenes by its perturbation in vobtusine lactone (**1b**) in which, for example, the C(23′) shift, close in magnitude to the δ value of C(3′), is unaffected. The ca. 2 ppm lower field position of C(3′) than that in model **2b** can be ascribed to a diminished γ effect from the ring F′ oxygen of vobtusine (**1a**) in part as a consequence of the conformational transmission induced by the removal of trigonality at the C(2′) and C(16′) sites. As a spectral comparison of vobtusine (**1a**) and its lactone (**1b**) as well as 2β,16β-dihydrovobtusine (**1d**) and its lactone (**1e**) indicates, conversion of ring F′ from a tetrahydrofuran to a γ-lactone unit introduces small, constant shift modifications which with the exception of C(17′) are confined to ring D′ carbons. The shift alteration of C(5) in the dihydro derivatives **1d** and **1e** provides a means of distinguishing this center from C(5′) in the natural product. Carbon 6′ is difficult to differentiate from C(22′). Whereas these two centers and C(17′) and C(23′) have hydrogens 1,3-diaxially disposed toward the 2′-hydroxy group, the expected γ effect is distributed unsymmetrically to the four sites. The shifts of the remaining carbons, those of ring D perturbed by C(14) disubstitution from like centers in vandrikine (**2b**), are constant among the three alkaloid "dimers". All δ values of these compounds are listed in Table I.[12]

A vobtusine (**1a**) congener in *Voacanga thouarsii* Roehm and Schult was shown to be a $C_{43}H_{48}O_7N_4$ substance possessing the infrared absorption characteristics of the vinylogous amide function of **1a–c** and a six-membered lactam.[1,5] These facts suggest that the new base could be vobtusine with C(3) or C(3′) in the form of a carbonyl group, a proposal easily tested by the compounds' ^{13}C NMR spectra. Were C(3) in-

Table I. Carbon Shifts of Compounds 1a–e[a]

	3a[b]	1a	1b	1c	1d	1e		2b[b,c]	1a	1b	1c	1d	1e
C(2)	166.7	166.6	166.6	166.7	67.5	67.6	C(2′)		93.7	93.3	75.6	93.7	93.4
C(3)		53.7	53.8	53.8	53.0	53.1	C(3′)	45.7	48.7	48.0	47.8	48.6	48.2
C(5)		50.9	50.9	51.2	55.0	55.1	C(5′)	51.2	51.9	51.8	52.7	51.9	51.8
C(6)		44.9	44.9	45.0	42.1	42.1	C(6′)	45.1	31.1	30.8	37.7	31.2	31.0
C(7)		54.8	54.8	55.0	52.2	52.2	C(7′)	54.2	55.9	55.8	51.0	55.8	55.9
C(8)	137.8	137.6	137.5	137.5	135.4	135.5	C(8′)		134.2	133.0	135.6	134.3	133.1
C(9)	121.4	121.2	121.2	121.4	118.3	118.5	C(9′)		114.5	114.6	114.8	114.5	114.4
C(10)	120.5	120.4	120.4	120.5	122.8	122.9	C(10′)		118.1	118.8	118.3	118.3	119.2
C(11)	127.6	127.4	127.5	127.6	127.7	127.9	C(11′)		110.8	111.1	110.9	110.1	110.7
C(12)	109.2	109.1	109.1	109.2	108.5	108.6	C(12′)		144.9	144.9	145.1	145.2	145.2
C(13)	143.1	142.8	142.8	142.9	150.1	150.2	C(13′)		137.2	136.9	137.9	136.9	136.7
C(14)		39.6	39.5	40.0	39.5	39.6	C(14′)	26.6	25.7	24.7	25.3	25.7	24.8
C(15)		87.4	87.3	87.5	90.0	90.0	C(15′)	79.8	80.3	81.4	82.0	80.3	81.5
C(16)	92.2	94.3	94.2	94.1	38.3	38.4	C(16′)		31.5	31.1	29.4	30.9	30.7
C(17)		27.3	27.3	27.5	26.5	26.6	C(17′)	27.4	32.4	31.7	33.7	32.4	31.8
C(18)		64.2	64.2	64.3	64.6	64.8	C(18′)	64.7	65.1	175.3	175.5	65.1	175.3
C(19)		34.8	34.8	34.8	40.4	40.5	C(19′)	34.6	36.6	41.4	41.5	36.5	41.6
C(20)		47.6	47.6	47.8	40.4	40.5	C(20′)	46.4	44.1	43.4	44.0	44.1	43.4
C(21)		68.9	68.8	68.8	69.8	69.9	C(21′)	68.7	63.6	63.9	65.3	63.5	64.0
C=O	168.8	168.3	168.3	168.4	175.8	175.8	C(22′)		34.1	33.5	39.0	34.1	34.0
OMe	50.8	50.9	50.9	51.0	51.6	51.8	C(23′)		46.1	46.0	52.7	45.4	45.4
							OMe		55.0	55.0	54.9	54.6	54.7

[a] In parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] From ref 9. [c] The previously undifferentiated C(14) and C(17) shifts are resolved by the present study.

Table II. Carbon Shifts of Vobtusine 3-Lactam and Its N_b'-Oxide[a]

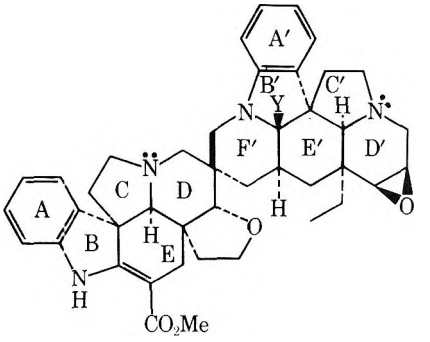
	1f	1g		1f	1g
C(2)	162.6	162.7	C(2′)	93.3	91.3
C(3)	171.2	171.5	C(3′)	48.7	58.9
C(5)	39.1	39.1	C(5′)	51.8	66.9
C(6)	44.9	45.2	C(6′)	31.9	44.9
C(7)	57.4	57.4	C(7′)	55.8	54.9
C(8)	137.5	138.1	C(8′)	133.0	132.3
C(9)	121.2	121.2	C(9′)	113.9	112.7
C(10)	120.8	120.8	C(10′)	118.4	117.9
C(11)	128.4	128.5	C(11′)	112.2	112.7
C(12)	109.5	109.6	C(12′)	146.8	146.8
C(13)	142.8	142.8	C(13′)	135.1	135.2
C(14)	49.0	48.9	C(14′)	25.6	22.6
C(15)	87.2	87.2	C(15′)	80.3	78.5
C(16)	92.4	92.6	C(16′)	31.9	31.0
C(17)	27.1	27.4	C(17′)	32.5	33.4[b]
C(18)	67.6	67.5	C(18′)	65.2	64.8
C(19)	36.2	36.3	C(19′)	36.2	33.9[b]
C(20)	47.8	48.0	C(20′)	43.9	39.2
C(21)	67.1	66.9	C(21′)	63.5	72.2
C=O	167.9	168.0	C(22′)	29.4	29.3
OMe	51.0	51.0	C(23′)	44.1	44.1
			OMe	56.1	56.2

[a] In parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] Signals may be interchanged.

volved in the structural change, an aminomethylene signal can be expected to be replaced by a keto signal and serious shift changes introduced at the spiro carbon and its close neighbors. Inspection of the spectra shows this expectation to be fulfilled and thus the alkaloid to be vobtusine 3-lactam (**1f**). The dramatic shielding of C(5) is in consonance with observations on lactam models.[14] All shifts of **1f** are listed in Table II.

A second vobtusine (**1a**) congener in *V. thouarsii*, a $C_{43}H_{48}O_8N_4$ substance, has been reported to possess closely related infrared absorption bands to those of vobtusine 3-lactam (**1f**).[1,5] The extra oxygen thus most likely is part of an ether linkage or amine oxide moiety. The ^{13}C NMR spectrum of the alkaloid reveals the carbons of the 11-demethoxyvandrikine (**2a**) 3-lactam portion of **1f** and C(22′) and C(23′) to be unchanged and all other nonaromatic carbon shifts to be modified. The 9–15-ppm deshielding of the amino carbons of rings C′ and D′ is in agreement with the shift behavior on conversion of a tertiary amine into an amine oxide.[15,16] Thus the natural base is vobtusine 3-lactam N_b'-oxide (**1g**). Its shifts are cited in Table II. The drastic shift differences between vobtusine 3-lactam (**1f**) and its N_b'-oxide (**1g**) points up the usefulness of monoamine oxide formation as a means of differentiation of individual monomer units of a "dimeric" alkaloid.

Voafolidine (**4a**) and its 2′-deoxy derivative voafoline (**4b**), leaf alkaloids of *Voacanga africana* Stapf., have been shown



4a, Y = OH
b, Y = H

to be related to vobtusine (**1a**), the 15′-oxy substituent being bridged to C(14′) instead of C(18′).[2,4] As a consequence pachysiphine (**3b**)[17] serves as a good ^{13}C NMR spectral model for most of the ring D′ carbons of the alkaloids. The δ values for the monomer base **3b**, shown in Table III, were derived from the aromatic shifts of tabersonine (**3a**)[9] and the nonaromatic shifts of hazuntinine (10,11-dimethoxy-**3b**).[9] The vandrikine-like portion of voafolidine (**4a**) is ^{13}C NMR spectrally identical with the same part of the molecular framework of vobtusine (**1a**). The same relationship exists between voafoline (**4b**) and vobtusine (**1a**). The aromatic carbon shifts of

Table III. Carbon Shifts of Pachysiphine, Voafolidine, and Voafoline[a]

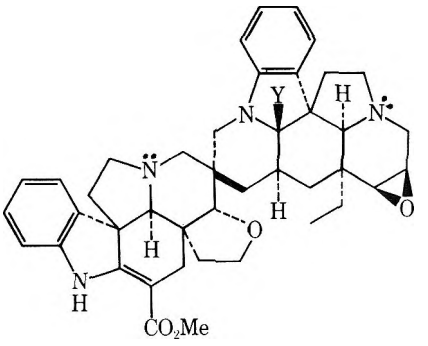
	2b[b]	4a	4b		3b[c]	4a	4b
C(2)	167.4	166.6	166.1	C(2′)	164.9	93.9[d]	76.0
C(3)	45.7	53.7	53.4	C(3′)	49.4	53.4[e]	53.0
C(5)	51.2	50.6	50.3	C(5′)	51.0	52.6[e]	53.0
C(6)	45.1	44.1	44.6	C(6′)	43.9	31.8	39.0
C(7)	54.2	54.6	54.4	C(7′)	54.7	55.4	51.5
C(8)		137.5	137.1	C(8′)	137.5	133.8	135.6
C(9)		121.2	121.5	C(9′)	121.3	121.8	120.8
C(10)		120.5	120.2	C(10′)	120.3	117.4	116.2
C(11)		127.6	127.3	C(11′)	127.6	127.3	127.0
C(12)		109.2	108.9	C(12′)	109.2	107.3	106.3
C(13)		142.9	142.5	C(13′)	142.9	148.8	149.8
C(14)	26.6	40.4	40.3	C(14′)	52.0	53.0	52.5
C(15)	79.8	87.3	87.0	C(15′)	56.2	56.7	56.5
C(16)	93.9	94.1[d]	93.7	C(16′)	90.4	28.5	25.6
C(17)	27.4	27.7	27.4	C(17′)	23.5	28.1	29.9
C(18)	64.7	64.4	64.0	C(18′)	7.1	7.6	7.3
C(19)	34.6	34.9	34.6	C(19′)	26.5	28.1	28.0
C(20)	46.4	47.5	47.3	C(20′)	37.0	36.1	35.9
C(21)	68.7	69.8	69.4	C(21′)	70.9	66.3	67.5
C=O	168.5	168.0	167.8	C(22′)		33.2	38.1
OMe	50.8	51.0	50.6	C(23′)		44.9	48.2

[a] In parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] From ref 9. [c] $\delta(C{=}O) = 168.6$ ppm; $\delta(OMe) = 50.8$ ppm. [d,e] Signals may be reversed.

N_a-methyl-2β,16β-dihydrotabersonine[10] lead to those of ring A′ of **4a** and **4b**, while the shifts of carbons 14′, 15′, 18′, 19′, and 20′ are derived from resonances of like carbons in pachysiphine (**3b**). The aminomethylenes of voafolidine, C(3′) and C(5′), are undifferentiated, the alkaloid's C(6′) and C(22′) shifts are similar to those of vobtusine (**1a**), and of the remaining pairs of methines and nonprotonated carbons one each is deshielded by a directly bound heteroatom. Carbons 17′ and 23′ are shielded in voafolidine (**4a**) vs. vobtusine (**1a**) by the proximate epoxide, as in pachysiphine (**3b**) vs. vandrikine (**2b**), and the removal of a δ effect from the 12′-methoxy group of vobtusine (**1a**), respectively. The fact of the $\Delta\delta$(C-21′) values of voafolidine (**4a**) vs. pachysiphine (**3b**) being nearly identical with those of vobtusine (**1a**) vs. vandrikine (**2b**) shows the stereochemistry of the epoxide unit of **4a** to be the same as that in pachysiphine (**3b**). The strong similarity of the shift differences of all carbons of voafolidine (**4a**) and voafoline (**4b**) vs. those of vobtusine lactone (**1b**) and 2′-deoxyvobtusine lactone (**1c**), except the $\Delta\delta$(C-23′) values, vouch for the identity of the stereoconfigurations of **4a** and **4b**. The conformational environment around C(23′) is different in compounds with the sterically encumbering 12′-methoxy group from those lacking this function, as indicated by a variance of the strength of the γ effect on C(23′) due to the 2′-hydroxy group in the two cases. The carbon shifts of voafolidine (**4a**) and voafoline (**4b**) are listed in Table III.

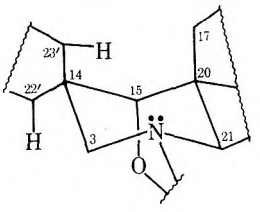
Isovoafoline, a congener of voafolidine (**4a**) and voafoline (**4b**) in *Voacanga africana* Stapf., has been shown to be an isomer of voafoline (**4b**) without the origin of the isomerism having been established.[2,4] A comparison of the ^{13}C NMR spectra of the two isomeric alkaloids establishes the identity of the chiral centers on the periphery of the bases and reveals significant shift differences only of C(18) and ring D and F′ centers, carbons 3, 14, 15, 16′, 22′, and 23′. Among these only C(3) and C(23′) have identical substituents, but can be differentiated by the γ effect of the 2′-hydroxy group on C(23′) in related substances (vide infra). Thus isovoafoline is the C(14) epimer of voafoline (**4b**), as depicted in formula **5b**. Its shifts are listed in Table IV.

As the conformational representations of rings D and F′ of

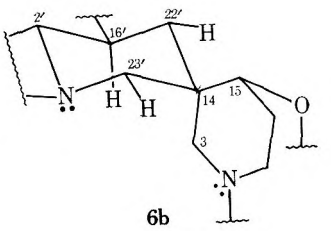


5a, Y = OH
b, Y = H

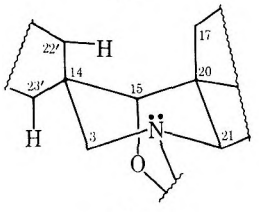
voafoline (**4b**), i.e., **6a** and **6b**, respectively, and isovoafoline (**5b**), i.e., **7a** and **7b**, respectively, illustrate N_a′ and C(16′) of



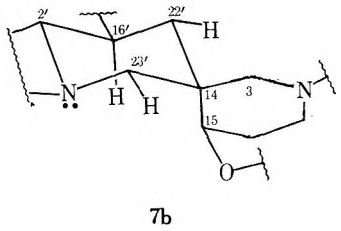
6a



6b



7a



7b

voafoline (**4b**) are involved in 1,3-diaxial interactions with C(3), while C(15), equatorially oriented toward ring F′, feels no such effects. Contrastingly, N_a′ and C(16′) of isovoafoline (**5b**) perturb C(15), while leaving C(3) unaffected. Owing to these specific γ effects C(3) is upfield and C(15) downfield in voafoline (**4b**) with respect to isovoafoline (**5b**). The 1,3-diaxial interactions of the N_b electron pair and C(17) with C(23′) in voafoline (**4b**), i.e., a strongly shielding γ effect and a mild deshielding δ effect, appears to be nearly balanced by the 1,3-diaxial involvement of the C(15) ether oxygen with C(22′), i.e., a strong γ effect. In view of this balance the inverted interactions of isovoafoline (**5b**) lead to only minimal shift differences at C(22′) and C(23′). Thus the C(3) and C(15) shifts establish the C(14) stereochemistry (see Table V). Had these alkaloids been 15-deoxy compounds, the C(22′) and C(23′) shifts would have been equally diagnostic.

Folicangine, another *V. africana* alkaloid, has been shown to be converted into isovoafolidine, an isomer of voafolidine (**4a**), on reduction with sodium borohydride.[2,4] Inspection of the ^{13}C NMR spectra of the reduction product showed it to be 14-isovoafolidine (**5a**). As in the case of voafoline (**4b**) and isovoafoline (**5b**) only the carbons sensitive to a configurational change at C(14) exhibit shift differences (cf. Table V). A similar study of the borohydride reduction products of subsessiline[1,2,4] and subsessiline lactone,[1,2] alkaloids of *Callichilia subsessilis*, proved them to be 14-isovobtusine (**8a**) and 14-isovobtusine lactone (**8b**), respectively (cf. Table V). Thus the alkaloids isovoafoline (**5b**), folicangine, subsessiline, and subsessiline lactone, whose detailed structures were unknown, possess a common C(14) configuration opposite to that of vobtusine (**1a**). All carbon shifts of the 14-iso compounds **5a**, **5b**, **8a**, and **8b** are listed in Table IV.

The following general comments can be made on the basis of the shift difference data. In agreement with observations

Table IV. Carbon Shifts of Isovoafolidine, Isovoafoline, Isovobtusine, and Isovobtusine Lactone[a]

	5a	5b	8a[b]	8b[b]		5a	5b	8a[b]	8b[b]
C(2)	166.6	166.1	166.7	166.7	C(2′)	94.1	76.9	94.4[c]	94.3[d]
C(3)	58.0	57.7	58.0	58.3	C(3′)	53.5[e]	53.1[e]	48.8	48.2
C(5)	51.4	51.0	51.4	50.9	C(5′)	52.8[e]	52.7[e]	52.0	51.9
C(6)	44.4	44.1	44.4	44.4	C(6′)	31.7	39.1	31.3	31.3
C(7)	55.0	54.5	54.8	54.8	C(7′)	55.5	51.6	56.4	56.4
C(8)	137.8	137.4	137.9	137.8	C(8′)	133.5	135.9	134.2	133.1
C(9)	121.4	121.0	121.5	121.4	C(9′)	121.2	121.0	113.5	113.6
C(10)	120.5	120.2	120.5	120.5	C(10′)	117.4	116.3	118.5	119.4
C(11)	127.5	127.4	127.5	127.6	C(11′)	127.1	126.8	110.3	110.6
C(12)	109.1	108.8	109.1	109.2	C(12′)	109.0	108.1	146.0	146.1
C(13)	142.9	142.6	142.8	142.9	C(13′)	148.3	149.4	136.8	136.4
C(14)	39.0	38.8	38.9	38.9	C(14′)	53.0	52.5	25.5	25.0
C(15)	80.2	80.6	81.5	81.5	C(15′)	56.6	56.4	80.4	81.4
C(16)	94.3	93.9	94.3[c]	93.9[d]	C(16′)	28.8	26.1	32.4[e]	32.0
C(17)	27.9	27.9	28.1	28.4	C(17′)	29.6	29.6	32.6[e]	32.0
C(18)	62.7	62.5	63.7	64.0	C(18′)	7.6	7.3	65.3	175.4
C(19)	34.8	34.6	35.1	34.9	C(19′)	28.1	27.9	36.8	41.7
C(20)	47.1	46.8	47.9	47.9	C(20′)	36.3	36.0	44.4	43.5
C(21)	70.0	69.6	69.9	69.9	C(21′)	66.5	67.9	63.7	63.6
C=O	168.1	167.6	168.1	168.2	C(22′)	34.8	39.9	35.1	34.9
OMe	50.9	50.5	50.9	50.9	C(23′)	44.2	49.1	46.5	46.3
					OMe			55.0	55.0

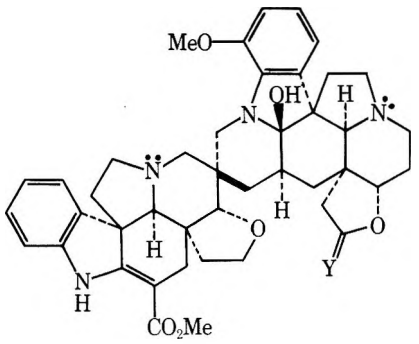
[a] In parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] Based on only a proton-decoupled spectrum because of low sample size. [c,d] Signals may be reversed. [e] Signals in any vertical column may be reversed.

Table V. Carbon Shift Differences Indicative of C(14) Configuration[a]

	4a	5a	4b	5b	1a	8a	1b	8b
δ(C-3)	53.7	58.0	53.4	57.7	53.7	58.0	53.8	58.3
δ(C-14)	40.4	39.0	40.3	38.8	39.6	38.9	39.5	38.9
δ(C-15)	87.3	80.2	87.0	80.6	87.4	81.5	87.3	81.5
δ(C-18)	64.4	62.7	64.0	62.5	64.2	63.7	64.2	64.0
δ(C-16′)	28.5	28.8	25.6	26.1	31.5	32.4	31.1	32.0
δ(C-22′)	33.2	34.8	38.1	39.9	34.1	35.1	33.5	34.9
δ(C-23′)	44.9	44.2	48.2	49.1	46.1	46.5	46.0	46.3
Δδ(C-3)	4.3		4.3		4.3		4.5	
Δδ(C-14)	−1.4		−1.5		−0.7		−0.6	
Δδ(C-15)	−7.1		−6.4		−5.9		−5.8	
Δδ(C-18)	−1.7		−1.5		−0.5		−0.2	
Δδ(C-16′)	0.3		0.5		0.9		0.9	
Δδ(C-22′)	1.6		1.8		1.0		1.4	
Δδ(C-23′)	−0.7		0.9		0.4		0.3	

[a] $\Delta\delta = \delta(\text{iso}) - \delta(\text{normal})$, in parts per million.

on quaternary carbon shifts[11] the δ values of the spiro carbon common to the two monomer units of the bis-indoline alkaloids suffers only minor perturbation from the normal to the 14-iso series, being slightly shielded in the latter. The aforementioned difference of ring F′ conformation depending on C(12′) substitution, as indicated by the magnitude of the γ effect of the 2′-hydroxy group on C(23′), is reflected also by the shift differences of C(15), C(18), and C(16′). The presence of a 12′-methoxy group reduces the magnitude of the reciprocal γ effects at C(15) and C(16′). The subtle conformational distortion of ring F′ is even observable through the shift of the distant C(18), presumably by conformational transmission via C(15)-H. In contrast to the sensitivity of all ring F′-related centers involved in strong steric interactions the sterically unencumbered C(3) is insensitive to ring F′ conformation.



8a, Y = H_2
b, Y = O

As the shift analysis of anhydrovobtusine[18,19] (cf. numbers on formula 9) indicates, dramatic substitution changes of ring F′ and consequent alteration of the interaction of ring F′ centers with ring D sites lead to shift modification of the carbons shown above to be diagnostic of the C(14) stereochemistry. Whereas the absence of models precludes complete shift assignment of the carbons, the C(15) shift can be recognized and is found to be anomalous for the normal vobtusine series.

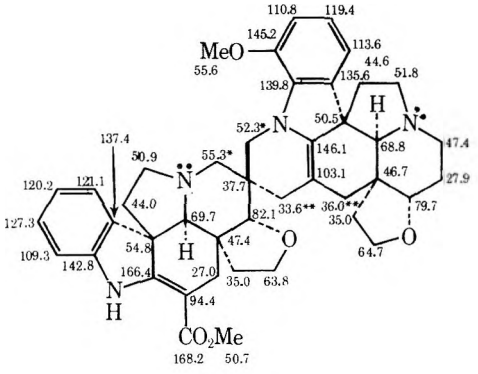
The chemical tie-up of folicangine with isovoafolidine (5a) by borohydride reduction[4] and the liberation of a 2′-hydroxy

Table VI. Carbon Shifts of Folicangine, Subsessiline, and Subsessiline Lactone[a]

	10	11a	11b		10	11a	11b
C(2)	165.8	165.9	165.7	C(2′)	93.9[b]	94.6[c]	93.9[d]
C(3)	91.8	91.9	91.9	C(3′)	53.7[e]	49.0	48.4
C(7)	59.1	59.1	*h*	C(5′)	53.3[e]	53.2	52.9
C(8)	136.1	137.1	*h*	C(6′)	30.5	31.1	31.5
C(9)	121.4	122.4	122.3	C(7′)	53.7	54.4	54.4
C(10)	121.0	120.9	120.9	C(8′)	135.9	136.0	135.8
C(11)	127.8	127.7	127.8	C(9′)	122.2	114.6	114.6
C(12)	109.1	109.0	109.1	C(10′)	118.1	118.8	119.1
C(13)	142.9	142.9	142.8	C(11′)	127.8	111.1	111.6
C(14)	38.1	38.1	38.2	C(12′)	106.9	145.8	145.9
C(15)	87.5	87.6	87.5	C(13′)	147.8	136.2	136.0
C(16)	93.0[b]	92.8[c]	92.7[d]	C(14′)	52.9	26.1	25.2
C(18)	67.3	67.2	67.3	C(15′)	56.5	80.9	81.9
C(20)	49.9	49.9	50.0	C(16′)	32.2	32.8	32.2
C(21)	70.6	70.6	70.7	C(17′)	29.6	34.4[f]	33.7[g]
C=O	168.1	168.1	168.0	C(18′)	7.6	65.0	175.2
OMe	51.0	50.9	51.0	C(19′)	28.0	35.8	40.6
				C(20′)	35.5	44.1	43.4
				C(21′)	67.7	65.8	65.9
				OMe		55.6	55.6

	10	11a	11b
NCH_2	47.5, 51.2	49.0, 50.9	48.9, 50.8
CH_2	33.9, 38.0, 38.6, 41.6	34.0,[f] 38.1, 38.6, 41.5	34.0,[g] 37.7, 38.6, 41.4

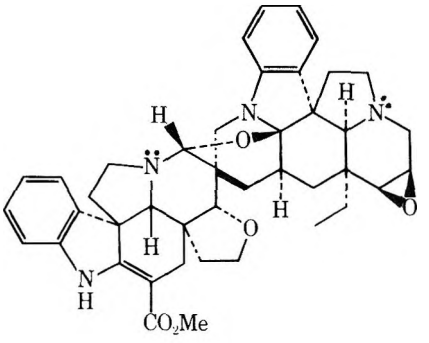
[a] In parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b-g] Signals may be reversed. [h] Signal missing because of low sample size.



9

group in this reaction indicates the tetradecacyclic, $C_{42}H_{46}O_5N_4$ alkaloid to be a didehydroisovoafolidine whose C(2′) oxygen is bridged to an amino carbon. In accord with this view the ^{13}C NMR spectra of folicangine differ from those of isovoafolidine (**5a**) primarily by the absence of one aminomethylene and the presence of a methine substituted by two heteroatoms. The spectra of monodeuterated isovoafolidine, prepared by the reduction of folicangine by sodium borodeuteride,[4] reveal the disappearance of the C(3) signal. Thus the structure of folicangine is **10**.[20] The relationship of folicangine to isovoafolidine (**5a**) is mimicked by that of subsessiline (amataine[19]) to isovobtusine (**8a**), even to the extent of sodium borodeuteride reduction of subsessiline placing a deuterium at C(3) of isovobtusine (**8a**).[1] Therefore the structure of subsessiline is **11a**.[20] Since the difference of the shifts of subsessiline and subsessiline lactone are like those of vobtusine (**1a**) and vobtusine lactone (**1b**), the structure of subsessiline lactone is **11b**.[20]

The chemical shifts of rings A′, B′, C′, D′, and E′ of the three 3,2′ ethers, **10**, **11a**, and **11b**, are altered only minimally from the values of their 2′-hydroxy alkaloid counterparts of either normal or 14-iso configuration. However, the introduction of the 3,2′-ether bridge causes dramatic shift changes at many of the carbons of the remaining rings, precluding rigorous shift assignment of the leftover methylenes (see Table VI). The drastic shift perturbations of the carbons of rings C, D, E, and the D-attached tetrahydrofuran cannot be accommodated by a H(3α) configuration, since this stereochemistry, depicted in conformation **12**, introduces merely a ring F′ boat form into the skeleta of the 2′-hydroxy-14-iso compounds, thus affecting, at worst, only the C(3), C(5), C(14), C(15), and C(21) shifts. More deep-seated conformational changes must be involved in shift alteration of centers far removed from the ether-bridging site, such as the lower limit Δδ values of 3, 4, 6, and 4 ppm for C(6), C(7), C(17), and C(19), respectively. Thus it appears that folicangine, subsessiline, and subsessiline lactone possess a H(3β) configuration, as illustrated in formulas **10**, **11a**, and **11b**. This stereochemistry demands that



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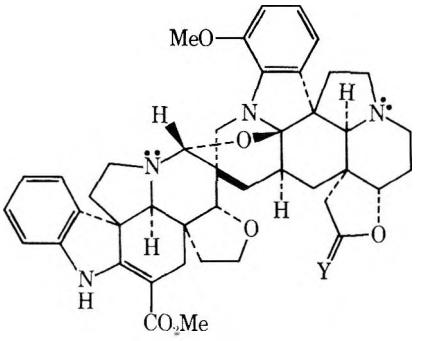
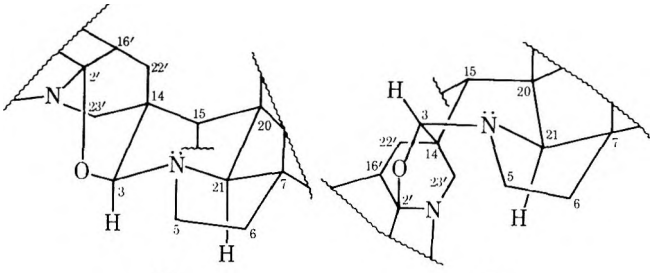
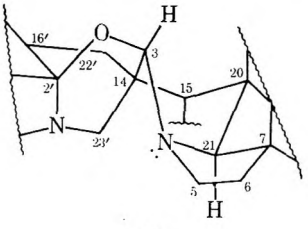


11a, Y = H_2
b, Y = O

ring D be constrained into a boat form. However, the resultant, strong, nonbonded interactions of H(21) and H(23′β) (cf.



12 13



14

conformation **13**) can be expected to convert the usual C/D trans configuration of the *Aspidosperma* bases[21] to a *cis*-indolizidine system. The consequently new nonbonded interactions in conformation **14** of the alkaloids **10**, **11a**, and **11b** are sufficiently complex and all-pervasive to lead to the observed general shift changes.

Experimental Section

The ^{13}C NMR spectra were recorded on a Varian XL-100-15 spectrometer operating at 25.2 MHz in the Fourier transform mode. All samples were run in 0.05–0.5 M deuteriochloroform solutions. Except for substances **8a**, **8b**, and **11b**, all compounds were submitted to proton-noise decoupling, single-frequency off-resonance decoupling, and low-power, noise-modulated decoupling,[22] to establish carbon shifts and degrees of protonation. In select instances partially relaxed Fourier transform spectra, obtained by the 180°–τ–90° inversion recovery method, were recorded for verification of the latter. For the alkaloids examined by this technique τ intervals in the range of 0.070–0.080 s were found to distinguish qualitatively methine from methylene carbons by making the latter null. The shifts enumerated on formula **9** are in parts per million downfield from Me_4Si [$\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm]. The starred numbers indicate possible signal reversal.

Anhydrovobtusine (9). The following represents an improved method of preparation of **9**.[18,19] A solution of 1.0 g of vobtusine (**1a**) in a minimum of methylene chloride was added to a solution of 2 g of *p*-toluenesulfonic acid in 200 ml of anhydrous benzene in the presence of a Dean-Stark water separator and the mixture refluxed for 4 h. It then was poured into 200 ml of water, made basic to pH 10, and extracted with chloroform. The extract was washed with water, dried over sodium carbonate, and evaporated. Chromatography of the resin, 1 g, on Baker silica gel (activity I) and elution with methylene chloride–methanol yielded 700 mg of **9** and 100 mg of apovobtusine, identical in all respects with the reported compounds.[18]

Registry No.—**1a**, 19772-79-3; **1b**, 19772-81-7; **1c**, 19772-80-6; **1d**, 59803-47-3; **1e**, 59796-71-3; **1f**, 50924-04-4; **1g**, 50924-05-5; **3b**, 2447-58-7; **4a**, 32063-91-5; **4b**, 31947-67-8; **5a**, 33055-38-8; **5b**, 31947-66-7; **8a**, 59829-32-2; **8b**, 59829-33-3; **10**, 32340-00-4; **11a**, 31148-60-4; **11b**, 59796-72-4.

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Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. 48. Dimeric Quinolinic *Melodinus* Alkaloids[1]

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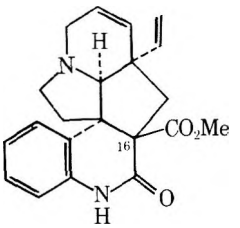
The *Melodinus* C_{41} alkaloids scandomelonine and episcandomelonine are shown by ^{13}C NMR spectroscopy to be 19 epimers of 10-(3′α-pachysiphinyl)meloscandonine. A similar study of the C_{42} *Melodinus* bases scandomeline and episcandomeline reveals them to be structurally related, 19-epimeric carbinolamines.

The New Caledonian plant *Melodinus scandens* Forst. has been shown to produce a large array of alkaloids containing inter alia the two unusual quinolones scandine (**1**) and meloscandonine (**2**).[2-7] Further fractionation of the plant extract now has yielded four "dimeric" alkaloids, scandomelonine,[6] episcandomelonine, scandomeline,[6] and episcandomeline. The present communication presents their structure analysis mostly by the use of ^{13}C NMR spectroscopy.

Scandomelonine and episcandomelonine are $C_{41}H_{42}O_5N_4$



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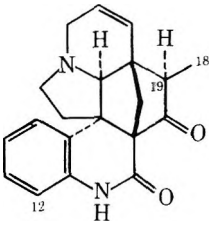
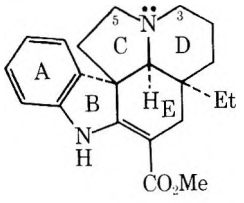


2

isomers whose common infrared bands at 3370, 1745, 1675, and 1610 cm^{-1} reveal the alkaloids to possess NH groups, two keto groups characteristic of meloscandonine (**2**), and a vinylogous amide unit reminiscent of vincadifformine (**3**), a congener of these alkaloids.[4,5] The ultraviolet absorption characteristics common to both compounds, λ_{max} 214 nm (log ϵ 4.40), 264 (4.08), 296 (4.03), 329 (4.18), $\lambda_{shoulder}$ 233 (4.11), can be interpreted to be a composite of the chromophores of meloscandonine (**2**) and vincadifformine (**3**). The exhibition of a peak of 456 mass units, corresponding to the loss of a $C_{13}H_{12}O_2N$ fragment represented by **4**, in the mass spectra



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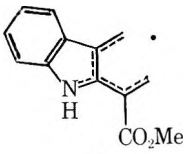


4

of the alkaloids shows the latter to possess the ABE ring system of vincadifformine (**3**).[8] Finally, the methyl doublet (J = 7 Hz) at 1.21 and 0.93 ppm in the ^1H NMR spectra of scandomelonine and episcandomelonine, respectively, is identical with H(18) shifts and multiplicities of meloscandonine (**2**)[4] and its 19 isomer[9] and suggests the two new bases to be 19 epimers of each other.

The above data facilitated the interpretation of the ^{13}C NMR spectra of especially scandomelonine by suggesting an early comparison with the ^{13}C NMR spectra of meloscandonine (**2**).[7] Such comparison showed all carbons of the monomer represented in the spectra of the "dimer", the aromatic carbon shifts and multiplicities having been modified. The last fact indicates that the second alkaloid monomer unit is attached to the aromatic ring of meloscandonine (**2**). The interdependent problem of the center of attachment and aromatic methine shift allocation can be solved most readily by analysis of the coupling characteristics of the aromatic methines. Single-frequency off-resonance decoupled (sford) spectra can be run under conditions in which aromatic methine carbons display coupling only with ipso and meta hydrogens, i.e., one-bond and three-bond carbon–hydrogen interactions. These conditions are met when the $^1J_{CH}$ value is reduced to ca. one-half its normal size.[10] Since every methine carbon of an ortho-disubstituted benzene has a hydrogen meta oriented to it, the sford spectrum of such an aromatic substance reveals the methines as doublets of doublets. This behavior is common to all ring A unsubstituted indole alkaloids as well as to meloscandonine (**2**). Carbon 12 of the meloscandonine portion of the "dimer" is recognized easily in view of its ortho relationship to the quinolone nitrogen placing its signal at a high field position. In contrast to all aromatic methines it appears as a sharp doublet in the sford spectrum, thereby showing C(10) to be the site of the tie-up with the nonmeloscandonine monomer unit and the latter to be unsubstituted on ring A of its indolic nucleus.

All resonances of the trigonal carbon centers of rings A, B and E of vincadifformine (**3**)[11] appear unchanged in the ^{13}C NMR spectra of scandomelonine. The one-bond coupling constants of 142 ± 2, 156 ± 2, 178 ± 2, and 179 ± 2 Hz of the tetrahedral methine carbons of the vincadifformine-like portion of the alkaloid reveal these carbons to be attached to heteroatom centers[12] and those of $^1J_{CH}$ = ca. 180 Hz to be part of an epoxide moiety.[12,13] To be incorporated into a vincadifformine-like structure, the remaining methines must be aminomethines, thus limiting the second site of coupling of the two monomer alkaloid units to C(3) or C(5) of **3**. These facts invited comparison of the shift data of scandomelonine

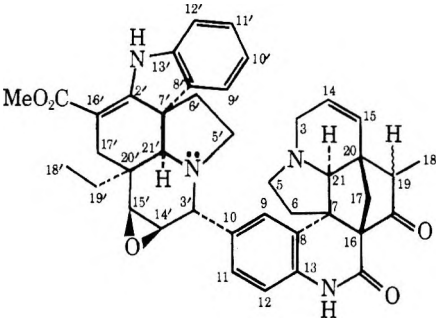
Table I. Carbon Shifts of Scandomelonine and Episcandomelonine[a]

	2[b]	**5a**	**5b**		**5a**	**5b**	**3a**[c]
C(3)	47.2	47.3	47.0	C(2′)	164.6	164.7	164.9
C(5)	54.8	54.7	54.9	C(3′)	57.4	57.6	49.4
C(6)	38.1	37.9	38.0	C(5′)	47.8	47.5	51.0
C(7)	54.8	54.7	56.7	C(6′)	42.1	42.3	43.9
C(8)	130.5	130.7	130.3	C(7′)	53.8	53.6	54.7
C(9)	123.5[d]	124.7	125.0	C(8′)	137.2	137.1	137.5
C(10)	123.4[d]	129.1	128.6	C(9′)	121.2	121.6	121.3
C(11)	127.6	127.1	126.8	C(10′)	120.8	121.1	120.3
C(12)	116.3	116.0	115.8	C(11′)	127.3	127.2	127.6
C(13)	136.5	136.3	136.3	C(12′)	108.9	108.7	109.2
C(14)	124.0	123.9	125.5	C(13′)	142.5	142.3	142.9
C(15)	127.4	127.7	128.0	C(14′)	56.2	56.2	52.0
C(16)	67.7	67.6	67.6	C(15′)	53.5	53.5	56.2
C(17)	36.0	36.0	40.0	C(16′)	90.2	90.1	90.4
C(18)	11.0	11.1	8.6	C(17′)	23.6	23.2	23.5
C(19)	50.7	50.8	52.6	C(18′)	7.3	7.27.1	
C(20)	44.3	44.5	45.4	C(19′)	26.6	26.3	26.5
C(21)	69.9	70.4	61.5	C(20′)	36.5	36.7	37.0
NC=O	169.0	169.0	168.7	C(21′)	61.5	61.5	70.9
C=O	210.0	209.8	208.4	C=O	168.4	168.4	168.6
				OMe	50.8	50.8	50.8

[a] In parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] From ref 7. [c] From ref 14. [d] Signals may be reversed.

with those of pachysiphine (14β,15β-oxido-3) (**3a**).[14] This comparison leads to the formulation of the "dimer" alkaloid as 10-(3′α-pachysiphinyl)meloscandonine (**5a**).[15] All its carbon shifts are listed in Table I.

Comparison of the ^{13}C NMR spectra of episcandomelonine with those of scandomelonine (**5a**) indicates that not only is



5a, 19α-H
b, 19β-H

the 3′α-pachysiphinyl moiety common to both alkaloids, but they also are very similar in the meloscandonine unit except within the vicinity of C(19). The shift changes at C(17), C(18), and C(21) provide conclusive evidence for the conversion of an *exo*-α-methylnorbornanone fragment to one of an *endo*-α-methyl structure.[16] Thus episcandomelonine proves to be 10-(3′α-pachysiphinyl)-19-epimeloscandonine (**5b**). Its chemical shifts are presented in Table I.

Scandomeline and episcandomeline are $C_{42}H_{46}O_6N_4$ isomers with common infrared absorptions at 3540, 3340, 1725, 1665, and 1610 cm^{-1}, characteristic of hydroxy and NH groups, an ester keto function, and a vinylogous amide moiety as that in vincadifformine (**3**). Their superimposable ultraviolet spectra, λ_{max} 214 nm (log ϵ 4.23), 257 (3.86), 300 (3.86), 325 (3.95), $\lambda_{shoulder}$ 233 (3.91), are a composite of the chromophores of vincadifformine (**3**) and o-toluidine. The mass spectra exhibit a peak at 488 mass units, representative of the loss of the $C_{13}H_{12}O_2N$ fragment **4**. Finally, the ^1H NMR spectra reveal the alkaloids to possess a carbomethoxy group

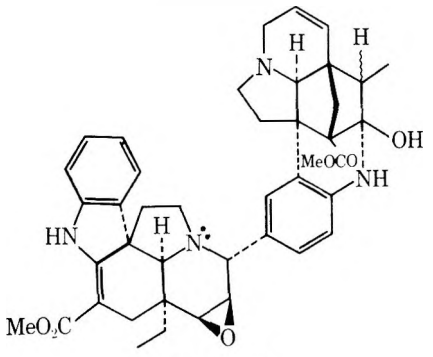
in view of the presence of a 3.68-ppm three-proton singlet and methyl doublets (J = 7 Hz) at different field positions, 1.18 ppm for scandomeline and 0.75 ppm for its isomer. These facts show that the third and fourth "dimeric" alkaloids differ from the other two by the replacement of the quinolone and cyclopentanone carbonyl groups by an ester function and nonacylated aniline system and, formally, by the addition of methanol.

The ^{13}C NMR spectra of scandomeline and episcandomeline indicate the alkaloids to possess a 3′α-pachysiphinyl unit attached to C(10) of the nonlactam equivalent of the quinolone unit. The aromatic shift modifications of the latter are reminiscent (in direction, albeit not in magnitude) of the shift differences of the aromatic oxindole and indoline carbons of gelsemine and its 2-deoxo-2,2,18,19-tetrahydro derivative.[17] The spectra reveal further the presence of a carbomethoxy function and the attachment of the remaining two heteroatoms to a single nonprotonated carbon site, i.e., a carbinolamine unit. Finally, the only difference between scandomeline and episcandomeline is their C-methyl orientation, ascertained by the shift differences between the compounds, as in the distinction between **5a** and **5b**. Interpretation of the combined physical data leads to structures **6a** and **6b** for scandomeline and episcandomeline, respectively. Their carbon shifts are listed in Table II.

Table II. Carbon Shifts of Scandomeline and Episcandomeline[a]

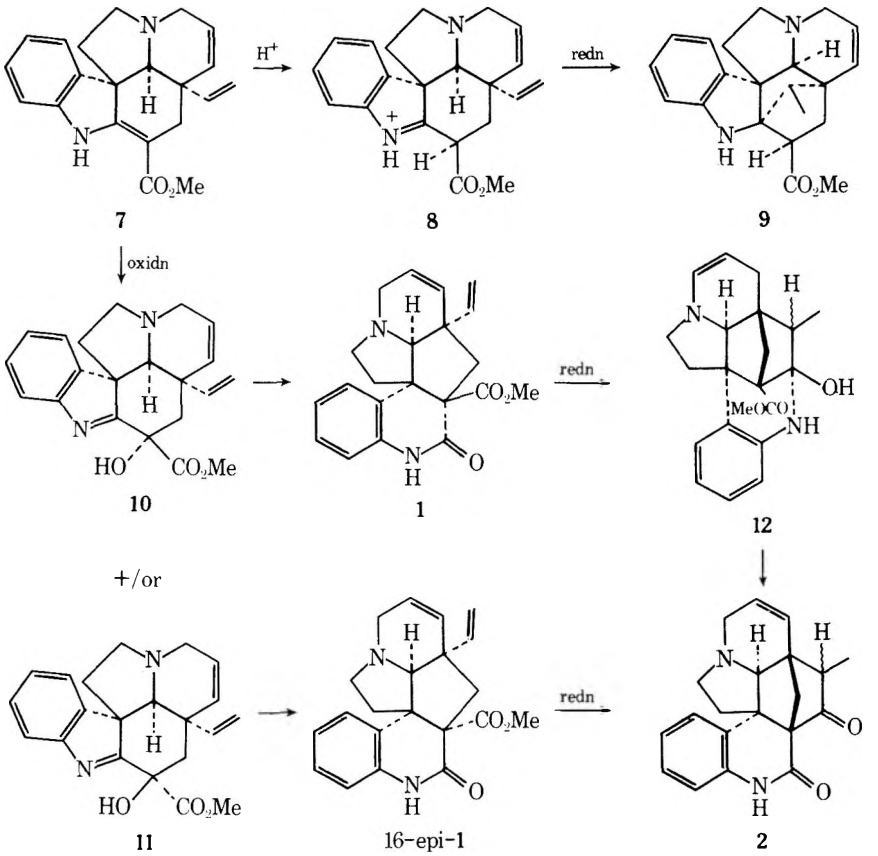
	6a[b]	6b		6a[b]	6b
C(3)	49.2	49.4	C(2′)	164.9	164.9
C(5)	52.7	52.9	C(3′)	58.2	58.2
C(6)	38.1	36.7	C(5′)	48.2	47.8
C(7)	50.9[c]	51.4	C(6′)	42.4	42.5
C(8)	124.5	124.6	C(7′)	54.1	53.8
C(9)	127.7[d]	127.4[e]	C(8′)	137.8	137.7
C(10)	123.5	123.2	C(9′)	121.6	121.2
C(11)	127.1[d]	127.3[e]	C(10′)	120.4	120.2
C(12)	114.6	112.8	C(11′)	127.4	127.3
C(13)	139.8	140.8	C(12′)	109.0	108.9
C(14)	125.8[d]	127.4	C(13′)	142.8	142.7
C(15)	129.4	129.9	C(14′)	56.4	56.3
C(16)	59.1	59.0	C(15′)	54.1	54.0
C(17)	40.3	41.9	C(16′)	90.6	90.5
C(18)	10.5	8.9	C(17′)	23.5	23.2
C(19)	49.8[c]	51.4	C(18′)	7.4	7.2
C(20)	46.5	47.6	C(19′)	26.9	26.7
C(21)	82.0	74.6	C(20′)	36.6	36.7
OCN	88.1	88.4	C(21′)	62.2	62.0
C=O	171.9	171.9	C=O	168.6	168.6
OMe	51.9	51.7	OMe	50.9	50.9

[a] In parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] Based solely on a proton-decoupled spectrum due to sample limitation. [c–e] Signals may be reversed.



6a, 19α-H
b, 19β-H

The relative stereochemistry of rings C and D of vincadifformine (**3**) and related *Aspidosperma* bases in solution has not been noted before. Models show that this indolizidine system remains unstrained in either cis or trans configuration. The association of the meloscandonine unit of **5a** and **5b** or its equivalent in **6a** or **6b** with the indolizidine part of pachysiphine offers some insight toward a choice between the



7 **8** **9**
10 **1** **12**
11 16-epi-1 **2**

two configurations. The C(3′α) substituent of all four "dimeric" alkaloids shields both C(5′) and C(21′), a phenomenon possible only in a trans configuration.[18]

The *Melodinus* alkaloids are structurally unusual by incorporating a quinoline moiety within the framework of an *Aspidosperma* skeleton. The biogenetic origin of such structure pattern has been ascribed to an oxidative rearrangement of 18,19-dehydrotabersonine (**7**).[2] Analysis of this oxidation and semibenzilic acid rearrangement along stereochemical lines suggests that 16α-oxidation (via **10**) of **7** is conducive to forming scandine (**1**) and 16β-oxidation (via **11**) 16-episcandine (16-epi-**1**). In order to formulate the origin of the biogenetically exceedingly unusual structure of meloscandonine (**2**) or its equivalent in **6**, an analogy can be drawn with the derivation of vindolinine (**9**).[19] If it be assumed that the enzymic reduction of the vinyl group, normally proceeding toward tabersonine, involves a sterically well-disposed, neighboring positive carbon center, coupling would ensue causing **8**, **1**, and 16-epi-**1** to yield **9**, **12**, and **2**, respectively. Finallly, since the unraveling of the carbinolamine of **12**, yielding an aniline and norbornanone, followed by lactam formation, leading to **2**, is facile (see Experimental Section), alkaloids of both structure types **2** and **12** may be produced as a consequence of solely the sterically more favorable 16α-oxidation of **7**.

Experimental Section

The ^{13}C NMR spectra were recorded on a Varian XL-100-15 spectrometer operating at 25.20 MHz equipped to operate in the pulsed Fourier transform mode with Transform Technology Inc. computer and pulse hardware.

Chromatography of the crude alkaloid extract (59.76 g) from 5.80 kg of dry stems and leaves of *Melodinus scandens* Forst.[5] was chromatographed on Sephadex LH 20 (2 g of extract on 65 g of absorbent) and eluted with 7:3 methanol–chloroform. The eluates were monitored by TLC on Kieselgel H (50:1 ether–methanol). This procedure gave two fractions, 12.70 and 5.56 g, rich in "dimeric alkaloids". The first fraction was chromatographed on 400 g of Merck alumina (activity I) and eluted with ether up to 9:1 ether–methanol. This led to 536 mg of **6a**, 120 mg of **6b**, and 1.014 g of a mixture of **5a**, **5b**, **6a**, and **6b**. Chromatography of the second fraction on 180 g of Merck Kieselgel 60 (30–70 mesh) and elution with 20:1 ethyl acetate–methanol yielded 806 mg of a mixture of the four alkaloids, 682 mg of a mixture of **5a** and **5b**, and 1.435 g of **6a**, **6b**, and another alkaloid. Finally, preparative TLC on Merck Kieselgel G and elution with 9:1 ether–methanol led to the separation of **5a** and **5b** and preparative TLC on Merck alumina and elution with 20:1 ether–methanol separated **6a** and **6b**.

Scandomelonine (5a), crystallized from acetone: mp >300 °C dec; $[\alpha]_{578}^{22}$ −25° (c 1, $CHCl_3$); ir (KBr) NH 3370 (m), C=O 1745 (s), 1675 (s), C=C 1620 cm^{-1} (m); uv (EtOH) λ_{max} 264 nm (log ε 4.08), 296 (4.03), 329 (4.18), $\lambda_{shoulder}$ 235 (4.11); (EtOH–NaOH) λ_{max} 287 nm (log ε 4.21), 329 (4.19); ^1H NMR ($CDCl_3$) δ 0.84 (t, 3, J = 7 Hz, 19′-Me), 1.19 (d, 3, J = 7 Hz, 19-Me), 2.56 [s, 1, H(21′)], 3.80 (s, 3, OMe), 4.58 [s, 1, H(3′)], 5.98 (m, 2, olefinic H's), 6.18 [dd, 1, J = 7, 1.5 Hz, H(12)], 6.6–7.3 (m, 6, aromatic H's); MS *m/e* 670 (M^+, 5), 292 (72), 291 (42), 221 (43), 214 (base); accurate mass measurements[20] calcd for $C_{41}H_{42}O_5N_4$, 670.3155 (found, 670.3122); $C_{40}H_{41}O_4N_4$, 641.3128 (found, 641.3111); $C_{38}H_{30}O_3N_3$, 456.2287 (found, 456.2268); $C_{13}H_{12}O_2N$, 214.0868 (found, 214.0881).

Episcandomelonine (5b), amorphous: $[\alpha]_{578}^{22}$ +25° (c 1, $CHCl_3$); ir, uv, and ^1H NMR the same as those of **5a** except for 0.81 (d, 3, J = 7 Hz, 19-Me); MS *m/e* 670 (M^+, 11), 227 (45), 214 (base); accurate mass calcd for $C_{41}H_{42}O_5N_4$, 670.3155.

Scandomeline (6a), crystallized from acetone: mp >300 °C dec; $[\alpha]_{578}^{22}$ −170° (c 1, $CHCl_3$); ir (KBr) NH 3340 (w), C=O 1722 (s), 1660 (s), C=C 1610 (m), 1590 cm^{-1} (m); uv (EtOH) λ_{max} 259 nm (log ε 3.94), 302 (3.92), 3.28 (4.01), $\lambda_{shoulder}$ 232 (3.93); (EtOH–HCl) λ_{max} 270 nm (log ε 4.08), 296 (3.92), 327 (3.94), $\lambda_{shoulder}$ 234 (3.85); ^1H NMR ($CDCl_3$) δ 0.76 (t, 3, J = 7 Hz, 19′-Me), 1.16 (d, 3, J = 7 Hz, 19-Me), 3.63 (s, 3, saturated ester OMe), 3.76 (s, 3, unsaturated ester OMe), 4.51 [s, 1, H(3′)], 5.73 (m, 2, olefinic H's), 6.3–7.1 (m, 7, aromatic H's); *m/e* 702 (M^+, base), 673 (80), 606 (40), 392 (60); accurate mass calcd for $C_{42}H_{46}O_6N_4$, 702.8581 (found, 702.8563).

Episcandomeline (6b), crystallized from acetone: mp >300 °C dec; $[\alpha]_{578}^{22}$ −112° (c 0.5, $CHCl_3$); ir (KBr) OH 3540 (w), NH 3340 (w), C=O 1725 (s), 1655 (s), C=C 1600 cm^{-1} (m); uv and ^1H NMR the same as those of **6a** except for 0.77 (d, 3, J = 7 Hz, 19-Me); MS *m/e* 702 (M^+, 72), 685 (47), 684 (86), 673 (66), 655 (71), 626 (50), 588 (62), 488 (63), 470 (94), 392 (51), 375 (base); accurate mass calcd for $C_{42}H_{46}O_6N_4$, 702.8581.

Conversions of 6a and 6b into 5a and 5b, Respectively. A solution of 47 mg of scandomeline (**6a**) in 10 ml of acetic anhydride was heated at 100 °C for 6 h. Evaporation of the solvent under vacuum, preparative chromatography of the residue on Merck Kieselgel H, and elution with 12:1 ether–methanol yielded 3 mg of uninvestigated material, 12 mg of *N*-acetylscandomeline, and 7 mg (15%) of scandomelonine (**5a**), spectrally identical in all respects with **5a** above.

The same treatment of 200 mg of episcandomeline (**6b**) with 50 ml of acetic anhydride, preparative chromatography on Merck Kieselgel G, and elution with 13:1 ether–methanol yielded 62 mg of starting compound, 11 mg of *N*-acetylepiscandomeline, and 26 mg (13%) of episcandomelonine (**5b**), spectrally identical in all respects with **5b** above.

Registry No.—**5a**, 59813-31-9; **5b**, 59830-06-7; **6a**, 59813-32-0; **6b**, 59830-07-8.

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(15) The arguments establishing the site and stereochemistry of attachment of meloscandonine (**2**) to the pachysiphine (**3a**) moiety are those used in the determination of the structure of criophylline, 10-(3′α-pachysiphinyl)-andrangine [A. Cavé, J. Bruneton, A. Ahond, A.-M. Bui, H.-P. Husson, C. Kan, G. Lukacs, and P. Potier, *Tetrahedron Lett.*, 5081 (1973)].
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(20) The authors are indebted to Dr. P. Bladon (University of Glasgow) for this measurement.

Olefin Inversion. 1. Reaction of Aliphatic Epoxides with Triphenylphosphine Dihalides

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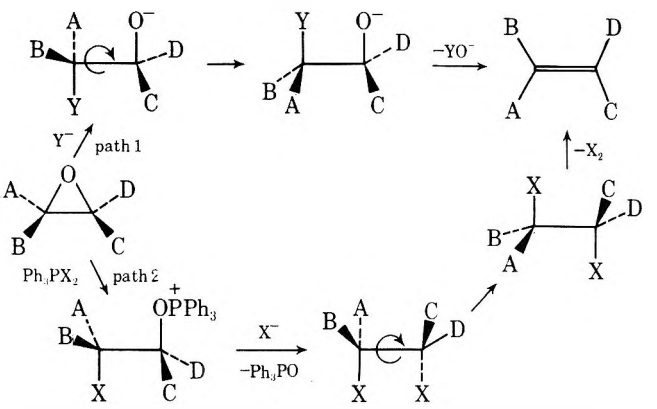
Triphenylphosphine dibromide and dichloride (Ph_3PBr_2 and Ph_3PCl_2) reacted with epoxides to produce the corresponding *vic*-dihalides in excellent yields. Ph_3PBr_2 reacted with cis epoxides in benzene to produce erythro dibromides exclusively, but less selectively with trans epoxides to give mixtures of threo and erythro dibromides. Ph_3PCl_2 reacted stereospecifically with both cis and trans epoxides in benzene or methylene chloride, in each case providing the dichloride derived from SN2 displacement on each C–O bond. By reacting epoxides first with hydrochloric acid and then with Ph_3PBr_2, it was possible to stereospecifically prepare *vic*-bromochlorides that were also products of two SN2 displacements. Zinc reduction of erythro dibromides was stereospecifically trans; thus the process (1) epoxidation, (2) Ph_3PBr_2 bromination, (3) Zn reduction affected a clean overall inversion of olefin geometry from *Z* to *E*. Reduction of threo bromochlorides to *Z* olefins could be made approximately 90% selective if carried out at 0–5 °C in dimethylformamide.

The ability to control and invert olefin geometry deservedly receives continuing attention in the chemical literature. Our own interest in such processes stems from the frequent uncertainty of the exact geometry of insect sex pheromones. The identities of pheromone components may be assigned by classical isolation–identification methods, or logical screening of synthetics,[1] but, in extreme cases, final adjustments have had to be made following ambiguous, or unsatisfactory, field tests.[2] Currently it is not clear whether the best use of a sex pheromone involves mimicking the exact composition of the natural product, or whether some other ratio of components might be more useful in an attempted disruption of mating processes. A convenient method of converting a sex pheromone, often an unsaturated acetate, to a geometric isomer would expedite the processes of determining pheromone isomer content and optimizing insect behavioral responses.

An elegant method of inverting olefin geometry has been described by Vedejs and Fuchs.[5] Epoxides were allowed to react with lithium diphenylphosphide, and the resulting oxy anions were alkylated on phosphorus with methyl iodide to produce betaines which, in turn, underwent cis eliminations to produce olefins of geometry opposite to those of the starting epoxides. A related method, described by Bridges and Whitham,[6] involved hydrogen peroxide oxidation of the same oxyanions; the resulting anions then eliminated the water-soluble lithium diphenylphosphinate. Very recent literature describes inversion via epoxides employing potassium selenocyanate,[7a] or hexamethyldisilazane/KOMe,[7b] and inversion via seleniranes and thiiranes.[7c] These processes involve addition of a single reagent to an epoxide (selenirane, thiirane in one case), with a stereochemical inversion, followed by cis eliminations from the initial adducts (Scheme I, path 1). A logical alternative would be a net cis addition (zero or two inversions) followed by trans elimination of the added groups (Scheme I, path 2). We describe here a route for olefin inversion via epoxides that is based on the latter principle and is thus complementary to those described earlier.

Scheme I[a]



[a] Path 1: one inversion, cis elimination. Path 2: two inversions, trans elimination.

Results and Discussion

Prior literature concerning reactions of epoxides with triphenylphosphine dihalides is sparse; information on stereochemistry is lacking, and indications were that mixtures of dihalides, haloalkenes, and other materials could be expected.[8] The few reaction conditions reported, however, had been quite vigorous. We recently observed that tetrahydropyranyl ethers were smoothly converted by triphenylphosphine dibromide (Ph_3PBr_2) to the corresponding bromides within minutes at room temperature,[9] and thus anticipated that milder conditions might be advisable in the application of this reagent to epoxides. The epoxide of (*Z*)-9-pentacosene (95% cis by ir, 965 cm^{-1} band) was therefore exposed to a slurry of Ph_3PBr_2 in benzene for 4 h. A dibromide was obtained nearly quantitatively; treatment with zinc in acetic (or propionic) acid produced (*E*)-9-pentacosene (94% trans by ir). The overall yield, olefin–olefin, was ca. 75%, and, within the limits of error of the infrared method of analysis, the transformations were stereospecific. Assuming that the elimination of bromine was trans,[10] the dibromide must have been the erythro isomer.

The diastereomeric threo dibromide formed in considerable proportion, however, if more polar solvents were used for the Ph_3PBr_2 treatment. Thus when methylene chloride was substituted for benzene, the ultimate product was a 61:39 mixture of (*E*)- and (*Z*)-9-pentacosenes; a 48:52 *E*:*Z* mixture of alkenes was ultimately derived from reaction in acetonitrile.

Although pentacosenes were of interest to use [the sex pheromone of the "little housefly", *Fannia canicularis* (L.), is (*Z*)-9-pentacosene],[11] greater precision in measuring isomer content would be realized if olefins were used the epoxides of which could be examined by gas chromatography; all data described hereafter were obtained in that manner.

Epoxidation of (*Z*)-7-octadecene[12] with *m*-chloroperbenzoic acid gave the corresponding epoxide (90% cis) which was converted under the conditions described (Ph_3PBr_2 in benzene, Zn/HOAc, *m*-chloroperoxybenzoic acid) to give 7,8-

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epoxyoctadecane which was 94% trans. The sex pheromone of the gypsy moth, *Lymantria dispar* (L.), (*Z*)-7,8-epoxy-2-methyloctadecene (95% cis),[13] similarly gave the epoxide of opposite geometry (97.5% trans). A sample of 85% *cis*-7,8-epoxy-2-methyloctadecane provided 93% trans epoxide. The apparent stereoselectivity of >100%, while gratifying, was suspicious and was subsequently traced to a lack of selectivity in the conversion of the few percent of trans epoxides present in the starting cis epoxides.

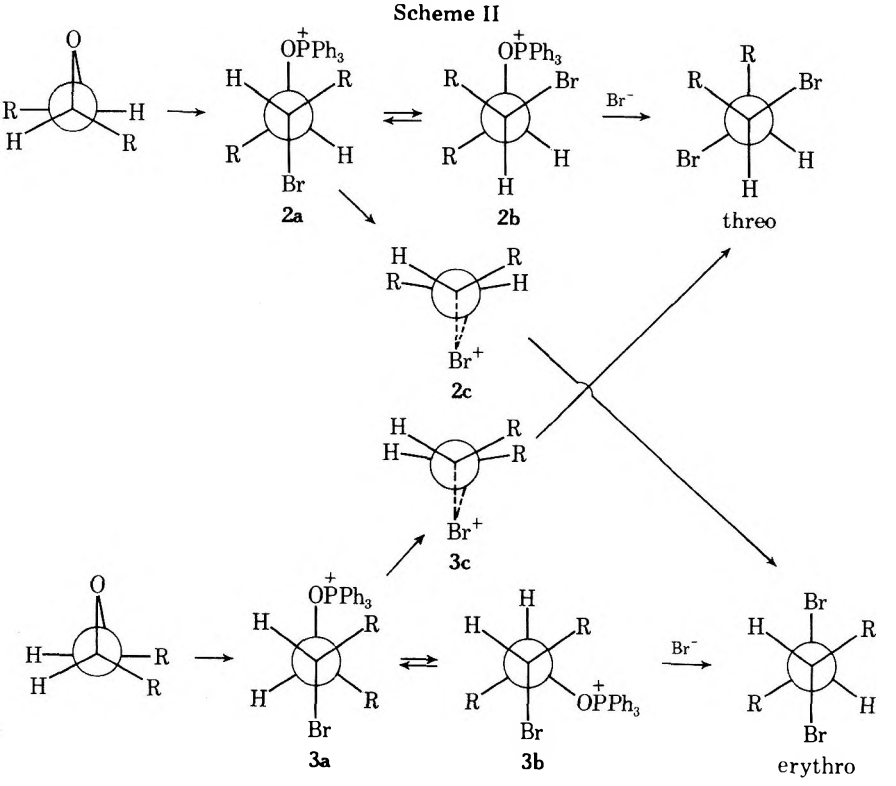
Two trans epoxides were then subjected to the three-step sequence: *trans*-7,8-epoxyoctadecene (94% trans) gave an epoxide mixture that was only 65% cis; *trans*-7,8-epoxy-2-methyloctadecane (97.5% trans) produced a 1:1 mixture of the cis and trans epoxides. The conditions of bromination and debromination were as stated, and overall yields were good (70–80%), but the stereoselectivity, if any, was clearly inadequate to be useful for *E–Z* conversions of olefins.

Since we had evaluated only the end product of a three-reaction sequence (Ph_3PBr_2 bromination, Zn/HOAc reduction, and peracid epoxidation), we now had to ascertain at what point the loss of specificity had occurred. Epoxidation with peracids is known to be highly selectively cis,[14] and we had encountered no exception in performing the oxidations of olefins with known geometry. Also reductive debromination with zinc in acetic acid is generally accepted to proceed trans, though Young and co-workers[10] had observed a few percent of diastereomer formation in their studies of zinc debromination–rebromination. To evaluate the zinc reduction under our conditions, we added bromine to (*Z*)-7-octadecene (90% cis) to produce the threo dibromide that we had sought to obtain from *trans*-7-octadecene oxide and Ph_3PBr_2. Zinc/acetic acid reduction of this threo dibromide and epoxidation of the product gave the cis epoxide (80% cis). Thus, as the earlier work had demonstrated,[10] the bromination, zinc–debromination sequence was not completely stereospecific for the threo dibromide. However, the deviation from specificity was insufficient to explain the results of our attempted trans–cis conversions.

We also examined the stereochemical stability of the *threo*-7,8-dibromooctadecane under the Ph_3PBr_2 bromination conditions. 5α,6β-Dibromocholesterol and some of its derivatives (trans-diaxial bromines) are known to isomerize spontaneously to the more stable 5α,6β-coprostane isomers,[15] but this type of isomerization is believed to involve a β-bromine-assisted ionization[15] and does not seem to have been considered important for aliphatic dibromides. When a sample of our *threo*-7,8-dibromooctadecane was exposed to a mixture of Ph_3PBr_2 and triphenylphosphine oxide in benzene for 24 h, reduction with zinc followed by epoxidation gave epoxide that was 73% cis. Whether the difference between the 80% cis realized earlier and the 73% cis obtained in this case was the result of dibromide isomerization or whether it indicated some limit of reproducibility in the reduction was not determined. What did become apparent was that the major stereochemical problem was encountered in the reaction of trans epoxides with Ph_3PBr_2, and not in the Zn reduction.

The reactions of cis and trans epoxides with Ph_3PBr_2 in benzene may be envisioned as shown in Scheme II. The trans epoxide reacts to produce the phosphorylated bromide **2a.** Direct SN2 displacement of triphenylphosphine oxide is possible, perhaps after an internal rotation to the more crowded rotamer **2b** in order to avoid eclipsing of bromine by incoming bromide; this would produce the threo dibromide. Alternatively, the triphenylphosphine oxide can be lost solvolytically with assistance from the adjacent bromine atom, generating a bromonium ion **2c** that would produce the erythro dibromide (a net front-side replacement of oxygen and thus a single inversion of configuration). The rotamer **2a** from which bromonium ion formation would be anticipated is probably more favored sterically than **2b.** The initial intermediate obtained from the cis epoxide, on the other hand, is the less sterically favored one **3a;** rotation to **3b** relieves crowding and also avoids potential eclipsing of bromine and incoming bromide. However, the functionalities of **3b** are not aligned for bromine-assisted solvolysis of triphenylphosphine oxide, and, in nonpolar solvents, the SN2 displacement occurs cleanly to provide the erythro dibromide. The loss of stereospecificity observed in the cis–trans isomerizations in the more polar solvents presumably results from the formation of the cisoid bromonium ion **3c** under those conditions.

Scheme II

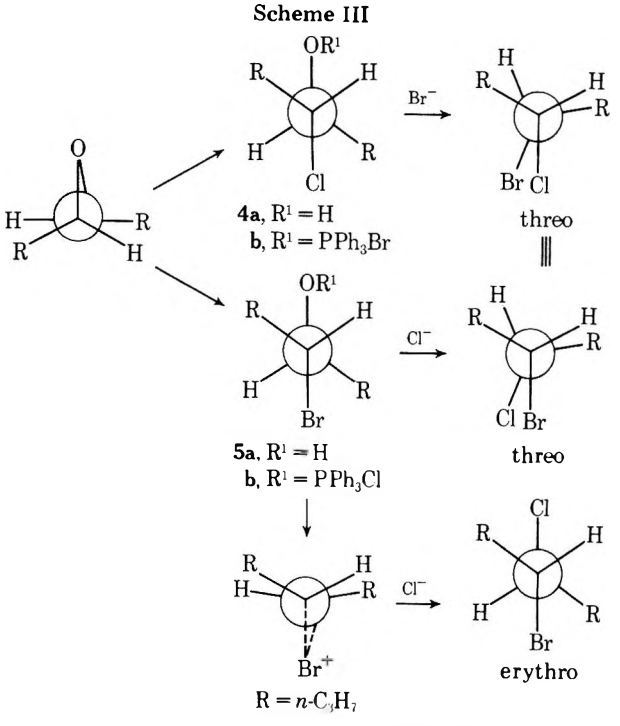


We next treated *trans*-7,8-epoxy-2-methyloctadecane with 48% hydrobromic acid in tetrahydrofuran. The resulting bromohydrin, presumed to be erythro resulting from SN2 attack by bromide on the protonated oxirane,[16] was reacted with Ph_3PBr_2 in benzene. The resulting dibromide was reduced with zinc, and the olefin was epoxidized; the resulting epoxide was only 23% cis. The erythro bromohydrin would also be expected to form an intermediate of the type **2a.** Formation of the bromonium ion **2c** seems to account for more of the product in this case, perhaps because of the presence of HBr in the reaction mixture.

Subsequent experiments further supported the idea of the bromonium intermediate. Since it is generally accepted that chloronium ions are of considerably higher energy than bromonium ions,[17] dichloride formation from epoxides and triphenylphosphine dichloride (Ph_3PCl_2) might be expected to be stereochemically more specific than the corresponding reactions in the Ph_3PBr_2 series. Indeed this was the case. We chose as models the *cis*- and *trans*-4,5-epoxyoctanes because we could analyze the dihalides directly by gas chromatography. In these cases, each epoxide reacted with Ph_3PCl_2 in either benzene or methylene chloride to produce a single dichloride; the dichlorides from the cis and trans epoxides corresponded to those obtained by direct (trans) addition of chlorine to the trans and cis olefins, respectively. Thus the reaction of the 1,2-disubstituted aliphatic epoxides with Ph_3PCl_2 had proceeded with the anticipated *back-side* displacement of *both* C–O bonds to give the equivalent of cis addition of chlorine to the alkenes. Chloronium ions evidently did not occur as intermediates.

The intermediacy of bromonium, but not chloronium, ions was further emphasized by converting *trans*-4,5-epoxyoctane to 4-bromo-5-chlorooctane. Samples of the trans epoxide were treated with hydrochloric and hydrobromic acids to give the erythro chlorohydrin **4a** and bromohydrin **5a,** respectively (Scheme III). The chlorohydrin **4a** was then treated with

Scheme III



Ph_3PBr_2 and the bromohydrin **5a** with Ph_3PCl_2. The bromochloride obtained from **4a** via **4b** was entirely threo (no chloronium ion participation), whereas that from **5a** via **5b** consisted of approximately equal parts of erythro and threo isomers (bromonium ion participation).

The reactions of triphenylphosphine dihalides with 1,2-epoxycyclohexane were also briefly examined. The epoxide reacted with Ph_3PBr_2 in such solvents as acetonitrile, benzene, and chlorobenzene to produce various mixtures of *cis*- and *trans*-1,2-dibromocyclohexane that often also contained some *trans*-1,2-bromohydrin. The latter could possibly be avoided by proper manipulation of reaction conditions, e.g., by using excess phosphorane, but a mixture of dibromides seemed unavoidable. On the other hand, Ph_3PCl_2 and cyclohexane epoxide in benzene or carbon tetrachloride produced *cis*-1,2-dichlorocyclohexane uncontaminated by the trans isomer. This reaction appears to be superior to the reported[18] conversion of cyclohexane epoxide to *cis*-1,2-dichlorocyclohexane with sulfuryl chloride in that the yields are better and the stereospecificity is much less subject to minor variations in the reaction conditions.

Since the means of converting epoxides to dichlorides with the required two inversions of configuration was now available, we turned our attention to reductive eliminations of the threo dichlorides. *trans*-7,8-Epoxyoctadecane was converted to the threo dichloride, and a variety of reaction conditions were investigated to effect a trans elimination. The dichloride required more vigorous reduction conditions than had the dibromides, and in all cases the reaction failed to exhibit the desired stereospecificity (Table I). Interestingly, sodium iodide in refluxing dimethylformamide (DMF) converted the threo dichloride to an olefin the epoxide of which was 91% trans; thus a cis elimination had occurred. This reaction and its potential for olefin interconversions are described in an accompanying paper.[19]

Since the transformations of epoxide to chlorohydrin to bromochloride with triphenylphosphine dibromide were proven to be stereospecific, threo bromochlorides were prepared from both *trans*-7,8-epoxyoctadecane and *trans*-7,8-epoxy-2-methyloctadecane in this manner. Various reduction procedures were studied and the results are given in Table I. The reductions of the bromochlorides proceeded under less vigorous conditions than those required for dichlorides but were still not completely stereospecific. To date the best procedure for converting trans epoxides to cis olefins via threo

Table I. Reductions of *vic*-Dichlorides and Bromochlorides

Dihalide (diastereomer content, %)[a]	Reduction conditions[b]	Isomer ratio (*E*:*Z*)[c]
threo-(7,8)-Dichloro-octadecane (94)	$LiAlH_4$, THF, reflux	30:70
	NaI, DMF, reflux	91:9
	Zn, HOAc, reflux	52:48
	Zn, DMF, 140 °C	30:70
threo-(7,8)-Bromo-chloroctadecane (90)[d]	Zn*,[e] DMF, H^+, 0–5 °C	28:72
threo-(7,8)-Bromo-chloro-2-methyl-octadecane (95)[d]	$LiAlH_4$, THF, reflux	48:52
	Zn, $C_2H_5CO_2H$, 25 °C	40:60
	Zn, DMF, 70 °C	24:76
	Zn*,DMF, H^+, 60–70 °C	18:82
	Zn*,DMF, H^+, 0–5 °C	13:87

[a] Estimated from purity of epoxides from which the dihalides were derived. [b] These conditions were for the most part approximately the mildest that would permit complete reduction in less than 24 h. Aliquots were worked up and examined by GLC; hence yields were not calculated except for the activated zinc reduction, which gave 80–87% yields. [c] Determined by GLC data using the epoxides. [d] Mixtures of 7-bromo-8-chloro and 7-chloro-8-bromo compounds. [e] Zinc was activated by brief treatment with dilute HCl as described by Tsuda et al.,[20] and 3 drops of acetic acid/5 ml of DMF was required to catalyze the reduction.

dihalides appears to be the activated zinc[20]–DMF treatment of bromochlorides which, at 0–5 °C, produced 87% cis alkene from 97.5% trans (ca. 90% selectivity).

The procedures thus far developed for inverting double bonds were then extended to unsaturated esters by examining their application to (*Z*)- and (*E*)-11-tetradecen-1-ol acetates. These two esters, which have been implicated repeatedly as sex attractants for lepidoptera,[21] were epoxidized (*m*-chloroperbenzoic acid). The trans epoxide was converted to the threo bromochloride via the two-step procedure (1) HCl/THF, (2) PPh_3·Br_2/CH_2Cl_2); and the cis isomer was treated directly with PPh_3·Br_2/benzene to give the erythro dibromide. Each dihalide was then reduced with activated zinc in DMF at 0–5 °C; the resulting unsaturated acetates were analyzed by GLC. The trans ester (99+% trans) gave the cis ester (92% cis); the cis ester (94% cis) gave the trans ester (>96% trans). The overall yields of these conversions were 70–80%.

Since the sensitivity of esters to lithium diphenylphosphide[5] appears to require protection of that group before an attempted olefin inversion via epoxide, the use of triphenylphosphine dihalides followed by zinc reduction of the resulting *vic*-dihalides should have considerable application. Triphenylphosphine dibromide is the reagent of choice when the object is to convert a *Z* alkene to a *E* isomer. Inversion in the opposite direction is best accomplished with HCl cleavage of the trans epoxide followed by reaction of the resulting chlorohydrin with triphenylphosphine dibromide. The *vic*-bromochloride may then be reduced with zinc–DMF at 0–5 °C with stereoselectivity of about 90%.

Experimental Section[22]

Infrared spectra were obtained with a Perkin-Elmer 457A spectrophotometer as 3% carbon tetrachloride solutions. More concentrated solutions were employed to estimate trans olefin content. NMR spectra were obtained with a Varian Associates T60 spectrometer; resonance frequencies were determined relative to internal Me_4Si. Gas chromatograms were obtained with Varian Aerograph 1520B, Hewlett-Packard 5700A, and Perkin-Elmer 3920 instruments. The following columns were employed: (1) SE-30, 5% on Chromosorb W (ABS), 92 cm × 6 mm; (2) Carbowax 20M, 5% on Chromosorb W (ABS), 1.83 m × 6 mm; (3) DEGS, 10% on Chromosorb W (AW), 1.83 m × 6 mm; (4) EGGS-X SCOT column, 15 m × 0.5 mm. Column chromatography was monitored with thin layer chromatography by using Brinkmann Instruments plates precoated with 0.25 mm of Sil G-25 UV_{254} and employing 15% ether/85% petroleum ether as the eluting solvent. Samples of (*Z*) and (*E*)-4-octenes were obtained commercially; (*Z*)-9-pentacosene[11] and (*Z*)-7-octadecene[12] were synthesized by Wittig condensation of an appropriate phosphorane with an aldehyde using HMPA–THF solvent to maximize the *Z*:*E* ratio.[23] Chemical analyses were performed by Galbraith Laboratories Inc., Knoxville, Tenn.

Epoxidations with *m*-Chloroperbenzoic Acid. The following procedure was typical. (*Z*)-9-Pentacosene (6.0 g, 17 mmol) was added to a stirred and ice-cooled solution of 85% *m*-chloroperbenzoic acid (4.1 g, 20 mmol) in methylene chloride (50 ml). The mixture was allowed to attain room temperature and, after 4 h, was washed with 25 ml of 5% NaOH and 25 ml of H_2O. The solution was dried ($MgSO_4$), and the solvent was removed yielding (*Z*)-9,10-epoxypentacosane (5.3 g, 86%). Recrystallization from petroleum ether provided a sample: mp 40–42 °C; NMR δ 0.90 (t, 6, CH_3), 2.68 (bs, 2, CHO). Anal. Calcd for $C_{25}H_{50}O$: C, 81.89; H, 13.75, Found: C. 82.20; H, 13.98.

Epoxides of (*Z*)- and (*E*)-4-octenes (96% *Z* and 99% *E*, respectively) were similarly prepared. The (*E*)-7-octadecene was synthesized from the *Z* isomer as described below. Relative GLC retention for (*Z*)- and (*E*)-4,5-epoxyoctanes using column 2 at 100 °C was 1.25:1.00; for (*Z*)- and (*E*)-7,8-epoxyoctadecanes using column 4 at 160 °C, it was 1.11:1.00; for (*Z*)- and (*E*)-7,8-epoxy-2-methyloctadecane[13] using column 4 at 160 °C, it was 1.10:1.00. These epoxides were sufficiently pure to be used directly for subsequent reactions.

Reactions of Epoxides with Triphenylphosphine Dibromide. The following procedure was typical. Bromine (2.7 g, 16.5 mmol) was added dropwise as a solution in CH_2Cl_2 (10 ml) to a stirred, ice-cooled solution of triphenylphosphine (4.4 g, 16.5 mmol) in CH_2Cl_2 (50 ml). Use of methylene chloride gave a visual end point, and the phosphine could be titrated with the bromine which obviated an exact weighing of the latter and produced a homogeneous solution. The solvent was removed and replaced with benzene (60 ml) to which was then added (*Z*)-9,10-epoxypentacosane (5.5 g, 15 mmol). The resulting slurry was stirred at room temperature for 4 h during which time the solid markedly changed character. The solvent was removed and the residue broken up under petroleum ether. Most of the triphenylphosphine oxide was removed by suction filtration. Removal of petroleum ether from the filtrate and recrystallization from petroleum ether (bp 30–60 °C) gave *erythro*-9,10-dibromopentacosane (6.5 g, 85%): mp 48–49 °C; NMR δ 4.02 (m, 2, CHBr). The CHBr resonance is consistent with an erythro as opposed to threo diastereomer.[24] Anal. Calcd for $C_{25}H_{50}Br_2$: C, 58.82; H, 9.87; Br, 31.31. Found: C, 58.92; H, 10.04; Br, 31.15.

erythro-7,8-Dibromo-2-methyloctadecane and *erythro*-7,8-dibromooctadecane were prepared similarly. Each was obtained as a liquid and was purified by passage through silica gel (~10 g/g dibromide) by elution with petroleum ether. After the solvent was removed and the purity was confirmed by TLC and GLC (column 1 at 250 °C), each was employed directly for reduction. A sample of *erythro*-7,8-dibromo-2-methyloctadecane was further purified by bulb-to-bulb distillation: bp 160 °C (0.02 mm); $n^{25}D$ 1.4803. Anal. Calcd for $C_{19}H_{38}Br_2$: C, 53.53; H, 8.98; Br, 37.49. Found: C, 53.86; H, 9.15; Br, 37.34.

Conversion of Epoxides to *vic*-Dichlorides with Triphenylphosphine Dichloride. The reactions of (*E*)- and (*Z*)-4,5-epoxyoctanes are typical. A 100-ml, three-necked flask fitted with a dry ice condenser, gas inlet, and addition funnel was charged with a solution of triphenylphosphine (2.0 g, 7.6 mmol) in anhydrous benzene (20 ml). The solution was stirred magnetically with external cooling (ice–water) and chlorine was admitted through the gas inlet until the mixture developed a permanent yellow color. A solution of the epoxide (0.64 g, 5 mmol) in benzene (5 ml) was added dropwise, then the dry ice condenser was replaced by a water-cooled condenser and the mixture was refluxed for 3.5 h. It was then cooled and treated with a little methanol to destroy excess Ph_3PCl_2. The benzene was stripped and replaced with petroleum ether (bp 30–60 °C) which caused the precipitation of triphenylphosphine oxide that was removed by filtration. The filtrate was concentrated, and the residue was added to a column of silica gel (15 g) and eluted with 100 ml of a solution of 15% ether in petroleum ether. Consentration of the eluate gave the 4,5-dichlorooctanes in 50–60% yields. The two dichlorooctanes were conveniently examined by gas chromatography on column 3. Each of the two products (from the isomeric epoxides) contained three minor, longer retention time impurities, but each was free from the isomeric dichloride. Samples of the two dichlorides were also prepared by chlorinating (*E*)- and (*Z*)-4-octenes with Cl_2 in CH_2Cl_2 at −78 °C; the chlorination product of the *E* olefin corresponded to the dichloride from the *Z* epoxide, and vice versa.

Conversions of Epoxides to Bromochlorides. A solution of (*Z*)-4,5-epoxyoctane (0.50 g, 3.9 mmol) in tetrahydrofuran (THF, 5 ml) was chilled to 0–5 °C. Concentrated HCl (0.5 ml) was added, and the solution was allowed to stand for 3 h at room temperature. The mixture was diluted with water and extracted thoroughly with ether. The extract was dried ($MgSO_4$) and concentrated to give the crude chlorohydrin which was then added to a solution of triphenylphosphine dibromide (6 mmol) in CH_2Cl_2 (20 ml) prepared as described previously. The resulting mixture was stirred overnight at ambient temperature, concentrated, and worked up with petroleum ether as previously described for the *vic*-dibromides. Purification, achieved by passage through silica gel as described for the *vic*-dibromides, gave, after solvent removal, *erythro*-4-bromo-5-chlorooctane (0.60 g, 67%): bulb-to-bulb distillation, bath temperature 125 °C (17 mm); $n^{25}D$ 1.4729; ir and NMR not distinct from those of the threo isomer. Anal. Calcd for C_8H_6BrCl: C, 42.22; H, 7.08; Br, 35.12; Cl, 15.58. Found: C, 42.50; H, 7.10; Br, 34.96; Cl, 15.30.

The threo isomer was similarly prepared (0.55 g, 62%): $n^{25}D$ 1.4714; relative GLC retention using column 2 was 1.15:1.00 (threo:erythro). Anal. Calcd for $C_8H_{16}BrCl$: 42.22; H, 7.08; Br, 35.12; Cl, 15.15. Found: C, 42.48; H, 7.04; Br, 34.95; Cl, 15.32.

The (*E*)- and (*Z*)-4,5-epoxyoctanes were similarly converted to erythro and threo bromohydrin, respectively (distinct from, and free from, each other, GLC column 3, 150 °C), with 48% HBr in dimethoxyethane (THF gave 4-bromo-1-butanol as a by-product that was bothersome to separate). The erythro bromohydrin was treated with a solution of Ph_3PCl_2 in methylene chloride as described for the conversion of epoxides to dichlorides. The product was an approximately equimolar mixture of *erythro*- and *threo*-4-bromo-5-chlorooctanes.

The threo bromochlorides derived from (*E*)-7,8-epoxyoctadecane and (*E*)-7,8-epoxy-2-methyloctadecane were similarly prepared and

purified. Purities were confirmed by TLC and GLC (column 1 at 250 °C).

Reductions of *vic*-Dihalides. A. Zinc–HOAc. The following procedure was typical. *erythro*-7,8-Dibromo-2-methyloctadecane (3.8 g, 8.9 mmol) was dissolved in acetic (or propionic) acid (40 ml). Zinc dust (3.8 g) was added, and the mixture was vigorously stirred. The reaction was mildly exothermic, and stirring was continued for 0.5 h. The mixture was diluted with H_2O and extracted with petroleum ether. The extract was washed with 5% $NaHCO_3$ until the washes were slightly alkaline, dried ($MgSO_4$), and concentrated to give (*E*)-7,2-methyloctadecene (2.16 g, 91%): bulb-to-bulb distillation, bath temperature 105 °C (0.02 mm); $n^{25}D$ 1.4545; ir 965 cm^{-1}; NMR δ 5.3 (m, 2 H, CH=); GLC analysis (column 4) of the epoxide indicated that the product was 97.5% *E*. Anal. Calcd for $C_{19}H_{38}$: C, 85.63; H, 14.37. Found: C, 85.67; H, 14.37. *erythro*-9,10-Dibromopentacosane and *erythro*-7,8-epoxyoctadecane were reduced in the same manner and gave (*E*)-9-pentacosene (95% *E* by ir) and (*E*)-7-octadecene (92% *E* judged by GLC analysis of its epoxide by using column 4 as described above).

B. Zinc–Dimethylformamide. The following procedure was employed in an attempt to achieve reduction under as mild conditions as possible. A solution of a *vic*-bromochloride (0.5 g) in dimethylformamide (DMF, 8 ml) was stirred and cooled with an ice bath. Activated[20] zinc dust (0.6 g) was pulverized with a mortar and pestle and added to the solution, then a solution of acetic acid (2–3 drops) in DMF (0.5 ml) was added dropwise (the reduction did not proceed at 0 °C in the absence of the acetic acid). The mixture was stirred magnetically in a refrigerator overnight (0 °C); then the solution was decanted from the metal (which was in the form of small, irregular spheres). Water was added, the product was extracted into hexane, and the hexane solution was washed with water, dried, and concentrated. In a few cases the residual zinc and zinc halides remained rather amorphous; in those instances the reaction mixtures were diluted with cold, dilute HCl, and the products were then extracted in hexane.

Conversion of (*Z*)- to (*E*)-11-Tetradecen-1-yl Acetate. The (*Z*)-11-tetradecen-1-yl acetate[2] was epoxidized by *m*-chloroperbenzoic acid as described. The crude epoxide (1.0 g, 3.7 mmol) was added to a slurry of triphenylphosphine dibromide (5.0 mmol) in benzene (25 ml) prepared as described previously. The mixture was stirred at ambient temperature overnight, concentrated, and worked up with petroleum ether, filtering to remove most of the triphenylphosphine oxide. The filtrate was concentrated, and the crude dibromoacetate was passed through silica gel (20 g) with 60 ml each of petroleum ether, 7.5% ether–petroleum ether, and 15% ether–petroleum ether. The eluate was concentrated, and the compound so obtained was added to a slurry of activated inc[20] (1.0 g) in DMF (10 ml) containing acetic acid (5 drops) at 5–10 °C. Stirring was continued at that temperature for 2 h. The reaction mixture was diluted with H_2O, and the product was obtained by extraction with petroleum ether in the usual manner (0.61 g, 70%). GLC analysis using column 4 (150 °C) indicated >96% *E*; relative retentions of the isomeric 11-tetradecen-1-yl acetates are 1.04:1.00 (*Z*:*E*).

Conversion of (*E*)- to (*Z*)-11-Tetradecen-1-yl Acetate. The *E* ester (99% *E*)[2] was epoxidized in the usual way, and the epoxide was treated sequentially with hydrochloric acid and Ph_3PBr_2 as described earlier. The mixture of bromochlorides was reduced by the zinc/DMF procedure to give 11-tetradecen-1-yl acetate (92:8 *Z*:*E*) in an overall yield of ca. 70%.

Registry No.—*m*-Chloroperbenzoic acid, 937-14-4; (*Z*)-9-pentacosene, 51865-00-0; (*Z*)-9,10-epoxypentacosane, 59906-99-9; (*Z*)-4-octene, 7642-15-2; (*E*)-4-octene, 14850-23-8; (*Z*)-4,5-epoxyoctane, 1439-06-1; (*E*)-4,5-epoxyoctane, 1689-70-9; (*E*)-7-octadecene, 7206-23-7; (*Z*)-7-octadecene, 7206-35-1; (*Z*)-7,8-epoxyoctadecane, 59907-00-5; (*E*)-7,8-epoxyoctadecane, 59907-01-6; (*Z*)-7,8-epoxy-2-methyloctadecane, 29804-22-6; (*E*)-7,8-epoxy-2-methyloctadecane, 42991-03-7; triphenylphosphine dibromide, 1034-39-5; *erythro*-9,10-dibromopentacosane, 59907-02-7; *erythro*-7,8-dibromo-2-methyloctadecane, 59840-28-7; *erythro*-7,8-dibromooctadecane, 59907-03-8; triphenylphosphine dichloride, 2526-64-9; *erythro*-4-bromo-5-chlorooctane, 59840-29-8; *threo*-4-bromo-5-chlorooctane, 59840-30-1; (*E*)-7,2-methyloctadecene, 40302-56-5; (*Z*)-11-tetradecen-1-yl acetate, 20711-10-8; (*E*)-11-tetradecen-1-yl acetate, 33189-72-9; *threo*-7,8-dichlorooctadecane, 59840-26-5; *threo*-7-bromo-8-chlorooctadecane, 59840-21-0; *threo*-7-chloro-8-bromooctadecane, 59840-22-1; *threo*-7-bromo-8-chloro-2-methyloctadecane, 59840-17-4; *threo*-7-chloro-8-bromo-2-methyloctadecane, 59840-18-5; DMF, 68-12-2; zinc, 7440-66-6.

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Olefin Inversion. 2. Sodium Iodide Reductions of *vic*-Bromochlorides and *vic*-Dichlorides

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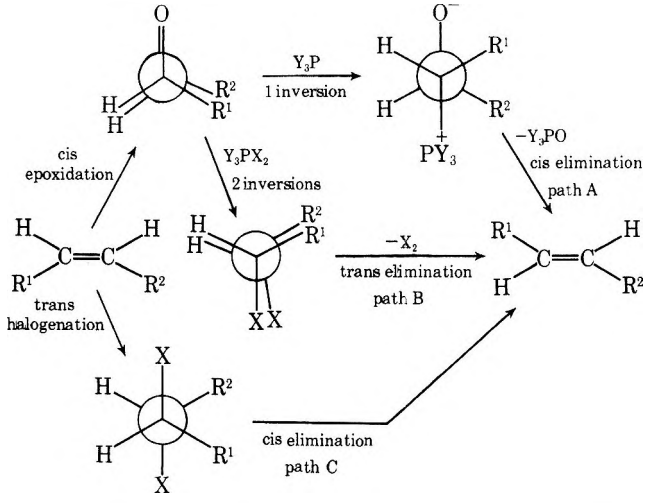
The stereochemistry of sodium iodide dehalogenations of *vic*-bromochlorides and *vic*-dichlorides was investigated and was found to be stereospecifically cis. This is opposite to the previously observed trans eliminations of *vic*-dibromides. It is proposed that the "cis" eliminations involve an initial SN2 displacement of Cl^- or Br^- by I^-, and that the resulting iodohalides then rapidly undergo trans elimination of ICl or IBr. A simple two-step sequence of halogenation (with Cl_2 or BrCl) and dehalogenation (with I^-) thus provides an efficient method of interconverting geometric isomers of olefins.

In the accompanying paper[1] we briefly reviewed methods of inverting geometries of olefins via their epoxides. Procedues that had been previously described involved SN2 openings of the epoxide by phosphides followed ultimately by cis eliminations of the oxygen and phosphorus moieties[2,3] (Scheme I, path A). Unsaturated hydrocarbons and acetates have frequently been identified as insect pheromones,[4] and simple means of inverting double bonds of pheromones would be extremely useful. Unfortunately, the methods just mentioned are not compatible with base-sensitive groups such as esters,[2] and we described complementary methods that did not affect that functional group.[1] In our processes, epoxides were converted to *vic*-dihalides with inversion of configuration at each of the oxygenated carbons (Scheme 1, path B). Trans elimination of the two halogens then provided olefins of geometries opposite those of the initial epoxides.

Scheme I. Olefin Inversion (Exemplified by *Z*–*E* Conversions)



Reductive eliminations of bromine from *vic*-dibromides initiated either by metals such as zinc[5] or by iodide ion[6] generally proceed in a trans fashion, and have occasionally been utilized as means of purifying olefins via (trans) bromination–(trans) debromination sequences.[7] However, deviations from absolute overall stereospecificity have been noted,[8] a dramatic one being the observation that the ethylene produced by sodium iodide reduction of isotopically labeled 1,2-dibromoethane was formed entirely by a net cis elimination.[9] We noted that *vic*-dichlorides and *vic*-bromochlorides were reduced less readily than were *vic*-dibromides by any of several reagents and that zinc reductions of the less reactive dihalides were less stereoselective than those of the dibromides.[1] In contrast, the NaI/DMF reduction of a *vic*-bromochloride was highly stereospecific, but not in the anticipated (trans) sense: the threo 7,8-bromochlorides of 2-methyloctadecane (a mixture of *threo*-7-bromo-8-chloro and *threo*-8-bromo-7-chloro) were cleanly converted to (*E*)-2-methyl-7-octadecene. Thus a net cis elimination had occurred. This was interesting and appeared potentially useful. Since direct additions of halogens to olefins proceed trans,[10] a general procedure for cis elimination of the added halogens would provide an even simpler means of inverting double bonds (Scheme I, path C). We therefore investigated iodide-promoted eliminations of a few dichlorides, bromochlorides, and dibromides to evaluate their potential for olefin inversions.

Typical NaI reductions of *vic*-dibromides have utilized large excesses of I^- in an alcoholic medium, e.g., refluxing 2-propanol.[11] The only dibromide we investigated, *erythro*-7,8-dibromo-2-methylocatadecane, was completely reduced by excess NaI in DMF at 50–55 °C (overnight). As noted previously, bromochlorides and dichlorides were reduced less readily. Bromochlorides required overnight exposure to a tenfold excess of NaI in DMF at >80 °C for complete reduction, and an entire week was required for the same reaction to proceed to completion in refluxing 2-propanol (82 °C). The *vic*-dichlorides were still less reactive, and refluxing DMF was found to provide a suitable medium. A few other conditions were briefly investigated for NaI reductions of *erythro*-7,8-dichloro-2-methyloctadecane, all employing excess NaI: the reduction was incomplete in refluxing acetonitrile after 4 days, and the reaction in Me_2SO was slow at 90 °C and appeared to offer no advantage over the reactions in DMF or hexamethylphosphoric triamide (HMPA). Indeed, in HMPA reduction was complete (and stereospecifically cis) after 2 h at 100–110 °C. Substitution of LiI for NaI appeared to offer no advantage. The results of I^- reductions of several dihalides are given in Table I. With the exceptions of the single dibromide (entry 10) and the one reaction in 2-propanol (entry 3), the reductions were at least 93% stereoselectively cis, and many were completely stereospecific within the limits of our analyses (2–4%).

Hine[6] has reviewed the subject of NaI reductions of *vic*-dibromides (dichlorides and bromochlorides apparently have not been investigated). Reduction of *meso*-1,2-dibromo-1,2-dideuterioethane gave *cis*-1,2-dideuterioethylene[9] (cis elimination). Since the reaction rate had almost exactly the value expected for nucleophilic displacement of primary bromide by iodide ion,[12] the reaction mechanism was rationalized as involving an initial SN2 displacement of Br^- by I^- followed by nucleophilic attack of a second iodide ion upon the iodine of the resulting *vic*-bromoiodide (Scheme II, path B, R = D). Since such an elimination would be expected to be trans antiplanar, the result is a net cis elimination (one in-

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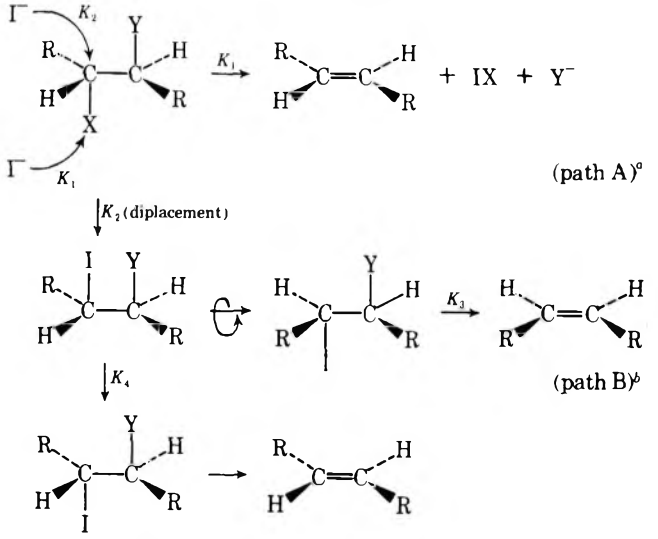
Table I. Elimination of *vic*-Dihalides

Run	Dihalide	Olefin	Conditions	Yield, %	Stereospecificity, %[a]
1	*threo*-7,8-Bromochloro-2-methyloctadecane	(*E*)-2-Methyl-7-octadecene	NaI, DMF, 80 °C, 18 h	c	100
2	*erythro*-7,8-Bromochloro-2-methyloctadecane	(*Z*)-2-Methyl-7-octadecene	NaI, DMF, 80 °C, 18 h	88	96
3	*erythro*-7,8-Bromochloro-2-methyloctadecane	(*Z*)-2-Methyl-7-octadecene	NaI, *i*-PrOH, 82 °C, 1 week	c	79
4	*threo*-7,8-Bromochlorooctadecane	(*E*)-7-Octadecene	NaI, DMF, 80 °C, 18 h	67	100
5	*erythro*-8,9-Bromochlorododecan-11-ol acetate	(*Z*)-8-Dodecen-1-ol acetate	NaI, DMF, 85 °C, 16 h	95	93
6	*erythro*-7,8-Dichloro-2-methyloctadecane	(*Z*)-2-Methyl-7-octadecene	NaI, DMF, 153 °C, 25 h	95	100
7	*threo*-7,8-Dichlorooctadecane	(*E*)-7-Octadecene	NaI, DMF, 153 °C, 25 h	79	97
8	*erythro*-8,9-Dichlorododecan-1-ol acetate	(*Z*)-8-Dodecen-1-ol acetate	NaI, DMF, 153 °C, 16 h	c	93
9	*erythro*-7,8-Dichloro-2-methyloctadecane	(*Z*)-2-Methyl-7-octadecene	NaI, HMPA, 100 °C, 2 h	80	100
10	*erythro*-7,8-Dibromo-2-methyloctadecane	(*E*)-2-Methyl-7-octadecene	NaI, DMF, 50–55 °C, 20 h	c	82[d]

[a] Product olefins were epoxidized with *m*-chlorobenzoic acid in CH_2Cl_2, and the epoxides were analyzed by GLC (EGGS-X SCOT column, 1.5 m × 5 mm at 140–170 °C). Unsaturated esters were analyzed directly with this column. [b] *vic*-Bromochlorides are presumably mixtures of positional isomers. For example, *threo*-7,8-bromochlorooctadecane would be a mixture of *threo*-7-bromo-8-chlorooctadecane and *threo*-8-bromo-7-chlorooctadecane. [c] Yield not determined (in several cases the reactions were followed by periodically withdrawing samples for GLC analysis). [d] 82% trans elimination.

Scheme II. Iodide-Induced Eliminations of *vic*-Dihalides (Exemplified for Meso/Erythro Dihalides)

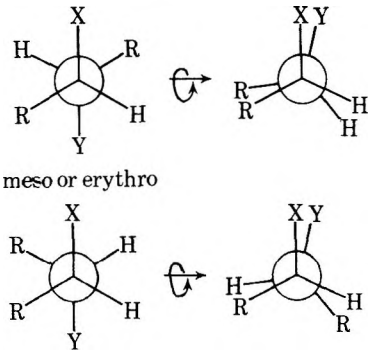


[a] Elimination. [b] Displacement followed by elimination.

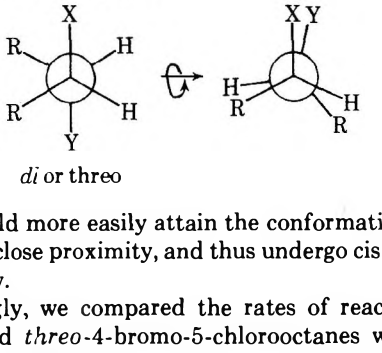
version, trans elimination). The more general case for dibromides of 1,2-disubstituted ethylenes is that of trans elimination.[10] Evidently direct displacement of Br^- by I^- (Scheme II, path B) is less favored than the attack by I^- on bromine with a concomitant expulsion of olefin and bromide (Scheme II, path A). At higher temperatures, losses in stereospecificity for this reaction were observed that were ascribed to a significant contribution from path B.

We feel that the reductions of *vic*-dichlorides and *vic*-bromochlorides probably proceed via path B. Evidently the replacement of bromine by chlorine either markedly increases the susceptibility of the other halogen to SN2 displacement, or, more probably, decreases the ability of the *vic*-dihalide to undergo the concerted reduction (path A). Interestingly, if the presumed intermediate *vic*-iodohalides are to eliminate stereospecifically, it is necessary that the iodide ion attack the bound iodine and initiate the concerted elimination (path B) much faster than it displaces the bound iodine from carbon (thus inverting that center a second time, i.e., $K_3 > K_4$). Yet iodide must first displace a chloride or bromide ion much faster than it can attack a bound bromine or chlorine to initiate a concerted elimination ($K_2 > K_1$). Apparently the nature of the halogen molecule being formed during the concerted elimination step is quite important, and the formation of I_2 is highly favored over that of IBr or ICl.

We also considered the possibility of a cis elimination with both halogens departing, more or less simultaneously, from the same side of the molecule. In the dibromide series, meso compounds react faster with I^- then do their *dl* isomers (trans eliminations), presumably because it is easier to attain the desired trans antiplanar alignment of bromines. If both halogens were to leave from the same side, the threo (or *dl*)



meso or erythro



dl or threo

isomer should more easily attain the conformation with the halogens in close proximity, and thus undergo cis elimination more readily.

Accordingly, we compared the rates of reaction of the *erythro*- and *threo*-4-bromo-5-chlorooctanes with NaI in DMF at 80–85 °C. The two reactions were run simultaneously under identical conditions, and were followed by gas chromatographic analysis of quenched aliquots. Although absolute temperature control of the heating bath was not precise enough to allow the calculation of a meaningful rate constant,

it was evident that the erythro isomer was reduced more rapidly. Thus we have no evidence to support any kind of concerted cis elimination of halogen.

The dihalides we initially reduced with NaI were those synthesized from epoxides as described in the accompanying paper.[1] Since their preparation had involved two SN2 reactions on epoxides, cis elimination of halogen simply regenerated the olefin from which the epoxide had been prepared. To illustrate the utility of the cis eliminations for olefin inversions we subjected several olefins to the two-step halogenation–dehalogenation sequence. Chlorinations of 1,2-disubstituted ethylenes can generally be controlled,[13] and entries 8 and 9 in Table I describes results of reductions of dichlorides prepared in that manner. Both the unsaturated acetate and the unsaturated hydrocarbon were efficiently inverted by this simple sequence. *erythro*-7,8-Dichloro-2-methyloctadecane, entry 9, was prepared both by chlorination of the corresponding *E* olefin and by treating *trans*-7,8-epoxy-2-methyloctadecane [the sex pheremone of the gypsy moth, *Porthetria dispar* (L.)] with triphenylphosphine dichloride.[1] Identical results were realized from both pathways.

Hageman and Havinga[14] described the in situ preparation of bromine chloride and the trans addition of the mixed halogen to several cyclohexene derivatives. We found their method, which consists of simply adding *N*-bromosuccinimide to a HCl-saturated solution of the olefin, both efficient and convenient. For example, the *erythro*- and *threo*-4-bromo-5-chlorooctanes were synthesized in 82 and 73% yields from (*E*)- and (*Z*)-4-octenes, respectively; the isomers were readily distinguished by gas chromatography, and each bromochloride was found to be free of its isomer. Entry 5, Table I illustrates an application to the principal component of the sex pheromone of the oriental fruit moth, *Grapholita molesta* (Busck). (*E*)-8-Dodecen-1-ol acetate was converted to the erythro bromochloride, and the bromochloride was treated with NaI/DMF without purification. (*Z*)-8-dodecen-1-ol acetate was obtained in an overall yield of 93%; the conversion was >93% stereospecific.

To date these methods have been successful only for inversions of 1,2-disubstituted olefins. We briefly examined (*E*)-3-methyl-3-hexene; predictably,[13] however, chlorination provided primarily substitution instead of addition products. Hageman and Havinga[14] successfully added BrCl to several 1-alkylcyclohexenes, but our single attempt to apply their procedure to (*E*)-3-methyl-3-hexene was unsuccessful since HCl addition to the double bond evidently occurred faster than BrCl was generated.

Experimental Section[15]

General experimental details (instrumentation, GLC analyses, epoxidation procedures, etc.) are described in the accompanying paper.[1]

***vic*-Bromochlorides** were prepared from epoxides as described,[1] or from olefins by the HCl–*N*-bromosucciminide method.[14] For the latter conversions, a solution of the olefin in CH_2Cl_2 (10 ml/g of olefin) was cooled to −78 °C and was saturated with anhydrous HCl. Freshly recrystallized (H_2O) *N*-bromosuccinimide (1.05 mol/mol of olefin) was added in a single portion, and the mixture was stirred and allowed to warm slowly to ca. −20 °C (while maintaining saturation of HCl). After the mixture assumed a permanent color, it was poured onto a mixture of ice and aqueous $NaHSO_3$. The layers were separated, and the organic phase was washed with H_2O, aqueous $NaHCO_3$, and again with H_2O; then it was dried ($MgSO_4$) and concentrated. The bromochlorides thus obtained were sufficiently pure for NaI reductions. Trans addition of the two halogens was established by applying the procedure to (*E*)- and (*Z*)-4-octenes (purchased from Chemical Samples Co.). In these cases the products were distilled; the former gave an 82% yield of *erythro*-4-bromo-5-chlorooctane, bp 100–105 °C (25 mm); the latter gave a 73% yield of *threo*-4-bromo-5-chlorooctane, bp 107–112 °C (24 mm). The isomeric bromochlorides were identical with those prepared from the epoxides,[1] and each isomer appeared to be free of the other as judged by gas chromatography (Carbowax or DEGS) whereby 5% would have been readily detected.

***vic*-Dichlorides** were prepared by bubbling Cl_2 through CH_2Cl_2 solutions of the appropriate olefins at −78 °C until a yellow color persisted, warming to ca. −20 °C, and following the workup procedure described for bromochlorides. Crude dichlorides were reacted with NaI without purification.

Sodium Iodide Reductions of *vic*-Dihalides. Typically, the dihalides (1 g) and NaI (10 g) were combined in DMF (or HMPA) (50 ml), and the resulting solutions were heated as described in Table I. It was convenient to follow the reactions by perioically withdrawing small aliquots and shaking them with hexane and H_2O; the hexane layer was examined by GLC for disappearance of dihalide. Workup consisted of cooling the dark solutions, pouring into H_2O, and extracting with hexane. The organic layers were washed with aqueous $NaHSO_3$, then washed twice with H_2O, and finally were dried and concentrated. The olefins thus obtained were purified by distillation or column chromatography on silica gel or were epoxidized directly for GLC analysis.

Comparative Eliminations of *erythro*- and *threo*-4-Bromo-5-chlorooctanes. Reaction mixtures containing the appropriate bromochloride (100 mg), 1-tetradecene (100 mg), NaI (1.00 g), and DMF (10.0 ml) were prepared in 25-ml flasks, and the flasks were heated simultaneously in an oil bath maintained at 78–85 °C. Aliquots (0.10 ml) were removed from each flask after 0, 1, 2, 4, and 7 h and added to small vials containing water (0.3 ml) and hexane (0.3 ml). The vials were shaken, and the hexane layers were withdrawn by pipet and analyzed by gas chromatography (SE-30, 125 °C). Peak areas of remaining bromochlorides and of the tetradecene standard were measured by planimetery. Although smooth curves were not obtained, it was evident that the erythro isomer reacted approximately twice as fast as did the threo isomer (that the erythro compound reacted faster was also apparent by visually observing the formation of iodine in the reaction mixtures).

Registry No.—*threo*-7-Bromo-8-chloro-2-methyloctadecane, 59840-17-4; *threo*-7-chloro-8-bromo-2-methyloctadecane, 59840-18-5; *erythro*-7-bromo-8-chloro-2-methyloctadecane, 59840-19-6; *erythro*-7-chloro-8-bromo-2-methyloctadecane, 59840-20-9; *threo*-7-bromo-8-chlorooctadecane, 59840-21-0; *threo*-7-chloro-8-bromooctadecane, 59840-22-1; *erythro*-8-bromo-9-chlorododecan-1-ol acetate, 59840-23-2; *erythro*-8-chloro-9-bromododecan-1-ol acetate, 59840-24-3; *erythro*-7,8-dichloro-2-methyloctadecane, 59840-25-4; *threo*-7,8-dichlorooctadecane, 59840-26-5; *erythro*-8,9-dichlorododecan-1-ol acetate, 59840-27-6; *erythro*-7,8-dibromo-2-methyloctadecane, 59840-28-7; *erythro*-4-bromo-5-chlorooctane, 59840-29-8; *threo*-4-bromo-5-chlorooctane, 59840-30-1; NaI, 7681-82-5.

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(15) Mention of a proprietary product or company does not imply endorsement by the U.S. Department of Agriculture.

Vitamin A Synthesis by Sulfone Alkylation–Elimination. C_{15} Halide, C_5 Hydroxy Sulfone Approach

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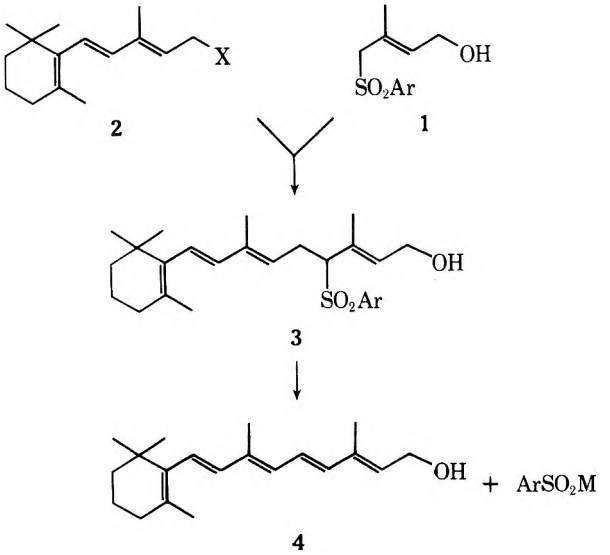
Condensation of 1-arylsulfonyl-2-methyl-4-hydroxy-2-butenes (**1**) with 1-chloro- and 1-bromo-3-methyl-5-(2,6,6-trimethylcyclohexen-1-yl)-penta-2,4-diene (**2**) to afford 1-hydroxy-3,7-dimethyl-4-arylsulfonyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,6,8-triene (**3**) and the subsequent elimination of sulfinic acid from **3** to give vitamin A alcohol has been studied. An efficient and stereoselective synthesis of halide **2** from vinyl-β-ionol (**14**) using HX in ether at low temperature has been achieved. The use of diethyl- and disilylamides with the *p*-tolyl sulfone compound **1b** and bromide **2b** gave **3b** in 83–84% isolated yield. Sodamide–ammonia–*tert*-butyl alcohol effected elimination of sulfinic acid in **3b** to afford, after acetylation, vitamin A acetate in 75% yield from **3b**. In a through process, crystalline, all-trans vitamin A acetate was obtained in 67–68 and 72–73% yield based on **14** and **1b**, respectively.

The alkylation of allylic sulfones and their subsequent 1,2 elimination to form olefins[1] is a synthetic method particularly suited to the synthesis of polyenes and vitamin A. This sequence was originally used by Julia to prepare the ester of vitamin A acid.[2] Because of the nutritional and commercial importance of all-trans vitamin A alcohol (β-retinol), strategic combinations of sulfone and halide directed toward the preparation of vitamin A alcohol have received great attention.[3] Approaches utilizing C_{13}[3b] and C_{15} sulfones[3c] and the appropriate halo alcohol partners have recently been described. An alternative in which the dianion of a C_5 hydroxy sulfone (**1**) is alkylated by a C_{15} halide (**2**) has now been studied in detail, and with appropriate choices of base, aryl sulfone, and C_{15} halide, this route affords a highly efficient and stereoselective synthesis of all-trans vitamin A (**4**) via the C_{20} hydroxy sulfone **3** (Scheme I).

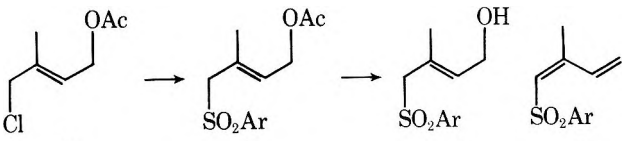
Scheme I

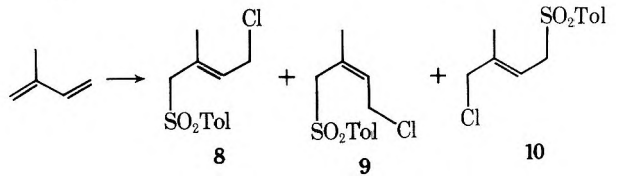


Results and Discussion

Preparation of C_5 Hydroxy Sulfones 1. Treatment of the isoprene hypochlorination product **5**[4] with sodium or lithium salts of sulfinic acids in warm dimethylformamide solution gives *trans*-acetoxy sulfones **6** in good yield (Table I). Reduction with $LiAlH_4$ or base hydrolysis affords the hydroxy sulfones **1** in high yield (Table II). The saponification, however, must be done under carefully controlled conditions to avoid elimination, particularly for the substituted sulfones.

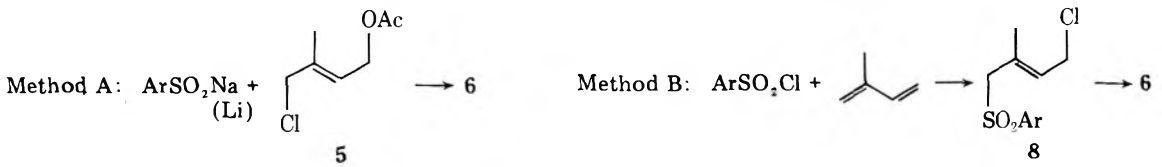
Thus, phenyl sulfone **6a** was unaffected by sodium carbonate in 80% aqueous ethanol but was cleanly hydrolyzed in 80% aqueous methanol, as was tolyl sulfone **6b**. Under more basic conditions (potassium carbonate–95% aqueous methanol) **6a** gave hydroxy sulfone **1a** contaminated with 25% of diene **7a**. Saponification of the *p*-methoxyphenyl derivative **6c** (sodium carbonate, 80% aqueous ethanol) was slow, but stronger base (potassium carbonate) in the same solvent gave exclusively diene **7c**. The 2-pyridyl sulfone **6f** gave 20% diene **7b** even with sodium carbonate in 80% aqueous ethanol.





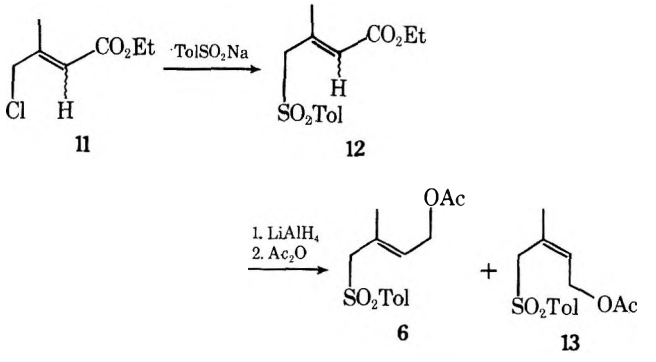
A second route to hydroxy sulfones was via solvolysis or acetolysis of halo sulfones (**8**) obtained from the copper(I)-catalyzed addition of sulfonyl halides to isoprene.[5] Thus, *p*-toluenesulfonyl chloride reacted with isoprene[6] to afford a mixture of chloro sulfones **8**, **9**, and **10** in 95% yield. The regio- and stereochemistry of the products of this reaction had not previously been rigorously established, and in the original report[5] **9** and **10** were not identified, so the structures of these adducts were proved by correlation with known compounds. *trans*-1-*p*-Toluenesulfonyl-4-acetoxy-2-methyl-2-butene (**6b**) was prepared from pure **8** by acetolysis and was identical with the product prepared from chloro acetate **5**. 1,4-Dichloro-2-methyl-2-butene reacted with sodium *p*-toluenesulfinate in ethanol to give a mixture of 1,4-disulfone and *trans*-1-*p*-toluenesulfonyl-3-methyl-4-chlorobut-2-ene. This latter compound displayed a methyl resonance in the NMR spectrum at 1.36 ppm (vs. 1.83 ppm in trans **8**) and was thus shown to be the compound which cocrystallizes with the desired trans **8** from ether. The crystallization mother liquors were repurified until the other compound, assumed to be the cis isomer **9**, was enriched to ca. 80% purity. The structure of this material was proved by correlation with *cis*- and *trans*-4-chlorosenecioic esters **11**[7] by displacement of the halide with *p*-toluenesulfinic acid to afford a cis/trans mixture of sulfone esters **12** from which a single isomer crystallized. Diisobutylaluminum hydride reduction of this crystalline compound followed by acetylation afforded the trans hydroxy and acetoxy sulfones **1b** and **6b**. Identical treatment of the mother liquors (80% cis isomer) afforded the cis acetoxy sulfone **13**.

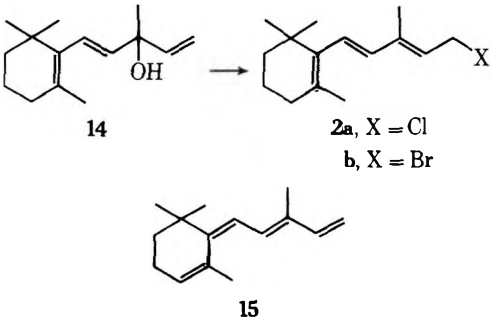
Table I. Preparation and Properties of C_5 Acetoxy Sulfones



Compd	Ar	% yield A	% yield B	Mp, °C	NMR ($CDCl_3$), δ	Anal., found, %	
6a	C_6H_5	95[a]		93–94	7.95–7.45 (m, 5, aromatic), 5.22 (t, 1, J = 7 Hz, HC=C), 4.48 (d, 2, J = 7 Hz, CH_2OAc), 3.75 (s, 2, CH_2SO_2), 2.00 (s, 3, CH_3CO), and 1.83 ppm (s, 3, CH_3C=C)	C 58.14 S 11.86	H 6.32
6b	p-$CH_3C_6H_4$	95[a]	70[a]	56.5–59	7.71 and 7.31 (AA'XX', 4, J = 8 Hz, aromatic), 5.25 (t, 1, J = 7 Hz, HC=C), 4.48 (d, 2, J = 7 Hz, CH_2OAc), 3.74 (s, 2, CH_2SO_2), 2.43 (s, 3, CH_3Ar), 2.00 (s, 3, CH_3CO), and 1.80 ppm (s, 3, CH_3C=C)	C 59.72 S 11.25	H 6.31
6c	p-$OCH_3C_6H_4$	96[a]	61	55–56	7.70 and 6.95 (AA'XX', 4, J = 10 Hz, aromatic), 5.23 (t, 1, J = 7 Hz, HC=C), 4.45 (d, 2, J = 7 Hz, CH_2OAc), 3.83 (s, 3, OCH_3), 3.72 (s, 2, CH_2SO_2), 1.97 (s, 3, CH_3CO), and 1.82 ppm (s, 3, CH_3C=C)	C 56.41 S 10.67	H 6.08
6d	p-$N(CH_3)_2C_6H_4$	99[a]		82–84	7.60 and 6.62 (AA'XX', 4, J = 9 Hz, aromatic), 5.26 (t, 1, J = 7 Hz, HC=C), 4.49 (d, 2, J = 7 Hz, CH_2OAc), 3.68 (s, 2, CH_2SO_2), 3.04 [s, 6, $N(CH_3)_2$], 2.00 (s, 3, CH_3CO), and 1.81 ppm (s, 3, CH_3C=C)	C 57.74 N 4.45	H 6.72 S 10.09
6e	p-$CF_3C_6H_4$	86		Oil	8.12–7.50 (m, 4, aromatic), 5.22 (t, 1, J = 7 Hz, HC=C), 4.48 (d, 2, J = 7 Hz, CH_2OAc), 3.78 (s, 2, CH_2SO_2), 2.00 (s, 3, CH_3CO), and 1.88 ppm (s, 3, CH_3C=C)	C 49.77 S 9.71	H 4.68
6f		47		59–61	8.74–7.58 (m, 4, pyridine), 5.39 (t, 1, J = 7 Hz, HC=C), 4.49 (d, 2, J = 7 Hz, CH_2OAc), 4.09 (s, 2, CH_2SO_2), 1.98 (s, 3, CH_3CO), and 1.88 ppm (s, 3, CH_3C=C)	C 53.48 N 5.06	H 5.71

[a] Crude material, >95% pure by NMR.





Fortuitously, the cocrystallized mixture of 8 and 10 upon acetolysis with sodium acetate–acetic acid yields mainly trans acetate 6 which after saponification and crystallization gives pure hydroxy sulfone **1b** in 70% yield from the mixture of 8 and 10. The hydroxy sulfones 1 could also be obtained directly from chloro sulfone 8 by solvolysis with aqueous silver carbonate at room temperature.

Preparation of C_{15} Halides 2. Reaction of vinyl-β-ionol (14), readily available from β-ionone,[8] with phosphorus trihalides generally affords the corresponding C_{15} halide 2 in ca. 60% yield together with a substantial amount of the hydrocarbon **15**.[2,9] We find that **14** is virtually quantitatively converted to the chloride **2a** or bromide **2b** by its reaction with ethereal HCl or HBr, respectively, at low temperature[10] and that these halides, while unstable at more than ca. 50% concentration at room temperature, are remarkably unaffected by base at low (−30 °C or below) temperature and are essentially inert to displacement by the lithium dialkyl- or disilylamides in THF at −70 °C. In addition, the stereochemistry (by NMR in CCl_4) about the trisubstituted double bond in these halides is >95% trans. By inference from the stereochemistry of the vitamin A produced (vide infra), the halides vary from 95 to 99% trans stereoisomer.

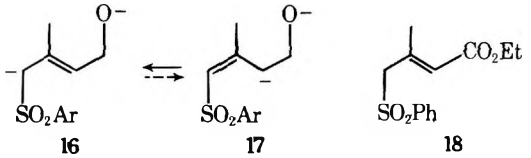
Alkylation Studies. Hydroxy sulfone 1 undergoes alkylation cleanly at the carbon α to the sulfonyl group, presumably owing to the displacement of the equilibrium between dianions 16 and 17 toward the more favorably charge-separated dianion 16. By contrast, the sulfone ester 18 was reported[2] to

Table II. Preparation and Properties of C_5 Hydroxy Sulfones 1

Method A: 6 $\xrightarrow[\text{aq MeOH}]{Na_2CO_3}$ 1 Method B: 6 $\xrightarrow[2.\ H_2O]{1.\ LiAlH_4}$ 1

Compd	Ar	% yield A	% yield B	Mp, °C	NMR ($CDCl_3$), δ	Anal., found, %	
1a	C_6H_5		97[a]	55–56.5	7.90–7.45 (m, 5, aromatic,), 5.34 (t, 1, J = 7 Hz, HC=C), 4.05 (d, 2, J = 7 Hz, CH_2OH), 3.75 (s, 2, CH_2SO_2), and 1.81 ppm (s, 3, CH_3C=C)	C 58.26 S 14.09	H 6.16
1b	p-$CH_3C_6H_4$	(69)[b]	97[a] (42.5)[c]	62.5–65	7.71 and 7.32 (AA'XX', 4, J = 8 Hz, aromatic,), 5.39 (t, 1, J = 7 Hz, HC=C), 4.07 (d, 2, J = 7 Hz, CH_2OH), 3.72 (s, 2, CH_2SO_2), 2.43 (s, 3, CH_3Ar), and 1.78 ppm (CH_3C=C)	C 60.16 S 13.19	H 6.88
1c	p-$OCH_3C_6H_4$		94[a] (60)[b]	45.5–47	7.67 and 7.25 (AA'BB', 4, J = 7 Hz, aromatic), 5.33 (t, 1, J = 7 Hz, HC=C), 4.03 (d, 2, CH_2OH), 3.70 (s, 2, CH_2SO_2), 2.75 (s, 1, OH), 2.33 (s, 3, CH_3Ar), and 1.75 ppm (s, 3, CH_3C=C)	C 56.02	H 6.29
1d	p-$N(CH_3)_2C_6H_4$		96[a] (60)[b]	160–164	7.65 and 6.62 (AA'XX', 4, J = 9 Hz, aromatic), 5.36 (t, 1, HC=C), 4.08 (d, 2, CH_2OH), 3.68 (s, 2, CH_2SO_2), 3.08 [s, 6, $N(CH_3)_2$], and 1.80 ppm (s, 3, CH_3C=C)	C 57.91 N 5.14	H 7.14 S 11.89
1e	p-$CF_3C_6H_4$		93[a]	63–68	8.17–7.54 (m, 4, aromatic), 5.33 (t, 1, J = 7 Hz, HC=C), 4.05, (d, 2, J = 7 Hz, CH_2OH), 3.78 (s, 2, CH_2SO_2), and 1.82 ppm (s, 3, CH_3C=C)	C 48.95 S 10.87	H 4.43 F 19.49
1f		53 (25)[b]		53–54	8.83–7.43 (m, 4, aromatic), 5.43 (t, 1, J = 7 Hz, HC=C), 4.03 (s, 2, CH_2SO_2), 4.02 (d, 2, J = 7 Hz, CH_2OH), and 1.75 ppm (s, 3, CH_3C=C)	C 52.97 N 6.21	H 5.63

[a] Crude product, >95% pure by NMR. [b] Overall yield of pure compound based on chloro acetate 5. [c] Overall yield of pure compound based on p-toluenesulfonyl chloride via chloro sulfone 8.



16 17 18

undergo almost exclusive γ-alkylation. The acetoxy sulfones 6 (precursors of 1) do not alkylate by either mode, but eliminate acetate rapidly under alkylation conditions to afford dienes 7.

The yield of C_{20} hydroxy sulfone 3 obtained in this reaction was found to depend to some extent upon the arylsulfonyl substituents and particularly upon the reaction conditions.

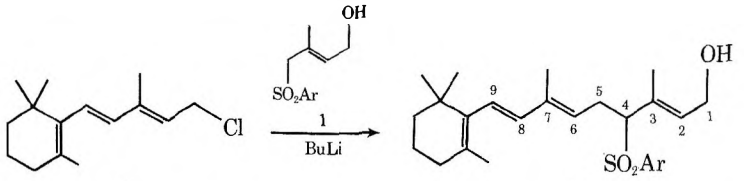
Substituent Variations (Table III). In initial studies, 2 equiv of n-butyllithium was added to a solution of the hydroxy sulfone in THF at −70 °C followed by slow, dropwise addition of the C_{15} chloride **2a** in ether. After 1 h at −70 °C and then warming to 0–25 °C, the reaction mixtures were quenched with water and extracted with ether. The crude products were chromatographed to give the substituted C_{20} sulfones **3.** The various substituted sulfones alkylated similarly to the phenyl sulfone **1a** except for the trifluoromethyl compound **1c** (low yield, **3c** unstable toward chromatography) and 2-pyridyl compound **1f** (eliminated to form diene **7f**). The somewhat higher yield observed with the dimethylamino compound **1d** may result from the amino group scavenging HCl from the decomposition of some excess C_{15} chloride prior to chromatography.

Since the p-tolyl (**1b**) and p-methoxy (**1c**) compounds gave the highest yields of vitamin A in the subsequent elimination step (vide infra), the alkylation of these two compounds was studied in detail with respect to base, halide, temperature, and mode of addition.

Alkylation with p-Tolyl Hydroxy Sulfone 1b. Variations of Base and C_{15} Halide (Table IV). In the alkylation of the p-tolyl hydroxy sulfone **1b** with the C_{15} chloride **2a** and n-butyllithium, unreacted **1b** was isolated after alkylation even though the dianion formation was complete at −70 °C (D_2O–DOAc exchange). Apparently, the rates of alkylation and base-promoted dehydrohalogenation of **2a** are similar at −70 °C. Higher reaction temperatures isomerized both C_5 and C_{20} sulfones. Thus, generation of the dianion **1c** with n-butyllithium at −20 °C in THF led to isomerization of the C_5 component prior to alkylation with C_{15} chloride **2a.** Similarly, formation of the dianion and alkylation at −70 °C followed by warming the mixture to room temperature overnight gave mainly the 2-cis C_{20} sulfone. No difference was seen between reactions run at −50 and −70 °C. Apparently, the dianion **1** has considerable stability toward cis/trans isomerization below −50 °C.

Because of its probable greater reactivity, the C_{15} bromide **2b** was substituted for the chloride **2a** in a butyllithium alkylation with little effect on the yield (33%). Changes in the base used, however, had a dramatic effect on the yield of sulfone in alkylation with the bromide **2b.** *Thus reaction of sulfone* **1b** *and bromide* **2b** *with 2 equiv of lithium diisopropylamide in tetrahydrofuran at −70 °C gave the desired* C_{20} *product* **3b** *in 83–84% yield.* Under the same conditions, chloride **2a** gave a 38% yield of product, while a mixture of chloride **2a** and 10 mol % of lithium bromide gave a 50% yield

Table III. Preparation of C_{20} Sulfones via C_{15} Chloride with Butyllithium



2a 3

Compd	Ar	Yield, %	Uv, λ_{max} (ϵ) Triene	Uv, λ_{max} (ϵ) Aryl	NMR ($CDCl_3$), δ	Anal., found, %
3a	C_6H_5	42	272–273 (16 800)	215 (18 200)	7.95–7.43 (m, 5, aromatic), 5.93 (s, 2, C_8 and C_9 vinyl H's), 5.33 (t, 1, J = 7 Hz, C_2 vinyl H), 5.17 (t, 1, J = 7 Hz, C_6 vinyl H), 4.03 (d, 2, J = 7 Hz, CH_2OH), 3.57 (m, 1, C_4 H), 2.83 (m, 2, C_5 CH_2), and 0.98 ppm (s, 6, *gem*-CH_3's)	C 72.77 H 8.47
3b	*p*-$CH_3C_6H_4$	41	262 (17 070)	228 (25 740)	7.70 and 7.30 (AA'XX', 4, J = 8 Hz, aromatic), 5.97 (s, 2, C_8 and C_9 vinyl H), 5.42 (t, 1, J = 6 Hz, C_2 vinyl H), 5.14 (t, 1, J = 7 Hz, C_6 vinyl H), 4.10 (d, 2, J = 6 Hz, CH_2OH), 3.56 (m, 1, C_4 H), 2.44 (s, 3, CH_3Ar), 1.77, 1.73, and 1.66 (3 s, 9, vinyl CH_3's), and 0.98 ppm (s, 6, *gem*-CH_3's)	C 73.51 H 8.95 S 6.79
3c	*p*-$OCH_3C_6H_4$	35–40	260 (16 515)	241–242 (24 625)	7.74 and 6.96 (AA'XX', 4, J = 8 Hz, aromatic), 5.96 (s, 2, C_8 and C_9 vinyl H), 5.31 (t, 1, J = 7 Hz, C_2 vinyl H), 5.12 (t, 1, J = 7 Hz, C_6 vinyl H), 4.06 (d, 2, J = 7 Hz, CH_2OH), 3.84 (s, 3, OCH_3), 3.50 (m, 1, C_4 H), 2.81 (m, 2, C_5 CH_2), 1.63, 1.71, 1.75 (3 s, 9, vinyl CH_3's), and 0.97 ppm (s, 6, *gem*-CH_3's)	C 71.29 H 8.35 S 6.51
3d	p-$N(CH_3)_2C_6H_4$	57		283–284 (35 600)	7.63 and 6.63 (AA'XX', 4, J = 9 Hz, aromatic), 5.96 (s, 2, C_8 and C_9 vinyl H), 5.41 (t, 1, J = 7 Hz, C_2 vinyl H), 5.15 (t, 1, J = 7 Hz, C_6 vinyl H), 4.10 (d, 2, J = 7 Hz. CH_2OH), 3.50 (m, 1, C_4 H), 3.03 [s, 6, $N(CH_3)_2$], and 0.99 ppm (s, 6, *gem*-CH_3's)	C 71.05 H 8.65 N 2.81 S 6.51
3e	*p*-$CF_3C_6H_4$	3.5	264–266	200–205	8.13–7.50 (m, 4, aromatic), 5.97 (s, 2, C_8 and C_9 vinyl H), 5.33 (t, 1, J = 7 Hz, C_2 vinyl H), 5.10 (t, 1, J = 7 Hz, C_6 vinyl H), 4.04 (d, 2, J = 7 Hz, CH_2OH), 3.57 (m, 1, C_4 H), and 0.99 ppm (s, 6, *gem*-CH_3's).	
3f		0				

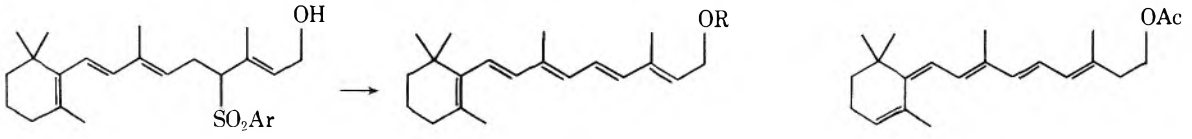
of product. Yields with other hindered amine bases were similarly high, regardless of the mode of addition (preformation of the dianion was unnecessary). These carefully defined working conditions for the tolyl sulfone **1b** were subsequently tried with the *p*-methoxyphenyl compound **1c** with a resulting 38% yield of adduct **3c**. Clearly the alkylation of C_5 hydroxy sulfones **1** is a reaction in which a delicate balance between rates of alkylation and dehydrohalogenation exists so that slight changes in the acidity of the sulfone[11] and its nucleophilicity due to substituent and medium effects can dramatically influence the product yield.

Elimination Step. Vitamin A Acetate Preparation (Table V). The elimination of sulfinic acid in **3** to afford vitamin A alcohol occurs smoothly and in high yield for the *p*-tolyl and *p*-methoxyphenyl sulfones **3b** and **3c** with an excess of sodamide (5 equiv) in liquid ammonia containing

Table IV. Alkylation of *p*-Tolyl Sulfone **1b** with C_{15} Halides **2**. Comparison of Bases

No.	Base	mmol	C_{15} halide,	mmol	C_5 sulfone, mmol	Mode of addition	Yield, %	
1	BuLi	26.0	Cl	19.7	13.0	Cl to dianion	41	
2	BuLi	9.5	Br	5.3	4.2	Base to substrates	33	
3	LDA	9.8	Cl	5.7	4.2	Base to substrates	31.5	
4	LDA	44.0	Br	25.0	21.0	Base to substrates	84	
5	LDA	44.0	Br	25.0	21.0	Rapid addition of Br to dianion	83	
6	LDA	9.8	Cl (+10 mol % LiBr)	5.7	4.2	Base to substrates	50	
7	$LiNEt_2$	19.7	Br	11.4	8.3	Base to substrates	68	
8	KO-*t*-Am	9.6	Br	5.5	4.2	Base to substrates	14.4	
9	$LiN(SiMe_3)_2$	19.0	Br	8.75	8.33	Base to substrates	74	(16% unreacted **1b**)
10	$NaN(SiMe_3)_2$	11.5	Br	4.3	4.2	Base to substrates	62	(21% unreacted **1b**)
11	$NaNH_2$	21.0	Br	15.8	8.3	Bromide to dianion	14.4	
12	NaC_6H_5	11.6	Br	5.40	4.15	Bromide to dianion	35	(43% unreacted **1b**)

Table V. Preparation of Vitamin A Acetate



3 **4** i

Compd	Ar	Conditions	Yields[a] (HPLC analysis)[12] 9-cis + 9,13-di-cis	11-cis	13-cis	Retro[b]	All-trans	Total
3a	C_6H_5	KOH, H_2O, *n*-BuOH, 120 °C	2	10			17	29
		$NaNH_2$, NH_3 anhydrous						0
		$NaNH_2$, NH_3, *t*-BuOH	4	2			45	51
3b	*p*-$CH_3C_6H_4$	$NaNH_2$, NH_3, *t*-BuOH	3	1	0.2	4	67	75.2
3c	*p*-$OCH_3C_6H_4$	$NaNH_2$, NH_3, *t*-BuOH	1		1	6	65	73
3d	*p*-$N(CH_3)_2C_6H_4$	$NaNH_2$, NH_3, *t*-BuOH	2		1	4	50	57
3e	*p*-$CF_3C_6H_4$	$NaNH_2$, NH_3, *t*-BuOH					1.4	1.5

[a] Of derived acetate; see Experimental Section. [b] Retro vitamin A = i. Found to be due to isomerization of vitamin A alcohol during prolonged reaction times in the elimination step.

tert-butyl alcohol. In the absence of alcohol, sulfone is recovered unchanged, suggesting that reprotonation of the acidic α-sulfonyl anion formed in a rapid initial step is essential. Substituent effects on the yield of vitamin A alcohol are observed (Table V), and although the yield is not a measure of reaction rate, the expected trend toward elimination of more acidic sulfinic acids faster and in higher yields is observed. Other alkaline conditions[3c] afford lower yields, and interestingly, the isomeric sulfones **3c** (sulfonyl at C_6) do not eliminate under sodamide–ammonia–*tert*-butyl alcohol conditions.

Crude vitamin A alcohol obtained from the elimination reaction was acetylated with acetic anhydride–triethylamine and the crude vitamin A acetate was analyzed by HPLC[12] to determine yields and isomeric composition. The results (Table V) show the crude reaction product to be surprisingly free of isomeric impurities. A small amount of "retro" vitamin A acetate observed in some cases was found to be due to prolongation of the reaction time after complete elimination. The low content of 9-cis/9,13-di-cis isomers reflects the stereochemical integrity of the C_{15} halide prepared by the above-described procedure.

The high yield in the alkylation and the very pure crude vitamin A acetate obtained by the elimination–acetylation procedure utilizing the *p*-tolyl sulfone **1b** suggested that the synthesis could be carried out without chromatographic purification of the intermediates. Indeed, alkylation of the crude C_{15} bromide **2b** with *p*-tolyl sulfone **1b** afforded the crude C_{20} sulfone **3b** which, after trituration with hexane and remove a small amount of C_{15} hydrocarbon by-product (**17**), was eliminated and acetylated to afford crude vitamin A acetate in an overall yield (by HPLC) of 67–68% based on vinyl-β-ionol (**14**) and 72–73% based on hydroxy sulfone **1b**.

By virtue of the high all-trans isomer content, the crude acetate crystallized from cold methanol in a very high weight yield. Crystalline samples were assayed by direct uv and Morton–Stubbs procedures[13] relative to the standard[14] for all-trans vitamin A acetate (2.906×10^6 IU/g). Thus, crystallization of the crude acetylation product from methanol afforded all-trans vitamin A acetate (assay 91.2–91.4%) in 63–65 and 67–70% overall yield based on vinyl-β-ionol (**14**) and hydroxy sulfone **1b**, respectively.

Experimental Section

Melting points were determined on a Kofler hot stage microscope and are uncorrected. Spectral measurements were performed on the following instruments: NMR, Varian T-60, HA-100, and XL-100 spectrometers using Me_4Si as internal standard and $CDCl_3$ as solvent; ir, Beckman IR 9 and Perkin-Elmer Model 621 and 237B spectrophotometers with $CHCl_3$ as solvent or as a liquid film; uv, Cary Model 14 and Perkin-Elmer Model 202 spectrophotometers with 2-propanol as solvent. Gas chromatographic analyses were performed on Hewlett-Packard Model 402B or 5721A instruments equipped with flame ionization detectors. High-pressure liquid chromatographic analyses (HPLC) were performed on apparatus constructed by members of our Physical Chemistry Department on silica gel columns impregnated with oxydipropionitrile[12] with uv monitoring at 254, 280, and 350 nm and using naphthalene as internal standard and crystalline, all-trans vitamin A acetate (Hoffmann-La Roche Inc.) as reference compound. The progress of reactions was generally followed by TLC

on Brinkmann silica gel GF 254 plates using uv and ceric sulfate spray followed by heating to detect spots. Products were isolated in general by extraction or dilution of the reaction mixture with the indicated solvent, washing, where appropriate, with H_2O, 20% HCl, saturated $NaHCO_3$, and brine, drying ($MgSO_4$), and solvent removal on a rotary evaporator at 30–50 °C. Column chromatography was carried out on Merck 0.05–0.2 mm silica gel or Woelm alumina, grade III. Tetrahydrofuran (THF) was dried by passage through Woelm neutral alumina, grade I. Lithium diisopropylamide (LDA) solutions were prepared from diisopropylamine (distilled from CaH_2) and *n*-butyllithium (Ventron Corp.) and were titrated[15] before use.

Preparation of *trans*-1-Arylsulfonyl-2-methyl-4-acetoxy-2-butenes (6) from 5. General Procedure. Acetoxy sulfones **6** (Table I, method A) were prepared by warming a suspension of the sodium or lithium arylsulfinate (1.2 mol) in dry dimethylformamide (DMF) at 60 °C with chloro acetate **5** (1.0 mol) for 3–6 h. Concentration of the suspension to ⅓ the original volume and dilution of the concentrate by pouring onto 10 volumes of ice water precipitated the crude product **6**. Filtration and dissolution of the filtrate in ethyl acetate, drying ($MgSO_4$), and evaporation of the solvent afforded sulfones **6** in 90–95% yield, >95% pure by NMR. Analytically pure samples were obtained by recrystallization from methanol, ether, and/or ethyl acetate.

***trans*-1-*p*-Toluenesulfonyl-2-methyl-4-acetoxy-2-butene (6b).** By the above method, sodium *p*-toluenesulfinate (273.0 g, 1.54 mol, Aldrich, 97%) and chloro acetate **5** (215.4 g, 1.33 mol) in 1100 ml of DMF at 60 °C for 4.75 h afforded 357.0 g of crude acetoxy sulfone **6b** as a waxy solid (95% yield). Recrystallization of a portion from methanol afforded an analytical sample, mp 56.5–59 °C.

Preparation of 1b from Isoprene via Chloro Sulfone 8 (Table I, Method B). By the published procedure[5a], *p*-toluenesulfonyl chloride (38.2 g, 0.2 mol) and isoprene (15.0 g, 0.22 mol) afforded a mixture of chloro sulfones **8–10** (49.4 g, 95%), mp 59–79.5 °C. Recrystallization of a 47.1-g portion from ether (235 ml) gave colorless crystals of the mixture of **8** and **10** (34.74 g, 74%), mp 68–83 °C, in a 4:1 ratio. In a similar experiment, slow crystallization from ethanol of 20.7 g of crude product afforded pure **8** (6.95 g, mp 86–88 °C): NMR δ 7.29 and 7.68 (AA'XX', 4, J = 8.5 Hz, aromatic), 5.30 (t, 1, J = 8 Hz, HC=C), 3.96 (d, 2, J = 8 Hz, CH_2Cl), 3.70 (s, 2, CH_2SO_2), 2.40 (s, 3, CH_3Ar), and 1.82 ppm (s, 3, CH_3C=C); ir 1320 (SO_2) and 1175–1138 cm^{-1} (SO_2).

Anal. Calcd for $C_{12}H_{15}SO_2Cl$: C, 55.70; H, 5.84; Cl, 13.70; S 12.39. Found: C, 55.77; H, 5.87; Cl, 13.68; S, 12.22.

Chromatography of the mother liquor from the ether crystallization afforded cis isomer **9** (85% pure) as an oil: NMR δ 7.78 and 7.32 (AA'XX', 4, J = 8 Hz, aromatic), 5.76 (t, 1, J = 8 Hz, HC=C), 3.85 (s, 2, CH_2SO_2), 3.77 (d, 2, J = 8 Hz, CH_2Cl), 2.45 (s, 3, CH_3Ar), and 1.85 ppm (s, 3, CH_3C=C).

To a mixture of chloro sulfones **8** and **10** (25.59 g, 0.1 mol) was added sodium acetate (51.2 g, 0.62 mol) and glacial acetic acid (360 ml). The mixture was refluxed for 5.25 h, poured into water, and neutralized. The crude acetate (26.35 g, 94%) was filtered off and a 20-g portion was warmed in methanol, filtered to remove insoluble material, and saponified (60 ml of methanol, 60 ml of water, 20.0 g of sodium carbonate; 3 h, 0–5 °C). Isolation with ethyl acetate gave crude hydroxy sulfone **1b** (15.45 g, 94%). Crystallization of a 15.22-g portion from ether gave pure **1b** (10.82 g, 43% based on *p*-toluenesulfonyl chloride).

Reaction of **9** (0.101 g, 0.39 mmol) with sodium acetate (0.214 g, 2.6 mmol) in acetic acid (1.5 ml) at reflux for 28 h afforded cis acetoxy sulfone **13** (0.105 g, 95% crude): NMR δ 7.79 and 7.35 (AA'XX', 4, J = 8 Hz, aromatic), 5.65 (t, 1, J = 7 Hz, HC=C), 4.20 (d, 2, J = 7 Hz, CH_2OAc), 3.93 (s, 2, CH_2SO_2), 2.47 (s, 3, CH_3Ar), 2.00 (s, 3, CH_3CO), and 1.87 ppm (s, 3, CH_3C=C).

Preparation of Cis Acetoxy Sulfone 13 from 12.[2] To a solution of diisobutylaluminum hydride (1.24 ml of a 25% toluene solution, 2.2 mmol) at 0 °C was added the ester **12** (0.209 g, 0.73 mmol, 1:1 cis/trans mixture) in toluene (1.8 ml). After 30 min at 0–5 °C the mixture was quenched with saturated NH_4Cl and the products isolated with ethyl acetate to give 0.145 g (82%) of a colorless solid from which the trans hydroxy sulfone **1b** crystallized. To a solution of the mother liquors from a similar crystallization (80% cis isomer, 0.156 g) in pyridine (1.5 ml) was added acetic anhydride (0.36 ml). The solution was warmed to 45 °C for 3 h and poured onto ice and the acetoxy sulfones (0.167 g, 92%, 3:2 mixture of **6b** and **13**) were isolated using ethyl acetate. The NMR peaks not assignable to **6b** were identical with the resonances observed in the product **13** of acetolysis of the cis chloro sulfone **9**.

Preparation of *trans*-1-*p*-Toluenesulfonyl-3-methyl-4-chloro-2-butene (10). Compound **10** was prepared[6] from sodium *p*-toluenesulfinate and 1,4-dichloro-2-methyl-2-butene: NMR δ 7.77 and 7.35 (AA'XX', 4, J = 8 Hz, aromatic), 5.60 (t, 1, J = 7 Hz, HC=C), 3.98 (s, 2, CH_2Cl), 3.83 (d, 2, J = 7 Hz, CH_2SO_2), 2.48 (s, 3, CH_3Ar), and 1.48 ppm (s, 3, CH_3C=C).

Preparation of *trans*-1-Arylsulfonyl-2-methyl-4-hydroxy-2-butenes (1) from 6. General Procedure, $LiAlH_4$ Reduction. Hydroxy sulfones **1** (Table II, method B) were prepared by addition of a THF solution of the crude acetoxy sulfones **6** (1 mol) to a −20 °C suspension of lithium aluminum hydride (0.5 mol) in THF. After 0.5 h at −20 °C excess hydride and aluminates were decomposed with saturated Na_2SO_4 or $MgSO_4$ and the supernatant solutions were filtered, dried ($MgSO_4$), and concentrated to give the crude hydroxy sulfones in the yields given in Table II.

Saponification of Acetoxy Sulfones 6 to Hydroxy Sulfones 1 with Sodium Carbonate. General Procedure. Hydroxy sulfones **1** (Table II, method A) were prepared by adding a 25% aqueous solution of sodium carbonate in portions to a cold (0–5 °C) solution of the crude acetoxy sulfones **6** in methanol such that the resulting solution was 20% water and 80% methanol. After stirring for 3–5 h the mixture was filtered, concentrated to ⅓ volume, and poured onto 3–4 volumes of H_2O. Isolation with ethyl acetate gave crude hydroxy sulfones **1** which were purified by crystallization from ether–ethyl acetate mixtures to afford **1** in the yields given in Table II.

***trans*-1-*p*-Toluenesulfonyl-2-methyl-4-hydroxy-2-butene (1b).** By the above method a solution of crude acetoxy sulfone **6b** (346.8 g, 1.22 mol) in methanol (2.2 l.) was cooled to 5 °C and a solution of sodium carbonate (194 g, 1.83 mol) in water (555 ml) was added with stirring in four portions, maintaining a temperature of 0–5 °C during the addition and for an additional 4.25 h. The mixture was filtered to remove sodium acetate and the filter cake was washed with ethyl acetate (100 ml). The filtrate was concentrated to a 600-ml volume, diluted with water (2 l.), and extracted with ethyl acetate (3 × 700 ml). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 288 g (97%) of crude **1b** as a white solid (80% pure by NMR). The crude **1b** was recrystallized from ether (1800 ml) containing ethyl acetate (50 ml) to give 198.8 g (69% yield) of **1b**, mp 59–64 °C. Recrystallization of a small portion from ether afforded analytically pure **1b**, mp 62.5–65 °C.

Preparation of 1b by Silver Carbonate Solvolysis of 8. A mixture of chloro sulfone **8** (0.1 g, 3.86 mmol), silver carbonate (0.1 g), water (1.0 ml), and acetone (3 ml) was warmed to 60 °C for 5 h. The mixture was cooled, filtered, and concentrated. The resulting oil was dissolved in ethyl acetate and the solution was washed with water and brine and dried ($MgSO_4$). Evaporation of the solvent gave hydroxy sulfone **1b** as a white solid (0.09 g, 97%, >90% pure by NMR).

Preparation of 1-Bromo-3-methyl-5-(2,6,6-trimethylcyclohexen-1-yl)penta-2,4-diene (2b). To a −70 °C cooled solution of vinyl-β-ionol (**14**, 26.75 g, assay 92.2%, 0.112 mol as 100%) in anhydrous ether (275 ml) was added over 1.5 min an ethereal solution of hydrogen bromide (32 ml of 4.12 M solution, 0.132 mol, prepared by bubbling HBr into ether at 0 °C until approximately 4 M and then titrating). The solution became pink and warmed to −60 °C during the addition and a red liquid was deposited on the walls of the flask (H_2O + HBr). After 15 min at −70 to −75 °C, the cooling bath was removed and the solution was warmed to −15 °C over 15 min with a warm air blower. After 3 min at −15 °C, the reaction was quenched by the addition of water (100 ml) whereupon the temperature rose to 5 °C. The mixture was transferred to a separatory funnel and the aqueous layer was drawn off. The pale yellow ether solution was washed with saturated sodium bicarbonate (75 ml) and was dried over $MgSO_4$ to which K_2CO_3 (1 g) had been added. The solution was filtered into a 1-l. flask and the solvent was removed on a rotary evaporator with the bath kept below 30 °C until a volume of ca. 60 ml was reached. The weight of the solution was 63 g.

In another experiment, an aliquot of the ether solution was replaced by CCl_4 by successive dilutions and evaporations in an N_2 stream: NMR δ 1.00 (s, 6, *gem*-CH_3's), 1.65 (s, 3, ring CH_3), 1.86 (s, 3, vinyl CH_3), 4.03 (d, 2, J = 8 Hz, CH_2Br), 5.63 (t, 1, J = 8 Hz, H_2), and 6.00 ppm (s, 2, H_3 and H_4).

1-Chloro-3-methyl-5-(2,6,6,-trimethylcyclohexen-1-yl)penta-2,4-diene (2a). The chloride was prepared in the same manner as the bromide **2b** except ethereal HCl was used intead of HBr: NMR δ 1.00 (s, 6, *gem*-CH_3's), 1.65 (s, 3, ring CH_3) 1.86 (s, 3, vinyl CH_3), 4.07 (d, 2, J = 8 Hz, CH_2Cl), 5.53 (t, 1, J = 8 Hz, H_2), 6.00 ppm (s, 2, H_3 and H_4).

Preparation of 1-Hydroxy-3,7-dimethyl-4-arylsulfonyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,6,8-trienes (3). General Procedure for Butyllithium Alkylation with Chloride 2a. A solution of butyllithium in hexane was added over 30–45 min to a stirred, −70 °C solution of the C_5 hydroxy sulfones **1** dissolved in THF. After an additional 30–40 min, a solution of the C_{15} chloride **2a** was added

in THF at −70 °C and the reaction mixture was stirred at −70 °C for ca. 1 h. The product was isolated by allowing the reaction mixture to warm to 0 °C over 15 min, pouring onto dilute HCl, and extracting with ethyl acetate or ether. After washing with bicarbonate and brine and drying ($MgSO_4$), the solvent was evaporated to give the crude product which was chromatographed on alumina (III) or silica gel to give the pure C_{20} hydroxy sulfones **3** in the yields and with the properties given in Table III.

Alkylation with Other Bases (Table IV). The sulfone **1b** and freshly prepared C_{15} halide **2a** or **2b** were stirred in THF at −70 °C during the addition of a freshly prepared solution of base over 15–60 min, or in the indicated experiments, the base was added at −70 °C to a THF solution of the hydroxy sulfone and the resulting solution was stirred for 15–45 min prior to addition of the freshly prepared C_{15} halide. Crude products were isolated by chromatography as described in the butyllithium procedure above. Yields of C_{20} sulfone **3b** are given in Table IV.

Elimination Reactions (Table V). To a suspension of sodamide (4–10 mol) in liquid NH_3 at reflux was added *tert*-butyl alcohol followed by an ether solution of the C_{20} hydroxy sulfones **3** (1 mol) (Table V). After 1–1.5 h, NH_4Cl was added and the NH_3 was evaporated. Water was added to the residue and the mixture was extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give crude vitamin A alcohol. The crude alcohol was dissolved in pyridine and was treated at −20 °C with acetyl chloride in dichloromethane and stirred at −15 to −20 °C for 20 min. The mixture was poured onto ice water and was extracted with ether. The extracts were washed with bicarbonate, saturated cupric sulfate, and brine and dried ($MgSO_4$). A crystal of BHT and a drop of pyridine were added and the solvent was removed to give crude vitamin A acetate which was assayed[12,13] by uv and HPLC (Table V).

Preparation of Vitamin A Acetate through Process via Bromide 2b and *p*-Tolyl Sulfone 1b. To a solution of hydroxy sulfone **1b** (25.0 g, 0.104 mol, mp 59–64 °C) prepared as described above in dry THF (125 ml) at −70 °C was added the crude bromide solution (**2b** plus ether, 63 g) from 0.112 mol of vinyl-β-ionol (**14**). The solution was stirred in a dry ice–acetone bath and a THF solution of lithium diisopropylamide (1.33 M, 0.226 mol) was added with vigorous stirring over 5 min. After 25 min at −75 °C the cooling bath was removed and the reaction mixture (at ca. −60 °C) was poured into a separatory funnel containing 1 l. of ice and H_2O. The mixture was extracted with ether (2 × 750 ml) and the combined extracts were washed with HCl (2.4%, 1 l.) and brine (2 × 500 ml) and were dried ($MgSO_4$). Pyridine (1.0 ml) was added, and the mixture was filtered and concentrated in vacuo to give a crude orange oil (50.71 g). To the crude oil was added hexane (50 ml) and the two-phase mixture was stirred and cooled to −20 °C for 2 h. The mixture was briefly cooled in a −70 °C bath to solidify the crude sulfone and the hexane was decanted. The trituration was repeated (50 ml of hexane) and the residual crude sulfone (48.2 g) was dissolved in ether (225 ml).

The solution was added over 15 min to a rapidly stirred suspension of powdered sodamide (21.65 g, 0.555 mol, Ventron) in 450 ml of liquid NH_3 to which *tert*-butyl alcohol (96 ml) had been added. The mixture was stirred at reflux (−33 °C) for 70 min. Ammonium chloride (18.5 g) was added followed by ether (250 ml) and the NH_3 was evaporated (adding ether as needed to replenish that lost by evaporation) until the mixture came to 0 °C. The mixture was poured into a separatory funnel containing ice water (500 ml). The organic layer was separated and the aqueous layer extracted with ether (300 ml). The combined organic solutions were washed with brine (600, 300 ml) and were dried ($MgSO_4$). Evaporation of the ether at aspirator pressure and the *tert*-butyl alcohol at 0.1 mm afforded crude vitamin A alcohol (35.62 g).

The crude material was dissolved in hexane (106 ml) and the solution was degassed (Ar) and triethylamine (21.61 ml) was added. Acetic anhydride (19.35 ml) was added to the solution over 15 min and the solution was degassed again and was stirred at room temperature overnight in the dark. The solution was then cooled to 0–10 °C during the addition (10 min) of 10% sodium carbonate solution (106 ml). After stirring for 30 min at room temperature, additional 10% sodium carbonate (30 ml) was added to bring the pH of the aqueous layer to 7.5. The layers were separated and the hexane layer was washed with H_2O (2 × 35 ml). The aqueous washes were extracted with hexane (30 ml) and the combined hexane solutions were dried ($MgSO_4$). After filtration, pyridine (0.3 ml) and a few crystals of BHT were added and the hexane was removed on a rotary evaporator under subdued light at <30 °C to afford crude vitamin A acetate as a dark orange oil (36.34 g). The crude acetate was dissolved in methanol (35 ml) and the solution was stirred mechanically at 2–3 °C and after 1 h was seeded with a crystal of all-trans vitamin A acetate whereupon crystallization commenced. After 18 h at 2–3 °C and 4 h at −20 °C the slurry was filtered and the crystals were washed with cold (−20 °C) methanol (35 ml). The solid was dried in vacuo to afford 24.01 g of light yellow, crystalline vitamin A acetate, mp 53–58 °C (lit.[14] 57–58 °C).

	Yield, %			Isomer ratio (HPLC), all-trans: 9-cis/ 9,13-di-cis
	Based on **1b**	Based on **16**	Purity (uv), %	
Crude oil	106		73.4	98.5:1.5
Crystals	70.3	65.3	91.4	98.8:1.2

Recrystallization of a 10-g sample of the mp 53–58 °C acetate from 85:15 methanol–pentane at 0 °C overnight afforded a first crop of 6.10 g of crystals, mp 56.5–60 °C, uv assay 99%.

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Registry No.—**1a**, 59830-37-4; **1b**, 59830-38-5; **1c**, 59830-39-6; **1d**, 59830-40-9; **1e**, 59830-41-0; **1f**, 59830-42-1; **2a** (X = Cl), 55732-70-2; **2b** (X = Br), 38987-92-7; **3a**, 59830-43-2; **3b**, 59830-44-3; **3c**, 59830-45-4; **3d**, 59839-81-5; **3e**, 59830-46-5; **4** (R = H), 68-26-8; **4** (R = Ac), 127-47-9; 9-*cis*-**4** (R = Ac), 29584-22-3; 9,13-di-*cis*-**4** (R = Ac), 29444-27-7; **5**, 24529-80-4; **6a**, 59830-31-8; **6b**, 59830-32-9; **6c**, 59830-33-0; **6d**, 59830-34-1; **6e**, 59830-35-2; **6f**, 59830-36-3; **8**, 59830-48-7; **9**, 59830-47-6; **10**, 59830-49-8; *trans*-**11**, 3621-52-1; *cis*-**11**, 3927-06-8; *trans*-**12**, 59830-50-1; *cis*-**12**, 59830-51-2; **13**, 59830-52-3; **14**, 31821-03-1; sodium *p*-toluenesulfinate, 824-79-3; *p*-toluenesulfonyl chloride, 98-59-9; isoprene, 78-79-5; 1,4-dichloro-2-methyl-2-butene, 29843-58-1.

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Synthesis of 1,3-Bishomoadamantane[1]

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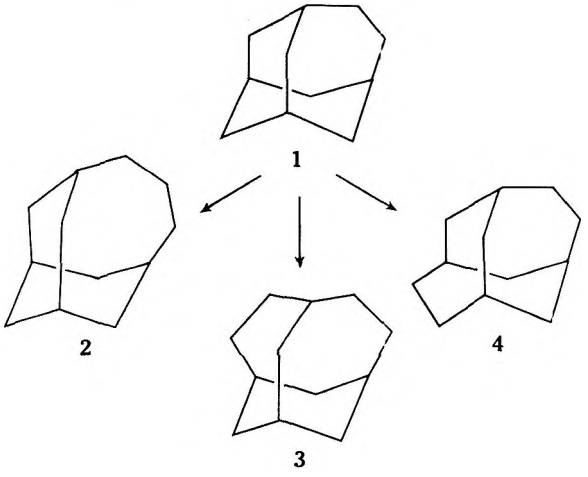
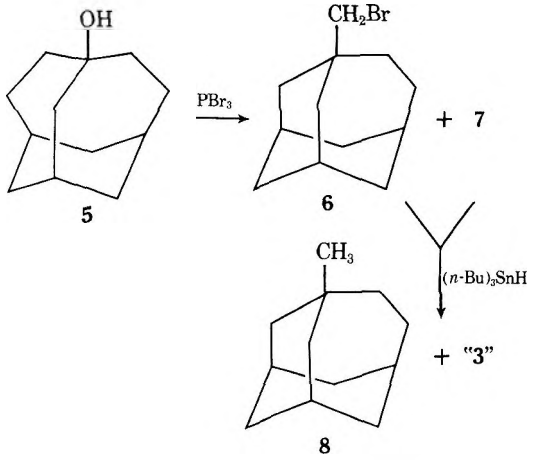
Three routes leading to 1,3-bishomoadamantane (**3**) have been developed. Homologation of homoadamant-4-en-2-one (**9**) by the Evans modification of the Tiffeneau–Demjanov ring expansion reaction gives a 90:10 mixture of tricyclo[4.4.1.1^{3,9}]dodec-7-en-4-one (**11**) and tricyclo[4.4.1.1^{3,9}]dodec-7-en-5-one (**12**), respectively. Reduction of **11**–**12** with sodium borohydride, followed by treatment of the resulting mixture of alcohols with phosphoryl chloride in pyridine, provides tricyclo[4.4.1.1^{3,9}]dodeca-4,7-diene (**23**). Catalytic hydrogenation of **23** affords **3**. Alternatively, homologation of 2-homoadamantanone by the same sequence of reactions employed for **9** → **11**–**12** gives a mixture of tricyclo[4.4.1.1^{3,9}]dodecan-4-one (**25**) and tricyclo[4.4.1.1^{3,9}]dodecan-5-one (**26**) which upon Wolff–Kishner reduction provides **3**. Finally, subjecting **25**–**26** to the same sequence of reactions utilized for **11**–**12** → **23** affords tricyclo[4.4.1.1^{3,9}]dodec-4-ene which gives **3** upon catalytic hydrogenation.

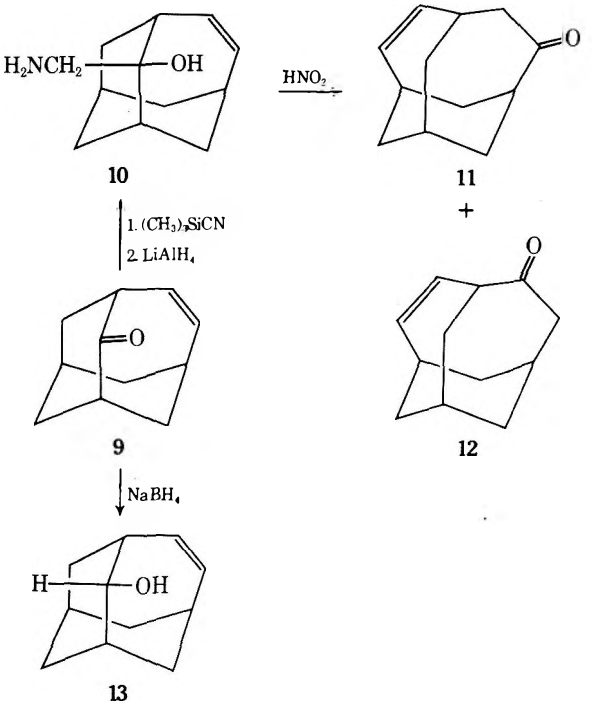
Insertion of a methylene group into any one of the carbon–carbon bonds in adamantane (T_d symmetry) gives but a single "homoadamantane" (**1**). By contrast, analogous homologation of **1** (C_{2v} or C_2 symmetry)[2] can afford three bishomoadamantanes (**2**–**4**). Sasaki has suggested the trivial names of 1,1-, 1,3-, and 1,5-bishomoadamantane, respectively, for these hydrocarbons.[3] Unequivocal syntheses of **2**[3] and **4**[4] have appeared and these compounds have been thoroughly characterized. However, the only reported synthesis of **3** is tenuous.[3] Treatment of an alcohol, presumed to have structure **5**, with phosphorus tribromide in *n*-hexane–benzene at 5–30 °C for 20 h gave in 25% yield a 6.5:1 mixture of 3-bromomethylhomoadamantane (**6**) and a "bridgehead bromide" (**7**), respectively. Subsequent reduction of this bromide mixture with tri-*n*-butyltin hydride in cyclohexane at 80–85 °C for 20 h and with Raney Ni catalyst at 40–50 °C for 2 days provided 3-methylhomoadamantane (**8**) and a minor product in a ca. 7.5:1 ratio, respectively. Since the minor product was not **2**, it was presumed to be **3**. However, the minor product was not isolated or characterized. We now wish to report an independent and unequivocal synthesis of 1,3-bishomoadamantane.





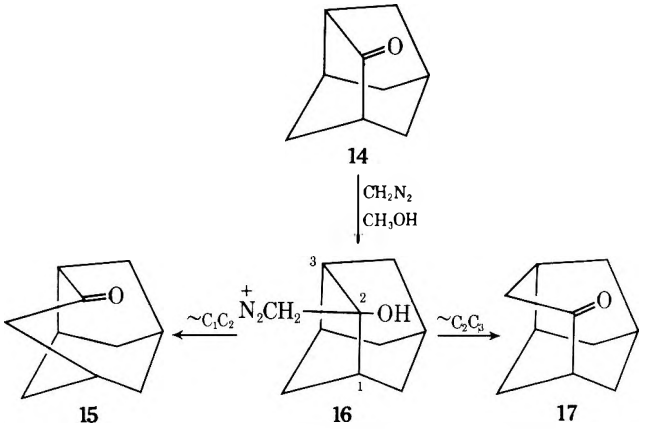
Results and Discussion

The skeletal framework of 1,3-bishomoadamantane was readily generated by Tiffeneau–Demjanov ring expansion of homoadamant-4-en-2-one (**9**).[5] Treatment of **9** with trimethylsilyl cyanide,[6] followed by reduction of the resulting trimethylsilyl cyanohydrin ether with lithium aluminum hydride, gave β-aminomethyl alcohol **10**. The stereochemical assignment of the substituents at C-2 in **10** follows from our earlier observation that sodium borohydride reduction of enone **9** gives 2-*endo*-homoadamant-4-enol (**13**) exclusively.[5] Treatment of **10** with nitrous acid provided in ca. 75% overall yield from **9** a 90:10 mixture of tricyclo[4.4.1.1^{3,9}]dodec-7-en-4-one (**11**) and tricyclo[4.4.1.1^{3,9}]dodec-7-en-5-one (**12**), respectively. Each of these enones shows a nonconjugated carbonyl absorption in the infrared at 1696 cm^{-1}. The assignment of the major product as the γ,δ-unsaturated ketone and the minor product as the β,γ-unsaturated ketone follows from the difference in chemical shift of the olefinic carbons in these compounds. As might well be expected, the difference

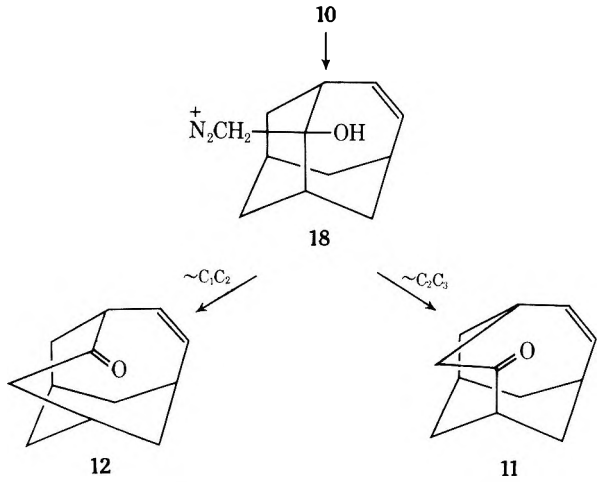


in chemical shift of the olefinic carbons in the γ,δ-unsaturated ketone (3.07 ppm) is significantly less than that for the β,γ-unsaturated ketone (10.14 ppm).[7] Moreover, the difference in chemical shift of the olefinic carbons in enone **9**, a β,γ-unsaturated ketone with a structure closely related to **12**, is 10.84 ppm.[7]

Recently, Schleyer and his co-workers have noted that homologation of 2-noradamantanone (**14**) with diazomethane proceeds with regioselective ring expansion of **14** to give 5-protoadamantanone (**17**) in 90–96% yield and 95% purity with no detectable amount of 4-protoadamantanone (**15**) present.[8]

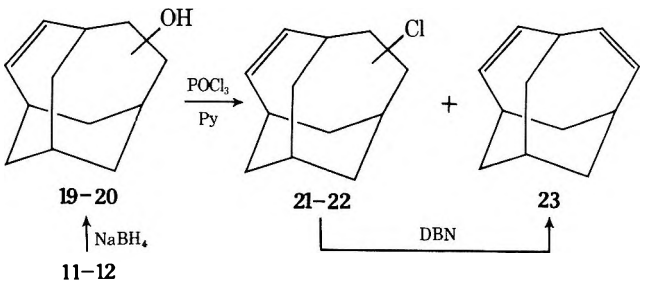


The complete migrational selectivity in intermediate **16** suggests a strong conformational preference of the two-carbon bridge in the protoadamantane products, i.e., migration of C_1–C_2 in **16** would lead to a transition state resembling ketone **15**, whereas C_2–C_3 bond migration in **16** would give **17**. Indeed, force field calculations on protoadamantane indicate that the conformation similar to **15** is ca. 6 kcal/mol higher in energy than the conformation resembling **17**.[8] It would appear that a similar analysis might explain the preferred migration of the C_2–C_3 bond in **18** to give **11** as the major product. It follows



that the preferred conformation of tricyclo[4.4.1.$1^{3,9}$]dodec-4-ene (**27**) probably resembles **11** rather than **12**.

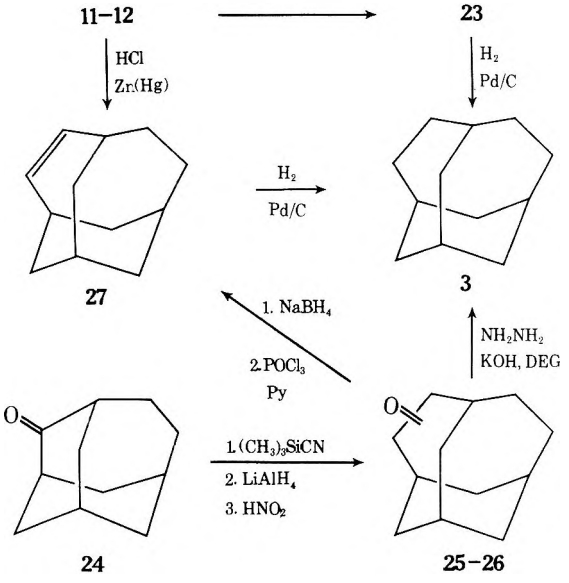
The synthesis of 1,3-bishomoadamantadiene (**23**) from **11–12** is straightforward. Sodium borohydride reduction of a 90:10 mixture of **11–12** gives a mixture of the corresponding alcohols (**19–20**) which when treated with phosphoryl chloride in pyridine at 5–15 °C affords a mixture of the corresponding chlorides (**21–22**) and diene **23** in a ratio of 45:55, respectively. If the mixture of reaction products is stirred with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) at 110 °C for 5 days,[9] the exclusive product is **23**. By this sequence of reactions, **23** can be obtained in ca. 40% overall yield from **11–12**. Consistent with the presence of a plane of symmetry in **23**, the ^{13}C NMR



spectrum of **23** contains only eight signals with four of the signals being twice as intense as the others.

Catalytic hydrogenation of diene **23** affords 1,3-bishomoadamantane (**3**). The ^{13}C NMR spectrum of **3** is consistent with the assigned structure. Alternative synthetic routes to **3** are summarized in Scheme I. Tiffeneau–Demjanov ring

Scheme I



expansion of 2-homoadamantanone[5] (**24**) by the same sequence of reactions employed for **9** → **11–12** provides in ca. 70% yield a mixture of tricyclo[4.4.1.$1^{3,9}$]dodecan-4-one (**25**) and tricyclo[4.4.1.$1^{3,9}$]dodecan-5-one (**26**). Attempts to separate **25** and **26** by GLC were unsuccessful. However, it is apparent that the mixture is highly enriched in **25** as catalytic reduction of a 90:10 mixture of **11–12** gives a mixture of **25** and **26** that cannot be differentiated from the product mixture obtained upon homologation of **24**. Wolff–Kishner reduction of **25–26** gives **3**.

A third route to **3** is via 1,3-bishomoadamantene (**27**). Subjecting a mixture of **25** and **26** to the sequence of reactions employed for **11–12** → **23** gives **27** in ca. 50% yield. Olefin **27** can also be obtained by Clemmensen reduction of **11–12** or by dechlorination of **21–22** with lithium in *tert*-butyl alcohol–tetrahydrofuran.[10] Catalytic hydrogenation of **27** gives **3**.

Experimental Section

Infrared spectra were obtained on Perkin-Elmer 180 or 337 spectrophotometers and proton magnetic resonance spectra were recorded with Varian A-60A or Perkin-Elmer R-12B 60-MHz spectrometers. Carbon magnetic resonance spectra were taken at an operating frequency of 22.63 MHz on a Bruker HFX-90 spectrometer equipped for Fourier transform pulsed NMR with a Nicolet 1085 data system. Electron-impact mass spectra were obtained with a Du Pont CEC 21-110B mass spectrometer. Unless noted otherwise, yields were obtained by integration of appropriate signals in the ^1H NMR spectrum of the product(s) vs. the signal of a predetermined amount of added standard (generally trichloroethylene) and are regarded as being accurate to ca. ±10%. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, Del.

Tricyclo[4.4.1.1^{3,9}]dodec-7-en-4-one (11) and Tricyclo-[4.4.1.1^{3,9}]dodec-7-en-5-one (12). 18-Crown-6 (106 mg) and potassium cyanide (25 mg) were dissolved in 2 ml of anhydrous methanol. Evaporation of the solvent at reduced pressure gave a white, waxy solid. This catalyst and trimethylsilyl cyanide (4.3 g, 0.04 mol) were added to homoadamant-4-en-2-one[5] (**9**, 2.0 g, 12 mmol) and the reaction mixture was stirred at room temperature under nitrogen for 72 h. The excess trimethylsilyl cyanide was removed from the reaction mixture by evaporation at reduced pressure to give a rust-colored viscous oil which showed no carbonyl absorption in the infrared. The resulting unpurified α-silyloxynitrile was dissolved in 10 ml of anhydrous ether and added dropwise under nitrogen to a stirred slurry of 1.0 g (26 mmol) of lithium aluminum hydride in 30 ml of anhydrous ether at a rate which maintained a gentle reflux of the reaction mixture. Stirring was continued for 2 h after the addition had been completed. The excess lithium aluminum hydride present was destroyed by cautious dropwise addition of 1.0 ml of water, followed by 1.5 ml of 10% sodium hydroxide and 3.2 ml of water. Stirring was continued until a granular white precipitate formed. Filtration provided a clear yellow ether solution which was dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided the crude amino alcohol as an orange solid.

A solution of 940 mg (13.6 mmol) of sodium nitrite in 10 ml of water was added over 15 min to a solution of the crude amino alcohol in 110 ml of water and 4 ml of acetic acid which was maintained at 5 °C. The resulting reaction mixture was stirred at 5 °C for 1 h and then at 20 °C for 1 h and 60 °C for 2 h. The reaction mixture was quenched with water (100 ml), saturated with sodium chloride, and extracted with ether (5 × 75 ml). The combined ether extracts were washed with 5% aqueous sodium bicarbonate (2 × 50 ml) and saturated aqueous sodium chloride (2 × 50 ml) and then dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave 1.68 g of a yellowish solid which by ^{1}H NMR analysis contained a ca. 75% overall yield of olefinic products. GLC analysis (10 ft × 0.25 in. DC-550 column, 200 °C) showed the presence of three components in a ratio of ca. 1:1:8 with retention times of 7.2, 11.5, and 12.8 min, respectively. The products were purified by GLC (above conditions). The compound of shortest retention time proved to be unreacted **9**. The other minor component of the reaction mixture was isolated as a white solid and identified as **12**: δ_{Me_4Si} ($CDCl_3$) 6.5–5.55 (m, 2 H, CH=CH) and 3.65–1.2 (br m, 14 H); ν (CCl_4) 3020, 2925, 2850, 1696, 1655, 1440, 1275, 1245, 1150, 1115, 1080, 1015, and 930 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 82.04; H, 8.98.

The major product was also obtained as a white solid and identified as **11**: ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 6.19–5.69 (m, 2 H, CH=CH) and 3.24–1.27 (br m, 14 H); ^{13}C NMR δ_{Me_4Si} ($CDCl_3$) 217.0 (C-4), 136.2 (C-8), 133.0 (C-7), 51.7 (C-5), 44.9 (C-3), 39.5 (t), 35.5 (d), 34.5 (t), 33.2 (t), 32.7 (d), 31.4 (d), and 30.7 (t); ν (CCl_4) 3015, 2915, 2900, 2850, 1696, 1445, 1330, 1270, 1190, 1090, and 1035 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.78; H, 9.09.

Tricyclo[4.4.1.1^{3,9}]dodeca-4,7-diene (23). A solution of 1.53 g (8.7 mmol) of a ca. 90:10 mixture of **11**–**12** in 20 ml of methanol was added dropwise to a stirred solution of 1.64 g (42.6 mmol) of sodium borohydride in 75 ml of methanol at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and then for 6 h at room temperature, at which point 150 ml of water was added. The resulting white suspension was saturated with sodium chloride and extracted with ether (5 × 100 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated at reduced pressure to give 1.52 g of a solid residue. Sublimation afforded 1.32 g (ca. 85% yield) of a white solid which was homogeneous by GLC analysis (10 ft × 0.25 in. DC-550 column, 200 °C). This material was purified by GLC to give a white solid which is presumed to be a mixture of **tricyclo[4.4.1.1^{3,9}]-dodec-7-en-4-ol (19) and tricyclo[4.4.1.1^{3,9}]dodec-7-en-5-ol (20)** that is highly enriched in **19**: δ_{Me_4Si} ($CDCl_3$) 6.38–5.77 (m, 2 H, CH=CH), 4.45–3.88 (br m, 1 H, CHOH), and 2.88–1.25 (br m, 15 H); ν (CCl_4) 3580, 3010, 2910, 2850, 1450, 1400, 1195, 1130, 1120, 1075, 1050, and 1015 cm^{-1}.

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.79; H, 9.91.

Phosphoryl chloride (1.604 g, 10.45 mmol) was added in five portions to a stirred solution of 1.24 g (6.97 mmol) of a mixture of **19** and 5.8 ml of pyridine. The temperature of the reaction mixture was 5 °C before each addition of phosphoryl chloride and ca. 15 °C after each addition. When the addition was suspension was stirred for 12 h at 25 °C and then for The reaction mixture was then cooled, diluted with 250 and extracted with ether (4 × 100 ml). The combined ether extracts were washed with water and saturated aqueous sodium chloride, and then dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave a yellowish oil which formed a precipitate when added to water. This precipitate was filtered and sublimed (60 °C, 5 mm) to afford 611 mg of a white solid. GLC analysis (10 ft × 0.25 in. DC-550 column, 200 °C) indicated two major products with retention times of 4.0 and 10.2 min and some very minor components of intermediate retention times. Purification by GLC (above conditions) gave **23** (shorter t_R) as a white solid: ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 6.74–5.92 (m, 4 H, CH=CH) and 3.3–1.3 (br m, 12 H); ^{13}C NMR δ_{Me_4Si} ($CDCl_3$) 137.4, 134.5, 39.5, 35.2, 33.8, 32.9, 32.1, and 27.2 in the ratio of 2:2:1:2:1:1:2:1, respectively; ν (CCl_4) 3015, 2905, 2840, 1650, 1430, 950, and 865 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 90.10; H, 9.76.

The product with t_R 10.2 min was also isolated by GLC (above conditions) as a white solid and is presumed to be a mixture of **7-chlorotricyclo[4.4.1.1.^{3,9}]dodec-4-ene (21) and 8-chlorotricyclo[4.4.1.1^{3,9}]dodec-4-ene (22)** that is highly enriched in **21**: δ_{Me_4Si} ($CDCl_3$) 6.48–5.68 (m, 2 H, CH=CH), 4.74–4.34 (m, 1 H,CHCl), and 3.22–1.08 (br m, 14 H); ν (CCl_4) 3010, 2920, 2850, 1445, 1195, and 945 cm^{-1}; *m/e* 196/198 = P/P + 2 = 3/1. Treatment of this material with lithium in *tert*-butyl alcohol–tetrahydrofuran (see below) gave **27**.

Analysis of the sublimed material by ^{1}H NMR showed that the ratio of **21**–**22**:**23** was 45:55.

The mixture of **21**–**22** and **23** (715 mg) and 1,5-diazabicyclo[4.3.0]-non-5-ene (1.362 g, 10.98 mmol) was stirred under a nitrogen atmosphere at 110 °C for 5 days. The reaction mixture was cooled, quenched in 250 ml of water, and then extracted with ether (6 × 75 ml). The combined ether extracts were washed with water (2 × 50 ml) and saturated aqueous sodium chloride (2 × 50 ml) and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided a white solid which by GLC analysis (10 ft × 0.25 in. DC-550 column, 200 °C) contained only **23**. Sublimation (60 °C, 4 mm) of the residue gave 484 mg (3.03 mmol, 74% yield) of **23**.

Tricyclo[4.4.1.1^{3,9}]dodecan-4-one (25) and Tricyclo-[4.4.1.1^{3,9}]dodecan-5-one (26). A. A solution of 60 mg (0.34 mmol) of a 90:10 mixture of **11**–**12** in 50 ml of ethanol was stirred with 20 mg of 10% palladium on charcoal under an atmosphere of hydrogen for 24 h. The reaction mixture was then filtered to remove the catalyst. The catalyst was washed several times with methanol and the filtrate and washings were combined. Evaporation of the solvent at reduced pressure gave 56 mg (93% yield) of a white solid. This material appeared to be homogeneous under a variety of GLC conditions: 10 ft × 0.25 in. DC-550 column at 225, 200, and 175 °C; 10 ft × 0.25 in. SE-30 column at 225 °C; 5 ft × 0.25 in. OV-1 column at 225, 200, and 170 °C; and 5 ft × 0.25 in. Porapak Q column at 260, 225, and 200 °C. The ketone mixture was purified by GLC (10 ft × 0.25 in. DC-550 column, 190 °C) to give a mixture of **25** and **26** as a white solid which was highly enriched in **25**: δ_{Me_4Si} ($CDCL_3$) 2.88–2.54 (m, 2 H, —CH_2C=O)and 2.54–1.28 (br m, 16 H); ν (CCl_4) 2910, 2850, 1686, 1445, 1405, 1355, 1180, 1075, 1025, and 930 cm^{-1}.

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.75; H, 10.21.

B. Treatment of 1.0 g (6.1 mmol) of 2-homoadamantanone[5] (**24**) by the sequence of reactions described for **9** → **11**–**12** gave in ca. 70% yield (by ^{1}H NMR analysis) a white solid whose infrared and ^{1}H NMR spectra were identical with those obtained for the 90:10 mixture of **25**–**26** generated in A.

Tricyclo[4.4.1.1^{3,9}]dodec-4-ene (27). A. Reduction of a mixture of 250 mg of **25** and **26** with sodium borohydride by the procedure described for **11**–**12** → **19**–**20** gave 253 mg of a white solid which was homogeneous by GLC analysis (10 ft × 0.25 in. DC-550 column, 200 °C). This material was purified by GLC to give a white solid which is presumed to be a mixture of **tricyclo[4.4.1.1^{3,9}]dodecan-4-ol (28) and tricyclo[4.4.1.1^{3,9}]dodecan-5-ol (29)** that is highly enriched in **28**: δ_{Me_4Si} ($CDCl_3$) 4.21–3.80 (m, 1 H, CHOH) and 2.77–1.18 (br m, 19 H); ν (CCl_4) 3630, 3400 (br), 2905, 1450, 1050, and 1020 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.95; H, 11.18. Found: C, 80.03; H, 11.01.

Treatment of 187 mg of a mixture of **28** and **29** according to the conditions employed for **19**–**20** → **23** afforded 87 mg (51% yield) of **27** which was isolated by GLC (10 ft × 0.25 in. DC-550 column, 175 °C) as a white solid: δ_{Me_4Si} ($CDCl_3$) 6.30–5.46 (m, 2 H, CH=CH) and 2.93–1.25 (br m, 16 H); ν (CCl_4) 3010, 2900, 2845, 1445, 1190, 1155, 1000, 950, 940, and 930 cm^{-1}.

Anal. Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 89.07; H, 10.98.

B. A solution of 50 mg of a 90:10 mixture of **11**–**12** in 1 ml of toluene was added to a mixture of 400 mg of amalgamated zinc, 0.5 ml of water,

and 1 ml of hydrochloric acid. The resulting mixture was vigorously refluxed for 4 days with portions of HCl and amalgamated zinc being added every 6 h. After cooling, the reaction mixture was diluted with 40 ml of water and extracted with ether (6 × 25 ml). The combined ether extracts were washed several times with 5% aqueous sodium bicarbonate, then with saturated aqueous sodium chloride (2 × 25 ml), and finally dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave a white solid which GLC analysis (10 ft × 0.25 in. DC-550 column, 200 °C) showed contained some unreacted starting material, a minor component which was not identified, and a major component with a relatively short retention time. Purification of the major product by GLC (above conditions) gave a white solid whose ir spectrum was identical with that of **27** obtained by procedure A.

C. Lithium (54 mg, 7.7 mmol) was added to a stirred solution of 19 mg (0.1 mmol) of a mixture of **21** and **22** in 2 ml of *tert*-butyl alcohol and 10 ml of dry tetrahydrofuran. The reaction mixture was stirred at room temperature for 3.5 h. Water (10 ml) was then added and stirring was continued for 30 min. The resulting solution was extracted with ether (3 × 40 ml) and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave a white solid which by GLC analysis (10 ft × 0.25 in. DC-550 column, 200 °C) contained a trace of starting material and a single major product. Purification of the product by GLC provided 3.5 mg of a white solid whose mass spectrum was identical with that of **27** obtained by procedure A.

Tricyclo[4.4.1.1^{3,9}]dodecane (3). A. A solution of 110 mg of **23** in 50 ml of ethanol was stirred at room temperature with 660 mg of 10% palladium on charcoal under an atmosphere of hydrogen for 24 h. The reaction mixture was filtered to remove the catalyst and the catalyst was washed several times with methanol. The filtrate and washings were combined and the methanol was removed by distillation to leave a solid residue which by GLC analysis (10 ft × 0.25 in. DC-550 column, 175 °C) contained a single component. Isolation of the product by GLC (above conditions) gave 47 mg of **3** as a white solid: ^{1}H NMR δ_{Me_4Si} ($CDCl_3$) 2.5–1.4 (br m); ^{13}C NMR δ_{Me_4Si} ($CDCl_3$) 44.65 (t), 40.99 (t), 36.62 (d), 34.35 (t), 32.57 (d), 31.76 (t), 31.06 (t), and 29.55 (d) in the ratio of 1:1:1:2:1:2:2:2, respectively; ν (CCl_4) 2910, 1450, 1260, 1200, 1140, 1110, and 1060 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.84; H, 12.09.

B. Hydrogenation of **27** under the conditions employed for **23** → **3**, followed by purification of the product by GLC, provided a white solid whose mass spectrum was identical with that of **3** obtained by procedure A.

C. A solution of 50 mg of **25–26**, 264 mg of potassium hydroxide, and 230 mg of 95% hydrazine in 1.5 ml of diethylene glycol was heated with stirring at 110 °C for 30 min, and then for 3 h at 180 °C. During this time, a white solid appeared on the water-cooled condenser. The system was cooled and the material on the condenser was dissolved in ether and then dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure afforded 30 mg of a white solid which by GLC analysis (10 ft × 0.25 in. DC-550 column, 175 °C) was homogeneous. Isolation of the product by GLC gave a white solid whose ir spectrum was identical with that of **3** obtained by procedure A.

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Registry No.—**3**, 36071-59-7; **9**, 55638-05-6; **11**, 59839-97-3; **12**, 59839-98-4; **19**, 59839-99-5; **20**, 59840-00-5; **21**, 59840-01-6; **22**, 59840-02-7; **23**, 59840-03-8; **24**, 55638-10-3; **25**, 59840-04-9; **26**, 59840-05-0; **27**, 59840-06-1; **28**, 59840-07-2; **29**, 59840-08-3; phosphoryl chloride, 10025-87-3.

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Kinetics and Mechanism of Acidic and Alkaline Hydrolysis of Hindered *N*-Methylarylhydroxamic Acids

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Thg kinetics of acidic and basic catalyzed hydrolysis of ortho-substituted *N*-methylbenzohydroxamic acids have been investigated at moderate acidity and high basicity. The results are interpreted in terms of a bimolecular mechanism for acidic catalysis and as reaction of the hydroxamic acid conjugate base with water and hydroxide ion for basic catalysis in the catalytic range investigated. Specific salt effects are reported.

We have investigated the kinetics and mechanism of the acidic and basic catalyzed hydrolysis of hindered benzohydroxamic acids in order to learn the effect of this increased hindrance upon the mechanisms of the reactions, the range of catalyst concentration required, and the importance of salt effects at these higher concentrations. The increased hindrance is provided by use of ortho-substituted *N*-methylbenzohydroxamic acids in comparison to unsubstituted benzohydroxamic acid. Smith and Yates[1] have studied the acid-catalyzed hydrolysis of benzamide, *N*-methyl- and *N,N*-dimethylbenzamide and have inferred from their data that all three compounds probably do not react via the oxygen protonated form *or* that benzamide does hydrolyze via oxygen protonation while the other N-substituted compounds do not. McClelland's[2] recent report of small but detectable ^{18}O exchange for the acidic hydrolysis of benzamide supports the latter conclusion.

Our present results indicate that there is no mechanism change in the acid-catalyzed hydrolysis upon introduction of an *N*-methyl and ortho groups in hydroxamic acids. There appears to be a significant rate of reaction in the absence of added acid or alkali at high salt concentrations. Specific sa[l] effects are also observed.

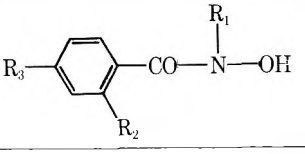
Acidic Catalysis. Equation 1 expresses the reaction

Table I. Rate Data for Acid-Catalyzed Hydrolysis of 2- and 4-Methyl-*N*-methylbenzohydroxamic Acids

HCl, M	Temp, °C	$10^5 k$[a]
2-Methyl-*N*-methylbenzohydroxamic Acid		
0.149	90.0	1.48
0.150	90.0	1.33[b]
0.225	90.0	2.04
0.451	90.0	2.99
0.595	90.0	3.78
0.751	90.0	4.61
0.751	80.0	1.86
0.751	70.0	0.818
4-Methyl-*N*-methylbenzohydroxamic Acid		
0.225	84.0	29.0
0.225	71.7	10.8
0.225	61.1	4.16

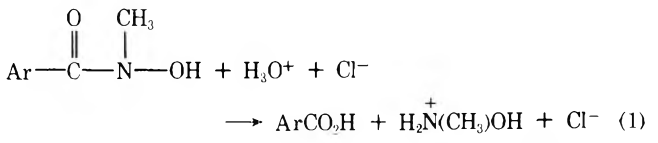
[a] Average pseudo-first-order rate constant, s^{-1}. Ionic strength maintained at 0.751 M with KCl except as noted. [b] Ionic strength maintained with CsCl.

Table II. Activation Parameters[a] for Acidic Hydrolysis of



R_1	R_2	R_3	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
CH_3	CH_3	H	20.8	−21.2
CH_3	H	CH_3	19.4	−17.8
H	H	H	19.4	−20.2[b]
H	H	H	20.2	−17.9[c]

[a] Calculated from second-order rate constants. [b] Calculated from data from ref 4 at two temperatures, HCl, ionic strength 0.577 M (KCl). [c] Reference 5, 1.00 M $HClO_4$.



$$\longrightarrow ArCO_2H + H_2\overset{+}{N}(CH_3)OH + Cl^- \quad (1)$$

acidic conditions. The reaction is cleanly pseudo-first-order in the presence of excess hydrochloric acid (Table I). A graph of the data for the *o*-methyl compound in Table I shows first-order dependence upon hydrochloric acid (extrapolation of the data outside the range studied is unwarranted owing to the specific salt effects discussed below). This dependence is similar to that observed for the hydrolysis of unsubstituted hydroxamic acids at comparable acidities.[3-5] Table II compares activation parameters for the compounds in Table I with those for the acid-catalyzed hydrolysis of benzohydroxamic acid under similar conditions.

These results are consistent with the acid-catalyzed bimolecular mechanism reported before for the unhindered RCONHOH compounds.[3-5] A tetrahedral intermediate likely is involved analogous to benzamide hydrolysis.[2,6] The activation parameters listed in Table II are in the usual range[1] for the bimolecular mechanism for amides. Furthermore, the enthalpy of activation is higher and the entropy of activation is more negative for the *o*-methyl-*N*-methylbenzohydroxamic acid hydrolysis than for the hydrolysis of the corresponding *p*-methyl compound. These results are consistent with the

lecular mechanism with the more hindered compound higher enthalpy and lower entropy of activa-

er reaction of 2-methyl-*N*-methylbenzohyd occurs in the absence of added hydrochloric ıe presence of 0.751 M potassium chloride and is about 6% of the rate observed with 0.149 N hydrochloric acid at ionic strength 0.751 M.

Specific ion effects[7] as well as ionic strength effects on reaction rates are expected at moderate salt concentrations. Specific cation effects, outside experimental error, can be seen by comparing the first two entries in Table I. Nonlinear specific cation effects have been reported for the acidic hydrolysis of 4-nitroacetanilide.[8]

Table III. Rate Data for Base-Catalyzed Hydrolysis of 2-Chloro-*N*-methylbenzohydroxamic Acid at 90.0 °C

NaOH, M	$10^6 k_{obsd}$[a]
7.31	2.57
6.58	2.28
5.47	1.89
4.40	1.44
3.23	0.92

[a] Average pseudo-first-order rate constant, s^{-1}. Ionic strength maintained at 7.31 M with NaCl.

Basic Catalysis. Pseudo-first-order rates are observed according to the equation $-dS/dt = k_{obsd}S$, where S is the total stoichiometric amount of hydroxamic acid present at any time. The data for *N*-methyl-2-chlorobenzohydroxamic acid are in Table III. A graph of this data shows linear dependence of the pseudo-first-order rate constant upon hydroxide ion concentration (extrapolation of the data outside the range studied is unwarranted owing to specific ion effects—see below).

$$\underset{\mathbf{1}}{ArCON(CH_3)OH} + \bar{O}H \rightleftharpoons \underset{\mathbf{2}}{ArCON(CH_3)O^-} + H_2O \quad (2)$$

Under the strongly alkaline conditions used in the kinetic studies 1 will be almost completely converted into **2**. (The pK_a's of *N-tert*-butylbenzohydroxamic[9] and *N*-phenylbenzohydroxamic[10] acids are 10.1 and 9.15, respectively.) A reasonable mechanism consistent with the data is represented by eq 3–5.

$$1 + \bar{O}H \overset{K}{\rightleftharpoons} 2 + H_2O \quad (3)$$

$$2 + \bar{O}H \xrightarrow{k_2} \text{products} \quad (4)$$

$$2 + H_2O \xrightarrow{k_3} \text{products} \quad (5)$$

The linear dependence upon hydroxide concentration for *N*-methyl-2-chlorobenzohydroxamic acid is similar to the rate law obtained at high base strengths for hydrolysis of the unhindered benzohydroxamic acid.[4] Thus the mechanisms for hydrolysis of these compounds in strong base are probably similar. Tetrahedral intermediates presumably are involved as they are in alkaline hydrolyses of amides;[6,11] however, the kinetic results cannot distinguish between these possibilities.

Ahmad, Socha, and Vecera[12] have recently reported a study of the alkaline hydrolysis of benzohydroxamic acid over a wide hydroxide ion concentration range and have considered various mechanisms. They have incompletely and incorrectly graphed our earlier data[4] on the alkaline hydrolysis of benzohydroxamic acid and state that attack of hydroxide on the acid anion is insignificant. Our present and earlier work[4] demonstrates a positive slope for a graph of the pseudo-first-order constant vs. hydroxide concentration *in the range studied* as does Ahmad and co-worker's curve 2 of their own Figure 1 for benzohydroxamic acid. Mechanisms will of course vary as the hydroxide ion concentration range changes; however, for the hydroxide ion concentration ranges reported in our earlier work and herein the hydroxamic acids will exist as

Table IV. Rate Data for the Uncatalyzed Hydrolysis of 2-Chloro-*N*-methylbenzohydroxamic Acid in the Presence of Salts at 90.0 °C

Salt	Concn, M	$10^6 k_{obsd}$[a]
NaCl	3.00	1.11
NaCl	6.31	1.94
NaBr	6.31	1.33

[a] Average first-order rate constant, s^{-1}.

their conjugate bases and the rate laws are best interpreted according to the mechanism of eq 3–5 for that range.

Specific salt effects[7] are expected at the high concentrations employed to maintain constant ionic strength in the alkaline hydrolyses. These effects are illustrated in Table IV. Note that the rate constants reported in Table IV are for reactions in the absence of any added hydroxide. Direct comparison of the rate constants in Tables III and IV is not possible since in one case the reaction involves the hydroxamic acid reacting with water and in the other its conjugate base reacting with hydroxide ion or water. These two cases involve different charge types; however, at the concentrations of catalytic acid or base employed in this study, there will be specific salt effects for all charge types.

Experimental Section

The *N*-methylbenzohydroxamic acids were synthesized by adaptation of the method used by Ulrich and Sayigh[13] for the preparation of *N*-methylacetohydroxamic acid. ^1H NMR and ir spectra are consistent with the structures listed. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

N-Methyl-2-methylbenzohydroxamic acid, crystallized successively from benzene and carbon tetrachloride, had mp 120–121 °C. Anal. Calcd for $C_9H_{11}NO_2$: C, 65.45; H, 6.72; N, 8.48. Found: C, 65.14; H, 6.48; N, 8.47.

N-Methyl-2-chlorobenzohydroxamic acid, crystallized as above, had mp 118–119 °C. Anal. Calcd for $C_8H_8ClNO_2$: C, 51.77; H, 4.34; N, 7.55. Found: C, 51.61; H, 4.38; N, 7.59.

N-Methyl-4-methylbenzohydroxamic acid had mp 119–120 °C dec (lit.[14] 122 °C).

Kinetic measurements were made by the spectrophotometric method reported previously[4] employing a Beckman DU spectrophotometer set at 520 nm for the 2-methyl- and 4-methyl-*N*-methylbenzohydroxamic acid runs and at 500 nm for the *N*-methyl-2-chlorobenzohydroxamic acid runs. The acidity of the $FeCl_3$ solution was adjusted as before[4] for the alkaline runs.

Pseudo-first-order rate constants were obtained from the slope of the appropriate graph[4] with numerical values computed by the method of least squares.

Each rate constant listed in Tables I, III, and IV is the average of two to five runs. Average deviation from the mean is less than 4.5%. Temperature control was ±0.1 °C. Initial hydroxamic acid concentrations were 0.01 M.

Registry No.—2-Methyl-*N*-methylbenzohydroxamic acid, 24962-87-6; 4-methyl-*N*-methylbenzohydroxamic acid, 1613-85-0; benzohydroxamic acid, 495-18-1; 2-chloro-*N*-methylbenzohydroxamic acid, 59686-63-4.

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Base-Catalyzed Hydration of α,β-Unsaturated Ketones

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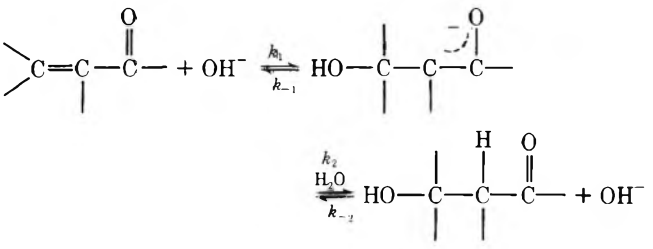
Homologues of 3-buten-2-one hydrate in dilute aqueous base to produce aldols, which in some cases undergo retro aldol condensation under the hydration conditions. Hydration of 3-buten-2-one proceeds with rate-controlling attack of hydroxide ion on C_4, $k_{H_2O}/k_{D_2O} = 0.6$, $\Delta H^{\ddagger} = 13.6$ kcal mol^{-1}, and $\Delta S^{\ddagger} = -30.1$ eu. Hydration of 4-methyl-3-penten-2-one is 10^{-2} as fast and proceeds via rate-controlling proton transfer from water to C_3 of the enolate ion formed by attack of hydroxide ion at C_4 of the substrate, $k_{H_2O}/k_{D_2O} = 1.1$, $\Delta H^{\ddagger} = 15.2$ kcal mol^{-1}, and $\Delta S^{\ddagger} = -25.6$ eu. Rates of hydration, dehydration, and retroaldol condensation were competitive for 3-penten-2-one and were calculated to be 7.6×10^{-3}, 2.3×10^{-3}, and 1.6×10^{-4} M^{-1} s^{-1}, respectively, at 40 °C. Equilibrium ratios calculated for the dehydration of aldols, [alkenone]/[aldol], show that dehydration is thermodynamically unfavorable for aldol condensation products of aliphatic aldehydes and ketones; kinetic measurements show the rate of dehydration to be comparable to or faster than the aldol condensation in many of these cases. Thus self-condensation of acetone (using a Soxhlet extractor) leads to the aldol product rather than the dehydration product for thermodynamic rather than kinetic reasons.

The acid-catalyzed hydration of α,β-unsaturated carbonyl compounds has received considerable study in recent years.[1-5] For a variety of aliphatic 3-alken-2-ones the hydration proceeds via a 1,4 addition of water to the conjugated C=C–C=O system followed by rate-controlling proton transfer to the enol thus formed. The hydration is characterized by a large solvent isotope effect (indicative of a primary isotope effect) and a large negative entropy (indicative of the covalent binding of a solvent molecule to the substrate prior to the rate-controlling step). The change in rate with acidity shows the carbonyl group to be significantly protonated in acidities beyond 4–6 M $HClO_4$.[5] The pK_a's of several α,β-unsaturated compounds have been measured recently and found to be adequately described by the Bunnett–Olson treatment.[6]

Studies of base-catalyzed hydrations are rare; apparently there are only two previous reports of base-catalyzed addition of water to α,β-unsaturated carbonyl systems. Fedor

shown that 4-aryloxy-3-buten-2-ones hydrate in base via rate-controlling attack of hydroxide ion (Michael addition). This hydration is characterized by very small substituent effects ($\rho = 0.1$) and solvent isotope effects ($k_{H_2O}/k_{D_2O} = 0.94$). In a more limited study, Vik[7] has shown propenals to be hydrated in base with a large negative entropy of activation. Base-catalyzed hydration is thus seen to be a two-step process formally resembling a Michael addition (Scheme I).

Scheme I



The above results form a basis for reporting a study of the base-catalyzed hydration of the same 3-alken-2-ones for which the acid-catalyzed mechanism has been elucidated.[5] Of particular interest is determination of the rate-controlling step (k_1 or k_2) and elucidation of factors leading to a change in rate-determining step.

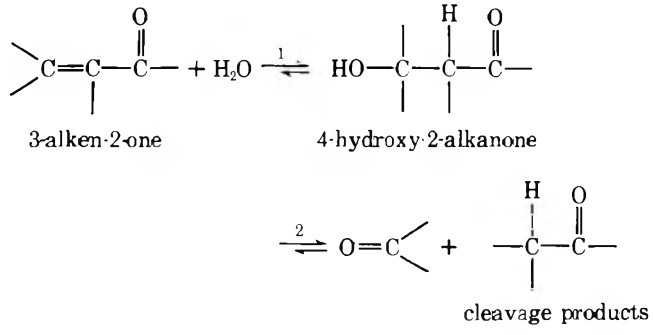
Experimental Section

All substrates were obtained from Aldrich Chemical Co. and were molecularly distilled just prior to each kinetic run. The general kinetic method (including calculation of rate constants for reversible reactions and calculation of activation parameters) was that described earlier.[8] Sodium deuterioxide solutions were made by diluting a 40% sodium deuterioxide solution (99% D, Stohler Isotope Chemicals) with deuterium oxide (99.8% D_2O, Stohler Isotope Chemicals).

Results

The reactions observed are reversible and at equilibrium the concentration of 3-alken-2-one is low (Scheme II).

Scheme II



3-alken-2-one 4-hydroxy-2-alkanone

cleavage products

Pseudo-first-order rate constants were measured spectrophotometrically in the traditional manner.[8]

Equilibrium ratios for step 1, [4-hydroxy-2-alkanone]/[3-alken-2-one], are known to be large from the earlier studies in acid solution.[5] Ratios vary from 3 to 20 depending on substrate and temperature (though exact comparisons cannot be made because of medium and acidity effects introduced by the rather concentrated acid solution required for acid-catalyzed hydration to occur at a convenient rate).[5] Equilibrium ratios for step 2, [cleavage products][2]/[4-hydroxy-2-alkanone], are also known to be large. For example, the equilibrium
for benzaldehyde + acetone and 10^4 for acetone +
.ge products identified). Because of (a) the
ıtration term in the numerator of the equilib-
step 2, (b) the low substrate concentration
l, 10^{-4} M), and (c) the large magnitude of the
ratios for steps 1 and 2, the overall equilibrium
in Scheme II lies almost totally (99.9%) to the right *when* the reverse aldol reaction (step 2) is kinetically important.

Experimentally, then, the observation is that about 5–10% of the reactant remains at equilibrium (similar to the acid-catalyzed hydration) for those cases where the reverse aldol condensation is not kinetically important whereas *no* reactant remains when it *is* kinetically important. Thus the conclusion is that reversible base-catalyzed hydration (step 1) occurs with 3-buten-2-one and 3-methyl-3-buten-2-one whereas a reverse aldol condensation (step 2) is predominant in determining the products of hydration of 4-methyl-3-penten-2-one. For 3-penten-2-one the two processes (steps 1 and 2) are competitive. The kinetic observations are a smooth pseudo-first-order *partial* disappearance of 3-buten-2-one and 3-methyl-3-buten-2-one, a smooth pseudo-first-order *total* disappearance of 4-methyl-3-penten-2-one, and a biphasic pseudo-first-order total disappearance of 3-penten-2-one.

Thus

$$k_{obsd} = k_{hyd} + k_{dehyd}$$

for 3-buten-2-one and 3-methyl-3-buten-2-one (1)

$$k_{obsd} = k_{hyd}$$

for 4-methyl-3-penten-2-one (2)

As eq 1 and 2 show, incursion of the reverse aldol condensation actually simplifies the measurement of rate of hydration by "draining off" the hydration product as formed.

Sorting out the experimental rate expression for hydration of 3-penten-2-one is somewhat more complex because of the biphasic nature of the rate plot. Early in the reaction (prior to attainment of steady-state concentration levels), the rate constant measured is essentially that expressed by eq 1 above. For the latter portion of the reaction, however, steady-state conditions apply and the appropriate rate expression is given by eq 3 (where k_2 is the rate constant for the reverse aldol condensation, step 2 of Scheme II).

$$k_{obsd} = \frac{k_{hyd}k_2}{k_{dehyd} + k_2} \quad (3)$$

All of the rate constants in eq 3 are calculable: k_{obsd} and $k_{hyd} + k_{dehyd}$ are measured experimentally; k_{hyd} and k_{dehyd} can be calculated from $k_{hyd} + k_{dehyd}$ and the equilibrium ratio. (Equilibrium ratio = k_{hyd}/k_{dehyd} and was measured in the acid-catalyzed hydration study;[5] since the position of an equilibrium is independent of pathway, equilibrium ratios for acid- and base-catalyzed hydrations should be equal.) Thus for 3-penten-2-one in 0.10 N NaOH at 40 °C, $k_{obsd} = 5.0 \times 10^{-5}\ s^{-1}$, $k_{hyd} = 7.6 \times 10^{-4}\ s^{-1}$, $k_{dehyd} = 2.3 \times 10^{-4}\ s^{-1}$, $k_2 = 1.6 \times 10^{-5}\ s^{-1}$. The value of k_{dehyd} is probably smaller than calculated because of the medium effect on the measured equilibrium ratio; i.e., $k_{hyd}/k_{dehyd} = 3.35$ at 40 °C in 1.05 M $HClO_4$ but the ratio *increases* as acidity *decreases* (a medium effect).[5] The net conclusion is that k_{dehyd} and k_2 are of the same order of magnitude; however, k_{dehyd} *is* slightly the larger.

Subsequent discussion is based on values of k_{hyd} (Tables I and II) calculated from k_{obsd} using eq 1–5, as appropriate.

$$\frac{[\text{4-hydroxy-2-alkanone}]}{[\text{3-alken-2-one}]} = \frac{A_0 - A_e}{A_e} \quad (4)$$

[4-hydroxy-2-alkanone] = molarity of the hydration product at equilibrium; [3-alken-2-one] = molarity of the reactant at equilibrium; A_0 = absorbance at time zero (i.e., upon mixing); A_e = absorbance at equilibrium (i.e., at time "infinity").

$$\frac{[\text{4-hydroxy-2-alkanone}]}{[\text{3-alken-2-one}]} = \frac{k_{hyd}}{k_{dehyd}} \quad (5)$$

Table I. Values of k_{obsd} and k_{hyd} in Aqueous NaOH Solution[a]

N_{NaOH}	Temp, °C	$10^4 k_{obsd} = 10^4 k_{hyd}$
	3-Buten-2-one[b]	
0.010	30	2.67 (4.43)
	40	5.71 (9.4)
	50	11.5 (20.6)
	60	35.5
0.10	30	27.2 (48.4)
	4-Methyl-3-penten-2-one[c]	
0.50	50	4.43
1.00	40	3.87 (3.54)
	50	8.91 (7.18)
	60	17.9 (14.7)

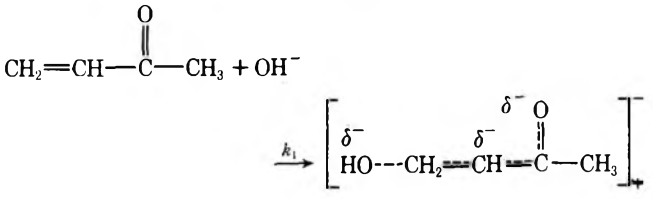
[a] Means of replicate determinations, average deviations from mean values ≤±3%. Values in parentheses are for NaOD/D_2O solutions. [b] Followed at 220 nm. Equilibrium ratios (eq 4 and 5) are sufficiently large so that k_{obsd} and k_{hyd} are not meaningfully distinguishable. [c] Followed at 250 nm. See discussion of eq 2.

k_{hyd} = rate constant for step 1 (forward), Scheme II; k_{dehyd} = rate constant for step 1 (reverse), Scheme II.

Discussion

Hydration. The mechanism described by Scheme I is consistent with our data; either step may be rate controlling depending on substrate structure. The solvent isotope effect (k_{H_2O}/k_{D_2O} = 0.6) for the hydration of 3-buten-2-one indicates rate-controlling attack of hydroxide ion; the solvent isotope effect (k_{H_2O}/k_{D_2O} = 1.2) for the hydration of 4-methyl-3-penten-2-one indicates rate-controlling proton transfer from water to the enolate ion. The kinetically important step in the hydration of 3-buten-2-one is formally similar to a nucleophilic substitution reaction at carbon, as illustrated in Scheme III.

Scheme III



Dependent on transition state structure, Bunton and Shiner[10] have calculated a solvent isotope effect of 0.54–0.88. A value of 0.6 indicates maximum C–OH covalent interaction consistent with minimal negative charge on the incipient enolate oxygen. That is, the transition state is neither very "early" nor very "late". Although a solvent isotope effect of 0.6 for this general type of reaction appears to be the smallest yet observed, Pocker[11] reported a value of 0.67 for rate-controlling attack of hydroxide on the carbonyl carbon of 2-pyridinecarboxaldehyde; Jones[12] reported 0.75 for rate-controlling attack of hydroxide on the carbonyl carbon of ethyl acetate; Long[13] reported 0.86 for the SN2 reaction of hydroxide with an alkyl sulfonic ester.

The kinetically important steps in the hydration of 4-methyl-3-penten-2-one give rise to a solvent isotope effect composed of secondary *and* primary effects, as illustrated in Scheme IV.

A Bunton–Shiner[10] calculation of the expected solvent isotope effect on the first step of Scheme IV (an equilibrium) yields k_{H_2O}/k_{D_2O} = 0.76, requiring a small isotope effect on the second step of about 1.6. Using the Bunton–Shiner procedure again on step 2 of Scheme IV produces a primary isotope effect of 2.3.[14] Though somewhat smaller than expected for such a proton transfer,[16] the value is reasonable considering the extended calculation required to produce it.

Table II. Values of k_{obsd} Equilibrium Ratios, and k_{hyd} in Aqueous NaOH Solution[a]

N_{NaOH}	Temp, °C	$10^4 k_{obsd}$	[4-hydroxy-2-alkanone]/[3-alken-2-one]	$10^4 k_{hyd}$
	3-Methyl-3-penten-2-one			
0.75	50	2.08	4.7	1.77
	60	3.80	9.0	3.40
	70	7.23	9.3	6.53
	80	13.6	12.7	12.0
0.50	40	1.94	6.6	1.68
	50	3.85	10.1	3.51
	60	7.80	7.0	6.83
1.00	30	1.88	13.5	1.75
	40	3.26	10.2	2.97
	50	7.72	9.4	7.01
	3-Penten-2-one[c]			
0.10	40	0.50		9.5
	50	1.1		21

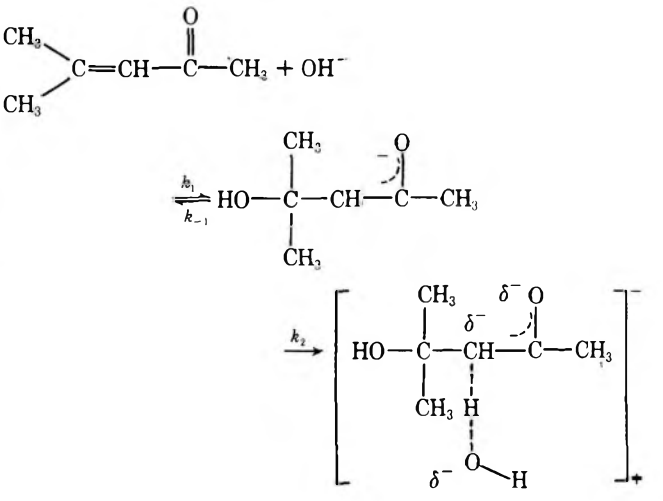
[a] Means of replicate determinations; average deviations from mean value ≤±5%. [b] Followed at 240 nm. See eq 1, 4, and 5 for method of calculation. [c] Followed at 230 nm. See eq 1, 3, 4, and 5 discussion.

Table III. Activation Parameters for Base-Catalyzed Hydration of Alkenones[a]

Reactant	N_{NaOH}	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
3-Buten-2-one	0.010	13.6 ± 0.1	−30.1 ± 0.2
4-Methyl-3-penten-2-one	1.00	15.2 ± 0.5	−25.6 ± 1.6
3-Methyl-3-penten-2-one	0.25	13.8 ± 0.1	−33.1 ± 0.4
	0.50	13.9 ± 0.2	−31.5 ± 0.5

[a] Values calculated at 25 °C, ± standard deviation. Enthalpy and entropy of activation were calculated by a least-squares treatment of data in Tables I and II. Calculations were carried out on a CDC 3150 computer.

Scheme IV



The change in rate-controlling step arises because of rather different effects on k_{-1} (Schemes I and IV) with substrate structural changes: k_{-1} is the rate constant for a process which may have many of the features of an SN1 reaction and thus when the leaving group (OH) is located on a tertiary carbon (4-methyl-3-penten-2-one), k_{-1} is much larger than when the leaving group is on a primary carbon (3-buten-2-one). An alternate picture of this process produces the same conclusion: the k_{-1} process produces an alkene and thus the most highly

Table IV. Solvent Isotope Effects for Base-Catalyzed Hydration of Alkenones

Reactant	$N_{NaOH} = N_{NaOD}$	Temp, °C	k_{H_2O}/k_{D_2O}
3-Buten-2-one	0.010	30	0.60
	0.010	40	0.61
	0.010	50	0.56
	0.10	30	0.56
4-Methyl-3-penten-2-one	1.00	40	1.1
	1.00	50	1.2
	1.00	60	1.2

Table V. Equilibrium Ratios for Dehydration of Aldols at Room Temperature[a]

Registry no.	Aldol	[alkenone]/[aldol]
590-90-9	$HOCH_2CH_2\overset{O}{\overset{\|\|}{C}}CH_3$	0.05
4161-60-8	$CH_3\overset{OH}{\overset{\|}{C}}HCH_2\overset{O}{\overset{\|\|}{C}}CH_3$[b]	0.25[5]
123-42-2	$(CH_3)_2\overset{OH}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|\|}{C}}CH_3$[b]	0.11,[5] 0.06[9]
565-79-7	$CH_3\overset{OH}{\overset{\|}{C}}H-\overset{CH_3}{\overset{\|}{C}}H-\overset{O}{\overset{\|\|}{C}}CH_3$	0.07
2134-29-4	$HOCH_2CH_2CHO$	0.1[7]
38433-80-6	$HOCH_2\overset{CH_3}{\overset{\|}{C}}HCHO$	14[7]
107-89-1	$CH_3\overset{OH}{\overset{\|}{C}}HCH_2CHO$	25[7]
59434-71-8	$CH_3CH_2\overset{OH}{\overset{\|}{C}}HCH_2CHO$	50[7]
5381-93-1	$Ph\overset{OH}{\overset{\|}{C}}HCH_2\overset{O}{\overset{\|\|}{C}}CH_3$	40[9]

[a] Last five entries measured at 25 °C, others at 30 °C. Ratios increase with increasing temperature. [b] Values taken from ref 5 in 2.57 M $HClO_4$ and thus incorporate a medium effect.

substituted (most stable) alkene is produced fastest.[18] The second step in Schemes I and IV, proton transfer from water to enolate ion (k_2 process), is much less sensitive to changes in structure at C_4 since this step of the reaction involves changes only at the incipient carbonyl group (C_2) and the carbon α to it (C_3). That is, k_2 for 3-buten-2-one and 4-methyl-3-penten-2-one are similar in magnitude. Thus for 3-buten-2-one $k_2 > k_{-1}$ whereas for 4-methyl-3-penten-2-one $k_2 < k_{-1}$. Other studies[4,7] have rather implicitly assumed $k_2 > k_{-1}$ (i.e., k_1 rate controlling) but it is not possible to establish the rate-controlling step apart from determination of the solvent isotope effect, since relative rates and activation parameters are inconclusive (Tables I–III).

Dehydration in the Aldol Condensation. It is widely recognized that the aldol condensation is synthetically useful for self-condensation of aldehydes or in those cases when a favorable equilibrium can be established by converting the aldol product to another; commonly dehydration of the aldol is convenient.[19] However, values of equilibrium constants for the dehydration process are scarce. Table V lists equilibrium ratios, [alkenone]/[aldol], for a variety of unsaturated aldehydes and ketones in aqueous solution. Of course these ratios are temperature and solvent dependent, but for the cases given in Table V equilibrium ratios increase somewhat with increasing temperature (i.e., raising the temperature favors dehydration). For condensation of aliphatic aldehydes and ketones with acetones, dehydration is thermodynamically unfavorable in aqueous solution. Dehydration of 4-hydroxy-2-pentanone, 4-methyl-4-hydroxy-2-pentanone,[9] and 4-phenyl-4-hydroxy-2-butanone[9] occurs faster than condensation of the respective aldehydes and ketones, but only for the latter case is the dehydration/hydration equilibrium favorable.

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Registry No.—3-Buten-2-one, 78-94-4; 4-methyl-3-penten-2-one, 141-79-7; 3-methyl-3-penten-2-one, 565-62-8; 3-penten-2-one, 625-33-2.

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(16) Proton transfer from acetic acid to methylacetylacetonate produces a primary isotope effect of 4.3; the difference in basicity between acetate (pK_b 9.3) and methyl acetylacetonate (pK_b 4.7) is comparable to that between hydroxide ion (pK_b 15.7) and enolate ion (pK_b 20).[10,15]
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(18) The reverse of Scheme I is an E1cB process and thus k_{-1} is dependent on the alkene nature of the transition state.[17]
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Preparation of Vinylketene by 1,4-Elimination. Cycloaddition and Isomerization to Form α-Ethylidenecyclobutanones[1,2]

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Vinylketene (1) was shown to result from triethylamine initiated 1,4-dehydrochlorination of *trans*-2-butenoyl chloride. In the presence of 1,3-cyclopentadiene a $_{\pi}2 + _{\pi}2$ cycloaddition occurred to form adduct **2**. With a trace of excess triethylamine **2** isomerized chiefly to a 73:27 mixture of the *E* and *Z* isomers **3** and **4**, whose structures were securely assigned using lanthanide induced shift nuclear magnetic resonance techniques. The possible participation of ethylideneketene ($CH_3CH{=}C{=}C{=}O$) was judged remote since triethylamine, 3-butenoyl chloride, and 1,3-cyclopentadiene gave an identical reaction mixture. With either isomeric acid chloride if less than 1.0 molar equiv of triethylamine was used a 60:01:39 mixture of **2**:**3**:**4** was formed, which upon addition of triethylamine equilibrated to the 73:27 mixture of **3** and **4**.

Ketenes ($RR'C{=}C{=}O$) react with conjugated dienes in a highly perispecific and regiospecific manner to form 3-vinylcyclobutanones.[4] Since the olefinic component reacts suprafacially, the fusion geometry is consistently cis. When the two ketene substituents differ in steric bulk the larger one tends to assume the more hindered position in the product.[5,6] Ketene cycloadditions represent one of the few synthetic approaches to four-membered rings,[7] and also serve as sensitive mechanistic probes of the rare and difficult $_{\pi}2_s + _{\pi}2_a$ allowed concerted[8] pathway. A review of the available evidence[4] and recent theoretical analyses[9,10] indicate that both concerted and nonconcerted routes may be traversed, depending on the steric and electronic characteristics of ketene and ketenophile.

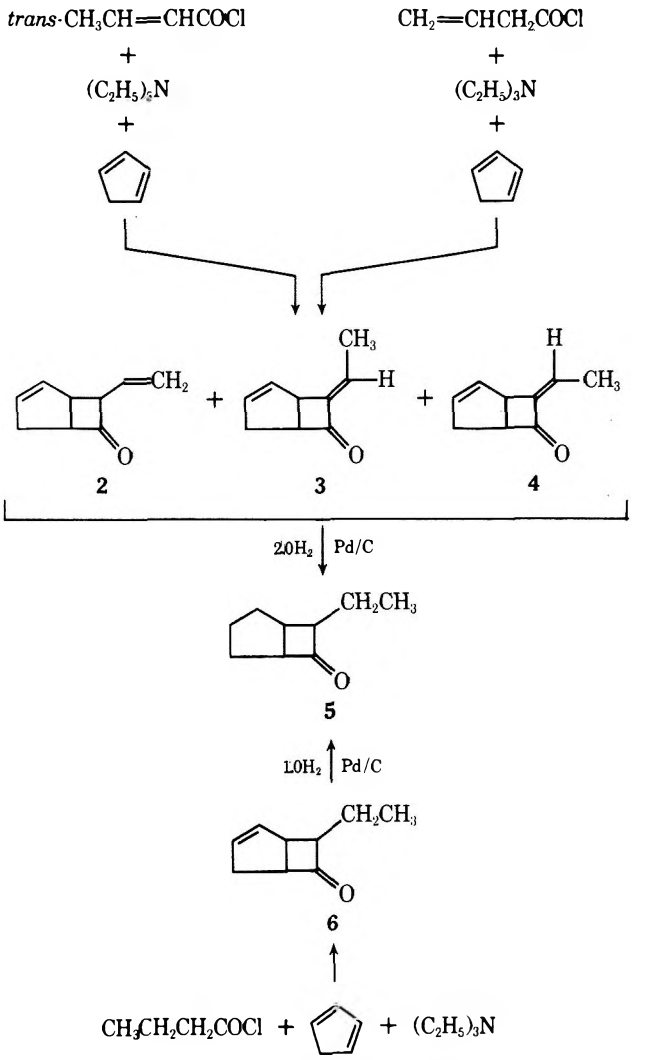
It is, therefore, of considerable synthetic importance and mechanistic interest to explore further the scope and nature of the ketene cycloaddition reaction. One approach is to study the reactions of especially unstable ketenes, such as the vinylketenes[11] and the alkylideneketenes ($RR'C{=}C{=}C{=}O$)[12,13] in which an additional carbon–carbon double bond is conjugated or cumulated with the ketene moiety. Although alkylideneketenes have been proposed as possible intermediates in the Einhorn reaction of α,β-unsaturated acid chlorides,[14–16] and may have been formed by dehydrochlorination of 3-methyl-2-butenoyl chloride,[17] the only unambiguous preparations involve photochemical[13] or flash vacuum pyrolytic[12] methods. Even with these techniques the simpler members of the class, such as the parent methyleneketene ($CH_2{=}C{=}C{=}O$) and ethylideneketene ($CH_3CH{=}C{=}C{=}O$), have not been detected.

We wish to describe our results involving a simple in situ preparation and subsequent cycloaddition of vinylketene (**1**), which acts as an ethylideneketene surrogate to afford cyclobutanones conveniently functionalized at the α position.

Results

When *trans*-2-butenoyl chloride was treated with 0.95 molar equiv of dry triethylamine in the presence of 6.0 molar equiv of 1,3-cyclopentadiene and worked up after 3 h a product mixture of 60% 7-vinylbicyclo[3.2.0]hept-2-en-6-one (**2**),[18] 1% (*E*)-7-ethylidenebicyclo[3.2.0]hept-2-en-6-one (**3**), and 39% (*Z*)-7-ethylidenebicyclo[3.2.0]hept-2-en-6-one (**4**) resulted (Scheme I). The adduct isomer **2** could be detected by NMR or rapid analytical vapor phase chromatography (VPC) at temperatures below 100 °C, but could not be isolated by preparative VPC since at temperatures above 100 °C or with long retention times it suffered apparent cycloreversion.[19] The entire adduct mixture, after purification by distillation in vacuo (yield 41%), took up 1.9 ± 0.1 molar equiv of H_2 over Pd/C to form only *endo*- and *exo*-7-ethylbicyclo[3.2.0]heptan-6-one (**5**), identified by independent synthesis (hydrogenation of the adducts of ethylketene and 1,3-cyclopentadiene; see Experimental Section).

Scheme I



The cycloaddition procedure was repeated with 3-butenoyl chloride replacing *trans*-2-butenoyl chloride and an identical adduct mixture was isolated (Scheme I).

When a trace of triethylamine was added to the above adduct mixtures before workup, equilibration occurred to give, ultimately, a mixture of 0.4% **2**, 63.7% **3**, 24.0% **4**, and two unidentified components (A, B). This isomerization is quite

complex, and we have not investigated it completely. The rate of equilibration seems to depend on surface effects, as well as the solvent and the particular equilibration catalyst present. We have established, however, that in pentane at 25 °C in the presence of triethylamine adduct **2** disappears very rapidly (half-life < 30 min) to form chiefly **4** with some **3** present.[22] The composition of this mixture continues to change for about 7 days, at the end of which time the 3:4 ratio has reached the equilibrium value of 72.6 ± 0.1:27.4 ± 0.1 (K_{eq} = 0.38, ΔG_{25} = +0.58 kcal/mol).

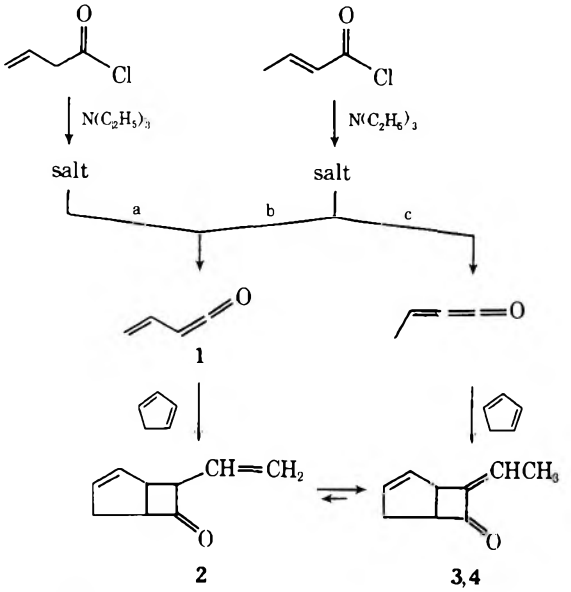
When a trace of triethylamine was added to pentane solutions of VPC-purified samples of **3** or **4** (vide infra) isomerization occurred at room temperature within 7 days to afford the same equilibrium mixture of the five components (**2, 3, 4,** A, B). When the entire cycloaddition was carried out beginning with either isomeric acid chloride and 1.05 molar equiv of triethylamine the relative amount of **2** in the mixture decreased with increasing reaction time. Delaying workup for 1 week or more (not an uncommon procedure with ketene cycloadditions[23]) again provided the equilibrium mixture.

Isomeric adducts **3** and **4** were obtained in >98% purity by preparative vpc; each gave an acceptable C, H analysis and each took up 2.0 ± 0.1 molar equiv of H_2 over Pd/C to give **5**. Mass, infrared (ir), nuclear magnetic resonance (NMR), and ultraviolet (uv) spectra confirmed the gross structural features of **3** and **4**. Lanthanide induced shift (LIS) NMR using a serial doping technique[24] and plots of shifts vs. added lanthanide reagents for H_8 and methyl (Table I) served to assign the exocyclic double bond geometry. It is noteworthy that these LIS–NMR studies support earlier assignments of double-bond geometry of α-ethylidene ketones made by comparisons of chemical shift data alone.[25,26]

Discussion

Although both mechanistic pathways b and c shown in Scheme II could operate when *trans*-2-butenoyl chloride

Scheme II

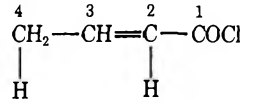


reacts with triethylamine and 1,3-cyclopentadiene, since the equilibrium between adduct **2** and the **3, 4** pair lies almost entirely toward the conjugated species[27] the ethylideneketene route c can at most be minor. Actually, no unambiguous evidence implicating the presence of this elusive alkylideneketene has been found in this work, and the evident failure to prepare it by flash-vacuum pyrolysis (a method successful for other alkylideneketenes)[12] indicates that its participation here is unlikely. All of our data are most economically explained as illustrated by routes b and c in which both *trans*-2- and -3-butenoyl chlorides react with triethylamine to form (presumably different) acylammonium salts,[29] which decompose by 1,4- and 1,2-elimination, respectively, to afford vinylketene (**1**). This species is trapped by 1,3-cyclopentadiene as adduct **2**, which subsequently provides **3** and **4** by isomerization.

Table I. NMR Chemical Shift Values for Ketones 3 and 4 Doped with Successive Amounts of Eu(fod)$_3$

Ratio of ketone:Eu(fod)$_3$	Ketone 3		Ketone 4	
	H_8	CH_3	H_8	CH_3
No doping	6.23	1.81	5.60	2.05
161.04:1.00	6.25	1.81	5.60	2.08
53.68:1.00	6.36	1.86	5.63	2.15
23.01:1.00	6.52	1.93	5.67	2.27
10.74:1.00	6.86	2.06	5.77	2.52
4.42:1.00	7.70	2.41	6.01	3.13

This view is supported by CNDO/2 charge density calculations for 2-butenoyl chloride,[33] which confirm the intuitive view of a much higher acidity for H_4 (lost in 1,4-elimination → vinylketene) than for H_2 (lost in 1,2-elimination → ethylideneketene):



CNDO/2 charge density + 0.0629 + 0.0306

We have devised no control experiment which can rule out the formal possibility that triethylamine catalyzes the equilibration of 3-butenoyl chloride and 2-butenoyl chloride prior to acylammonium salt formation. The known facility of the latter reaction, however,[29-32] and the slow isomerization of the corresponding esters[22] makes it a relatively unlikely mechanistic alternative.

In any case, owing to the facile isomerization subsequent to cycloaddition, vinylketene has been shown to be an effective ethylideneketene surrogate. When the reaction is carried out in the normal manner only adducts **3** and **4** are isolated. This reaction seems of some potential value, since (1) 1,4-dehydrochlorination of *trans*-2-butenoyl chloride represents a straightforward and economical route to vinylketene; and (2) cyclobutanones functionalized at the α carbon are obtained in moderate yields. Baeyer–Villager oxidation of species like **3** and **4** might provide a favorable synthetic approach to close analogues of α-methylene-γ-lactones,[34] some of which show antitumor activity.[35]

Experimental Section

Elemental analyses were performed by Ms. Ruby Ju of the University of New Mexico. Melting points are uncorrected. Mass spectra were measured[36] on a Du Pont Model 21-491 double focusing instrument at an ionizing voltage of 70 eV. Infrared (ir) spectra were recorded as thin films between NaCl plates on Perkin-Elmer 237, 337, or 521 spectrophotometers; all recorded absorptions were corrected by reference to polystyrene bands in the appropriate spectral regions. Nuclear magnetic resonance (NMR) spectra were obtained on Varian T-60, EM-360, or A-60 instruments. Ultraviolet (uv) measurements were made with a Perkin-Elmer Model 402 spectrophotometer. Preparative VPC separations were obtained with a Varian Aerograph Model 920 instrument equipped with a thermal conductivity detector with helium as the carrier gas. Analytical VPC determinations were measured using a Hewlett-Packard Model 5750 gas chromatograph equipped with flame ionization detector with nitrogen as the carrier gas. Quantitative VPC analyses resulted from automatic integration of peak areas by a Varian digital integrator Model 480 and calibration of detector response factors from known mixtures.[37,38] The VPC columns used are identified as column A, 10 ft × 0.25 in. 10% FFAP on 60–80 Chromosorb W; column B, 5 ft × 0.125 in. 4% FFAP on 100–120 Chromosorb P (AW, DMCS).

Analytical hydrogenations were carried out in ethyl acetate solutions over prereduced 10% Pd/C at atmospheric pressure. The volume H_2 adsorbed was compared with a control determination for cyclohexene + 1.0 H_2 → cyclohexane measured the same day. Thus for a typical determination 0.0408 g (4.967×10^{-4} mol) of cyclohexene adsorbed 13.40 ml of H_2. Immediately afterward 0.0318 g (2.370×10^{-4} mol) of VPC-purified **4** took up 13.35 ml of H_2. Adduct **4** thus has (4.967)(12.35)/(2.370)(13.40) = 1.93 double bonds. Repetitive determinations established a reproducibility estimated as ±0.1 double bond.

Reactions of *trans*-2-Butenoyl Chloride with Excess Triethylamine. Preparation of (*E*)-7-Ethylidenebicyclo[3.2.0]hept-2-en-6-one (3) and (*Z*)-7-Ethylidenebicyclo[3.2.0]hept-2-en-6-one (4). Under anhydrous conditions a solution of 15.25 g (0.15 mol) of dry (over KOH) triethylamine in 100 ml of low-boiling petroleum ether was added dropwise to a well-stirred mixture of 15.00 g (0.14 mol) of *trans*-2-butenoyl chloride, 57.11 g (0.86 mol) of freshly dedimerized 1,3-cyclopentadiene, and 600 ml of dry petroleum ether. Immediate formation of white solid was evident; the addition required 1.5 h, at the end of which time the mixture was brown in color and contained much solid. Stirring was continued for another 1.5 h, and the reaction mixture then sealed and allowed to stand at room temperature for 7 days. At the end of the time VPC analysis (column B, 95 °C) of the supernatant liquid showed (besides solvent and dicyclopentadiene) five components in the area ratio (order of elution times) 1.37:1.67:23.70:63.90:10.00.

Suction filtration afforded 9.1 g (46%) of triethylamine hydrochloride (mp 253–255 °C). The filtrate was washed with water, dried over $MgSO_4$, and concentrated to a brown oil by rotary evaporation. Distillation in vacuo resulted first in a large fraction of dicyclopentadiene and a second fraction of a pale yellow oil, 7.85 g (41%), bp 45–46 °C (0.1 mm). VPC analysis showed a small amount of dicyclopentadiene and the five components previously noted (area ratios essentially unchanged).

Preparative VPC (column A, 133 °C) resulted in isolation of the two major (third and fourth eluting) components in pure (>98% upon reinjection on column B) form. These were identified, respectively, as adducts **4** and **3** as described below. The second-eluting minor component had VPC retention time identical with adduct **2**, later identified by spectral analysis of an enriched mixture. The other two minor products remain unidentified.

(*Z*)-7-Ethylidenebicyclo[3.2.0]hept-2-en-6-one (4). The third-eluting component, which constituted 23.7% of the mixture, was assigned structure **4**: mass spectrum *m/e* (rel intensity) 134 (32), 106 (13), 105 (15), 91 (41), 69 (16), 68 (11), 66 (100), 65 (14), 51 (13), 41 (17), 40 (17), 39 (28); ir 3060, 2940, 2860, 1741, 1661, 1605, 1440, 1170, 1047, 896, 776, 741, 695 cm^{-1}; NMR (0.0392 g in 350 μl of $CDCl_3$) δ 5.8, m, 2 H (H_2, H_3); 5.60, q (J = 7 Hz) further split into a d (J = 1.5 Hz), 1 H (H_8); 3.8, m, 2 H; 2.6, m, 2 H; 2.05, d of d (J = 7.0, 1.5 Hz), 3 H ($-CH_3$). LIS NMR: to the above solution was added aliquots of a $CDCl_3$ solution of 0.0680 g (0.066 mmol) of Eu(fod)$_3$.[39] After each addition the NMR spectrum was run. Table I presents the chemical shifts of H_8 and $-CH_3$ as a function of the increasing Eu(fod)$_3$ concentration. The Δδ values extrapolated to a 1:1 molar ratio of **4**: Eu(fod)$_3$ are H_8 = 106 Hz, $-CH_3$ = 288 Hz. Taken with the complementary results of the other isomer these are sufficient to assign isomer **4** the *Z* configuration about the exocyclic double bond. Uv (95% ethanol) 209 nm (log ε 3.32), 238 (3.36).[40]

Reduction to 5. VPC-purified **4** (0.0318 g) took up 12.35 ml of H_2, thus having 1.9 ± 0.1 double bond. A larger sample of 0.40 g was hydrogenated in a Parr apparatus at 50 psi. After removal of the catalyst by suction filtration through sintered glass and concentration by rotary evaporation the residual oil showed by analytical VPC (column B, 135 °C) two components in a ratio (order of elution time) of 28.9:71.1. These were isolated by preparative VPC (column A, 130 °C) and had ir and NMR spectra congruent, respectively, with *exo*- and *endo*-7-ethylbicyclo[3.2.0]heptan-6-one (**5**), prepared and identified as described below.

Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.30; H, 7.43.

(*E*)-7-Ethylidenebicyclo[3.2.0]hept-2-en-6-one (3). The fourth-eluting component, which constituted 63.29% of the mixture, was assigned structure **3**: mass spectrum *m/e* (rel intensity) 134 (28), 106 (11), 105 (12), 91 (35), 78 (10), 69 (9), 68 (9), 67 (8), 66 (100), 65 (11), 51 (10), 41 (13), 40 (16), 39 (23); ir 3030, 2930, 2860, 1745, 1668, 1605, 1442, 1171, 1075, 793, 735, 690 cm^{-1}; NMR (0.0395 g in 350 μl of $CDCl_3$) δ 6.23, q (J = 7 Hz) further split into a doublet (J = 1.0 Hz), 1 H (H_8); 5.8, m, 2 H (H_2, H_3); 3.7, m, 2 H; 2.6, m, 2 H; 1.81, d of d (J = 7, 1.0 Hz), 3 H (CH_3). LIS NMR: sequential addition of a $CDCl_3$ solution of Eu(fod)$_3$[39] and spectral measurements were made as described above for isomer **4**. The results, presented in Table I, give shifts extrapolated to a 1:1 molar ratio of H_8 = 398 Hz, $-CH_3$ = 158 Hz. Taken with the complementary results of the other isomer these assign for adduct **3** the *E* configuration about the exocyclic double bond. Uv 223 nm (log ε 4.10).

Reduction to 5. VPC-purified **3** (0.0297 g, 2.214×10^{-4} mol) took up 12.10 ml of H_2, thus having 2.03 ± 0.1 double bond. A larger sample of 0.40 g was hydrogenated in a Parr apparatus at 50 psi. After removal of the catalyst by suction filtration through sintered glass and concentration by rotary evaporation the residual oil showed by analytical VPC (column B, 135 °C) two components in a ratio of 29.1:70.9. These were isolated by preparative VPC (column A, 130 °C) and had ir and NMR spectra congruent, respectively, with *exo*-**5** and *endo*-**5**, prepared and identified as described below.

Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.50; H, 7.64.

Reaction of *trans*-2-Butenoyl Chloride with Insufficient Triethylamine. Identification of 7-Vinylbicyclo[3.2.0]hept-2-en-6-one (2) in the Product Mixture. The reaction was carried out as described above except that 13.84 g (0.134 mol) of triethylamine was used, and workup was commenced after 3.0 h. Only 7.4 g (37%) of triethylamine hydrochloride (mp 252–254 °C) was obtained, and distillation afforded 2.5 g (13%) of pale yellow oil, bp 46–50 °C (0.1 mm). VPC (column B, 95 °C) showed evidence of some thermal decomposition (peak coincident with separately injected cyclopentadiene, polymer formation in injector sleeve), but eluted three components in the area ratio (order of elution times) 59.8:1.1:39.1. These corresponded (comparison of retention times) with the second-, third-, and fourth-eluting components, respectively, from the excess triethylamine cycloaddition. All attempts to isolate the major component of this mixture resulted either in irreversible cycloreversion (preparative VPC) or isomerization to **3** and **4** (column, thin layer, and high-pressure liquid chromatography). The identification of the first-eluting component as vinylketene adduct **2** was deduced from the following evidence. Ir: besides bands assigned previously to compound **4** there appeared absorptions at 1770, 1645, 970, and 930 cm^{-1}. NMR ($CDCl_3$): compatible with a 60:40 mixture of **2**:**4**. Subtracting the contributions of **4** the difference spectrum of **2** is δ 6.3, m, 1 H; 5.8, m, 2 H; 5.2, m, 2 H; 3.7, m, 2 H; 2.5, m, 3 H. The splitting pattern in the vinyl region is recognizably that of a $CH{=}CH_2$ moiety, but overlapping signals from minor component **4** preclude exact assignments.

Reduction to 5. The isomeric mixture (0.0513 g, 3.824×10^{-4} mol) absorbed 20.22 ml of H_2, thus indicating 1.96 ± 0.1 double bond. A larger sample of 0.40 g of the mixture was reduced in the Parr apparatus as described for isomers **3** and **4**. Workup provided a yellow oil which had VPC (column B, 135 °C) characteristic of 12.0% *exo*-**5** and 88.0% *endo*-**5**.[44] Ir and NMR spectra of VPC-collected samples (column A, 130 °C) were congruent with those of authentic material, prepared and identified as described below.

Anal. Calcd for $C_9H_{10}O$: C, 80.50; H, 7.51. Found: C, 80.27; H, 7.31.

Pyrolysis. Heating the mixture to 85 °C for 2.5 h resulted in formation of 1,3-cyclopentadiene and disappearance of the NMR signals assigned to adduct **2**. Analysis of VPC (column B, 95 °C) showed, besides cyclopentadiene and its dimer, the five previously observed components in the area ratio (order of elution times) 1.37 (unknown A):1.64 (component **2**):7.61 (component **4**):79.38 (component **3**):10.00 (unknown B).

Isomerization Experiments. A. 2 → 3 + 4. Addition of 2 μl of triethylamine to a $CDCl_3$ solution of 59.8% **2**, 1.1% **4**, and 39.1% **3** after 8 h resulted in the virtual disappearance of **2** as measured by NMR. VPC (column B, 95 °C) showed that the equilibrium mixture had been reached (1.37:1.65:23.70:63.29:10.00). Repetition of the experiment in a dry pentane solution afforded the same equilibrium mixture, but required nearly 7 days at room temperature before stabilization.

B. 3 → 3 + 4. Addition of 2 μl of triethylamine to a $CDCl_3$ solution of VPC-purified **3** resulted after less than 30 min in attainment of equilibrium between **3** and **4** (73:27 by NMR and VPC). Only trace amounts of the other three components were observed.

C. 4 → 3 + 4. Addition of 2 μl of triethylamine to a $CDCl_3$ solution of VPC-purified **4** resulted after less than 30 min in attainment of the **3**:**4** equilibrium (73:27). Again, only trace amounts of the other three components were detected.

Reaction of 3-Butenoyl Chloride with excess Triethylamine. Under anhydrous conditions a solution of 0.51 g (5.02 mmol) of dry triethylamine in 10 ml of low-boiling petroleum ether was added dropwise to a well-stirred mixture of 0.50 g (4.8 mmol) of 3-butenoyl chloride, 1.60 g (24.3 mmol) of freshly dedimerized 1,3-cyclopentadiene, and 50 ml of petroleum ether. A heavy, flocculent white solid

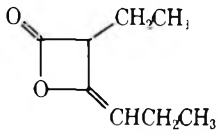
was formed immediately. Stirring was continued for 1.5 h, and then the mixture allowed to stand at room temperature for 7 days. VPC analysis (column B, 95 °C) of the supernatant liquid showed the five product components previously observed, in the area ratio (order of elution times) 1.38:1.62:23.71:63.29:10.00, and was virtually superimposable with that obtained from the analogous reaction of *trans*-2-butenoyl chloride with excess triethylamine.

Suction filtration provided 0.52 g (79%) of triethylamine hydrochloride (mp 251–255 °C). The filtrate was washed with water, dried over $MgSO_4$, and concentrated to an orange oil. Distillation in vacuo afforded 0.17 g (27%) of yellow oil, bp 46–55 °C (0.1 mm). Analysis by VPC showed no significant change in the area ratios of the five components due to fractionation during distillation.

Reaction of 3-Butenoyl Chloride with Insufficient Triethylamine. The reaction was carried out as described above except that 0.46 g (4.54 mmol) of triethylamine was used, and workup begun after 3.0 h. Filtration gave 0.45 g (68%) of triethylamine hydrochloride (mp 253–256 °C), and VPC analysis of the filtrate (column B, 95 °C) showed components 2:3:4 to be present in the area ratio 59.7:1.2:39.1. Concentration and distillation afforded 0.14 g (22%) of yellow oil, bp 45–55 °C (0.1 mm).

Preparation of 7-Ethylbicyclo[3.2.0]hept-2-en-6-one (6). Under anhydrous conditions a solution of 11.98 g (0.118 mol) of dry triethylamine was added dropwise to a well-stirred mixture of 11.30 g (0.106 mol) of butanoyl chloride, 19.44 g (0.294 mol) of freshly dedimerized cyclopentadiene, and 100 ml of dry benzene. There was immediate formation of a white precipitate, and the solution turned very dark. Addition required 20 min and stirring was continued for another 2.0 h. The reaction mixture was then allowed to stand for 42 h at room temperature.

Suction filtration afforded 14.75 g (100%) of triethylamine hydrochloride (mp 254–256 °C). The filtrate was concentrated by rotary evaporation to 14.20 g of dark oil, which was distilled in vacuo to provide 9.28 g (64%) of pale yellow oil, bp 30–145 °C (20 mm). The material was chromatographed on 34 g of silica gel using hexanes as eluent to remove 3.7 g of dicyclopentadiene. The remaining material was shown by VPC (column B, 135 °C) to be composed of three components in area ratio (order of elution times) 70.0:0.9:29.1. The first and third components were isolated by preparative VPC (column A, 130 °C) in >98% purity (checked by reinjection on column B) and assigned structures, respectively, as ethylketene β-lactone dimer **7**



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and *endo*-7-ethylbicyclo[3.2.0]hept-2-en-6-one (*endo*-**6**) on the basis of the following data.

Ethylketene β-Lactone Dimer (7): ir 2970, 2940, 2880, 1890, 1880, 1850, 1730, 1455, 1290, 1195, 938, 910, 845 cm^{-1}; NMR ($CDCl_3$) δ 4.72, d of t (J = 7.5, 1.5 Hz), 1 H; 3.91, broadened t (J = 7 Hz), 1 H; 2.4–1.6, m, 4 H; 1.06 and 1.03, overlapping triplets (J = 7.5, 7 Hz), 6 H.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.73; H, 8.70.

***endo*-7-Ethylbicyclo[3.2.0]hept-2-en-6-one (*endo*-6):** ir 3050, 2960, 2930, 2870, 1770, 1559, 795, 700 cm^{-1}; NMR ($CDCl_3$) δ 5.82, broad s, 2 H; 2.5, m, 3 H, 2.53, broad s, 2 H; 1.42, m, 2 H; 0.93, t (J = 7 Hz), 3 H ($-CH_3$).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.62; H, 9.07.

***exo*-7-Ethylbicyclo[3.2.0]hept-2-en-6-one (*exo*-6).** To a solution of 100.3 mg of VPC-purified *endo*-**6** in 10 drops of methanol was added 4 drops of 0.4 M sodium hydroxide in methanol. VPC analysis (column B, 100 °C) showed that after 2 days equilibration had occurred to form a 37.18:62.82 mixture of the second-eluting component from the cycloaddition described above and *endo*-**6**. The yellow solution was taken up in 8 ml of ether, washed with two 1-ml portions of water, dried over sodium sulfate, transferred by pipet, and concentrated by flash distillation to leave a cloudy, colorless oil, 99.3 mg. The minor, first-eluting component was isolated by preparative VPC (column A, 112 °C) and identified as *exo*-7-ethylbicyclo[3.2.0]hept-2-en-6-one (*exo*-**6**) from its method of preparation and on the basis of the following properties: ir 3070, 2980, 2945, 2890, 2865, 1780, 1603, 740, 720 cm^{-1}; NMR ($CDCl_3$) δ 5.77, broadened s, 2 H; 3.7, m, 1 H; 3.2, m, 1 H; 3.0–2.3, m, 3 H; 1.62, q (J = 6.5 Hz), 2 H; 1.00, t (J = 6.5 Hz), 3 H.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.08; H, 8.83.

***endo*-7-Ethylbicyclo[3.2.0]heptan-6-one (*endo*-5).** A mixture of 1.50 g of partially isomerized **6** (5% exo, 95% endo) was dissolved in 100 ml of 95% ethanol and hydrogenated in a Parr apparatus over 10% Pd/C at 45 psi. After 4.0 h a 0.8-psi pressure drop had occurred (ca. 1 molar equiv with this apparatus) and 1.51 g of yellow oil was isolated by suction filtration and rotary evaporation. VPC analysis (column B, 135 °C) showed two components in the area ratio (order of elution) 5:95. The larger, second-eluting component was isolated by preparative VPC (column A, 135 °C) and identified as *endo*-**5**: ir 2960, 2860, 1780 cm^{-1}; NMR ($CDCl_3$) δ 3.45, m, 1 H; 3.02, m, 2 H; 1.02–2.22, m, 8 H; 0.90, t (J = 6.5 Hz), 3 H.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.09; H, 10.11.

***exo*-7-Ethylbicyclo[3.2.0]heptan-6-one (*exo*-5).** To a solution of 95.0 mg of VPC-purified *endo*-**5** in 0.5 ml of methanol was added 5 drops of 0.4 M sodium hydroxide in methanol. After 4.0 h VPC analysis (column A, 135 °C) showed two components in the area ratio (order of elution times) 71.6:28.4. The latter component corresponded in retention time to reactant *endo*-**5**. The mixture was taken up in 5 ml of ether, washed with two 1-ml portions of water, dried over sodium sulfate, transferred by pipet, and concentrated by flash distillation to provide 85.0 mg of clear, colorless oil. The first-eluting, major component was isolated by preparative VPC (column A, 112 °C) and identified as *exo*-**5** from its method of preparation and on the basis of the following properties: ir 2955, 2865, 1770 cm^{-1}; NMR ($CDCl_3$) δ 3.42, broad s, 1 H; 2.52, m, 2 H; 2.4–1.3, m, 8 H; 0.98, t (J = 6.5 Hz), 3 H.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.49; H, 10.37.

Registry No.—**1**, 50888-73-8; **2**, 59796-68-8; **3**, 59796-69-9; **4**, 59796-70-2; *exo*-**5**, 54276-01-6; *endo*-**5**, 54235-96-0; *exo*-**6**, 54275-98-8; *endo*-**6**, 25975-87-5; **7**, 5659-15-4; *trans*-2-butenoyl chloride, 33603-82-6; 1,3-cyclopentadiene, 542-92-7; triethylamine hydrochloride, 554-68-7; 3-butenoyl chloride, 1470-91-3; butanoyl chloride, 141-75-3.

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(1) Presented in preliminary form: R. W. Holder and H. S. Freiman, Abstracts, 170th National Meeting of the American Chemical Society, Chicago, Ill., August 25–29, 1975, No. ORGN-99.

(2) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Research Corporation, the University of New Mexico Research Allocations Committee, and the Vassar College Beadle Fund for the support of this research.

(3) Address comments to this author at the University of New Mexico.

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(33) We are grateful to Professor W. T. Brady and Dr. G. A. Scherubel for performing these calculations for us.
(34) We thank Professor Owen Asplund for drawing our attention to this potential.
(35) For a review see P. A. Grieco, *Synthesis*, 67 (1975).
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(40) The low-wavelength absorption may be analogous to the weak charge transfer band of norbornen-5-one.[41-43]
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(44) The ratio of *exo*-**5** to *endo*-**5** observed from hydrogenation of the 60:40 **2**:**4** mixture, together with that measured from hydrogenation of pure **4**, allows the estimation that vinylketene cycloadds to 1,3-cyclopentadiene with better than 99% endo vinyl stereospecificity.

Metalation Reactions. 18. Polymetalation Substituted Acetophenones

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Received April 26, 1976

The lithium enolates of methyl-substituted acetophenones are metalated further by butyllithium in the presence of TMEDA to di- and trilithium derivatives. The sequence of preferential proton abstraction is *o*-methyl > o-H > *p*-methyl > *m*-methyl. A second proton can also be abstracted from the carbon α to the carbonyl group. The compound dilithiated α to the carbonyl undergoes a lithium oxide elimination to yield an acetylene. Abstraction of two protons from two *o*-methyl groups, or from one *o*- and one *p*-methyl groups, or from one *o*-methyl group and the α-methylene group, was also observed. The directive effects in these metalations are discussed in terms of charge alternation.

A preferential proton abstraction by base in hexamethylphosphoric triamide from the *p*-methyl group in 4-methylacetophenone (I) was reported by Dubois.[1] On the other hand, abstraction of two protons from the methyl α to the carbonyl in 2,4,6-trimethylacetophenone (II) by butyllithium was claimed.[2] This last result was not entirely reliable, since it was proved only by the production of III, which contained two deuterium atoms in the acetyl group, as confirmed by the NMR spectrum. However, the second proton could have been exchanged during the deuteration.

Our interest in polymetalation[3] has prompted us to investigate the possibility of polymetalation of the substituted acetophenones. Several other ketones such as acetophenone (IV), 2- (V) and 3-methylacetophenone (VI) were studied in addition to I and II.

In order to avoid the attack of butyllithium on the carbonyl group, it was necessary (except in the case of 2,4,6-trimethylacetophenone, that was hindered enough to avoid addition of butyllithium to the carbonyl group) to carry out the abstraction of the first proton with a different base to form the enolate. The following procedure was adopted. The enolates, obtained by the action of sodium hydride or lithium diisopropylamide on the ketones, were converted into trimethylsilyl enol ethers. Addition of 1 equiv of butyllithium to a solution of these o ethers transformed them into lithium enolates.[4] Further metalation of these enolates was performed by an excess of butyllithium in the presence of TMEDA.

Results

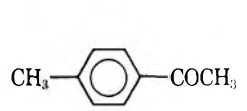
Metalation of II with butyllithium in hexane–TMEDA and subsequent treatment with trimethylchlorosilane yielded the disilyl (VIIb) and two trisilyl (VIIIb and IXb) derivatives, that are the products of the reaction of the dilithium (VIIa) and the trilithium (VIIIa and IXa) intermediates. Hydrolysis of these derivatives gave the corresponding ketones Xb, XIb, and XIIb.

The metalation of II in ether made it possible to follow by NMR the transformation of II into XIIIa and, after the addition of TMEDA, the further lithiation to VIIa. In the first stage the signals of XIIIa appeared: aromatic at 6.63 (s), $=CH_2$ at 3.9 (s, 1 H) (the second vinylic proton was hidden by ether), the *o*-methyls at 2.24 (s), and the *p*-methyl at 2.07 ppm (s). These signals disappeared on further metalation, giveing place to two aromatic signals at 5.37 (s) for the proton para and at δ9.97 ppm ortho to the CH_2Li. Meta coupling was observed by broadening of the singlets. The intensity of the *o*-methyls singlet was reduced and a new singlet for the CH_2Li appeared at 1.84 ppm. (s). Silylation of the ether solution led to VIIb. Similar results were obtained in THF (without TMEDA), but with an additional minor product XIVb formed by metalation of the *p*-methyl and subsequent silylation and hydrolysis of the enol ether.

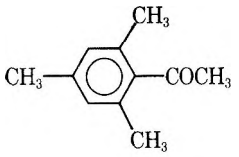
The appearance of two aromatic signals in the product of dimetalation proved its structure VIIa, since ring metalation or at the *p*-methyl would have led to a product showing one aromatic signal only. Quenching of the enolate XIIIa with D_2O in our hands led to a mixture of mono-, di-, tri-, and undeuterated products in the α-methyl group as shown by he M^+ peaks obtained in the mass spectrum. In our conditions, the reported[2] dideuterated II was not the product of dimetalation, but an artifact of exchange.

Preferential ring metalation at the position ortho to the enolate group was obtained on metalation of XVb in hexane–TMEDA. Treatment of the product of metalation with trimethylchlorosilane yielded preponderantly XVIb and two products of dimetalation, XVIIb (9%) and XVIIIb (10%). A small amount of an unidentified product was also formed.

The metalation at the ortho position was proved by the NMR of the ketone, product of deuterolysis of the metalated mixture. Instead of the A_2B_2 pattern of the aromatic protons in I, there appeared one proton only at the ortho position in this product. Metalation of XVb with butyllithium in THF

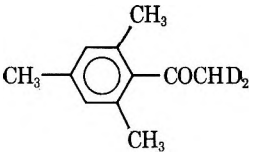


I



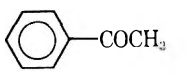
II

a, R = Li
b, R = $Si(CH_3)_3$

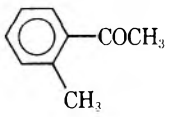


III

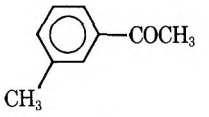
c, R = K
d, R = $OCOCH_3$



IV



V



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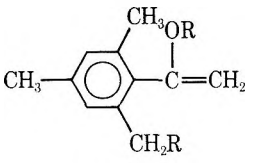

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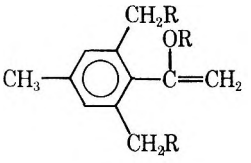

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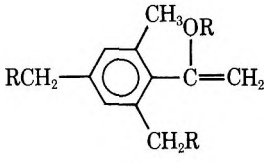

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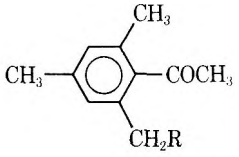

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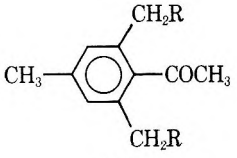

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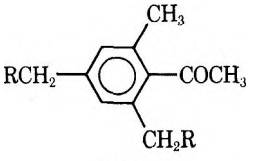

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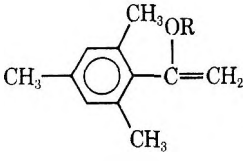

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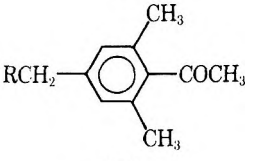

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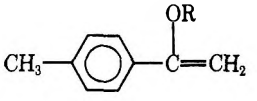

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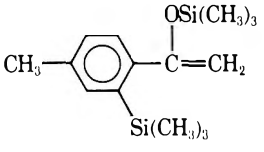

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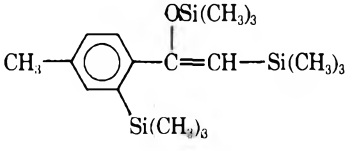
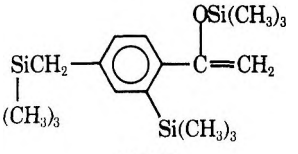


XVII



XVIII

and subsequent treatment with trimethylchlorosilane and hydrolysis yielded XIXb as the major product derived from the product of metalation at the *p*-methyl XIXa.

Metalation of the trimethylsilyl ether XXb derived from IV gave one product only, XXIa, metalated at the ortho position. Silylation of the product of metalation yielded XXIb. Alkylation of XXIa with methyl bromide gave a mixture of 2-methylacetophenone (V), 2-methylpropiophenone (XXII), and 2-methylisobutyrophenone (XXIII). The two ketones V and XXIII were products of transmetalation during the alkylation. The occurrence of transmetalation was proved by treatment of the enolate of 2-methylacetophenone with methyl bromide, that yielded the starting material, XXII, and XXIII.

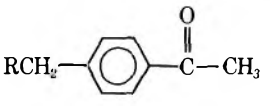
A mixture of products was obtained on metalation of the silyl ether XXIVb of V and subsequent treatment with trimethylchlorosilane, the most abundant being XXVb. In addition, there was obtained XXVIb, formed from the product of dimetalation XXVIa at the *o*-methyl, XXVIIb from the product of dimetalation XXVIIa at the methyl α to the carbonyl, and an acetylenic derivative XXVIIIb devoid of oxygen. XXIX was clearly formed by elimination of lithium oxide from the intermediate XXVIIa yielding then XXVIIIa with butyllithium and subsequently XXVIIIb with trimethylchlorosilane. An intermediate formed by abstraction of the lost proton from the carbon α to the carbonyl in XXVIIa is less probable.

No attack on the methyl was observed in the reaction of the enolate of VI, that yielded a product XXXIa of metalation at the ortho position exclusively and XXIb on subsequent treatment with trimethylchlorosilane. The NMR spectrum of this compound in the aromatic range consisted of a doublet, part of an AB signal at 7.35, and a not well-separated doublet at ~7 ppm, as well as a singlet at ~7.05. Hydrolysis of the enol silyl group of XXXIb to the ketone XXXII confirmed the structure assigned. The NMR spectrum of XXXII showed a doublet at 7.22 (1 H, J = 8 Hz), showing additional splitting of 2 Hz by a meta proton, a doublet at 7.52 (1 H, J = 8 Hz), and a singlet at 7.58 ppm (1 H, br s). Addition of $Eu(fod)_3$ produced a better resolved spectrum. The low-field singlet of the proton ortho to the carbonyl was shifted to lowerfield and the aromatic pattern showed in addition to it two doublets of the AB system. Deuterolysis of XXXIa introduced deuterium also at the ortho position. Alkylation with methyl bromide yielded a mixture of XXXIII, XXXIV, and XXV, which were separated and their structure determined by NMR. The aromatic pattern in the NMR spectra of these ketones showed a singlet (1 H) at lower yield, and a higher field singlet (2 H) in agreement with the NMR spectra of a series of similar compounds[3,5] with a 1,2,4-trisubstituted benzene ring. The NMR spectra

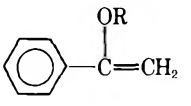
Table I. Products of Metalation–Silylation of Acetophenones

Substrate	Solvent	Catalyst: Ratio 1; ratio 2[a]	Duration of metalation, h	Products
II	Hexane	TMEDA: 4; 4	24	VII (56%); VIII (22%); IX (11%); 11% not identified.
II	Hexane	TMEDA: 2; 2	24	XIII (23%); VII (77%)
II	Hexane	TMEDA: 4; 1	48	VII (45.5%); VIII (34.5%); IX (17%)
II	THF	—: 4; —	24	II (28%); X (62.5%); XIV (9%)
II	THF	*i*-Pr_2NLi: 4; —	24	XIII (90%)
XV	Hexane	TMEDA: 4; 2	24	XVI (71%); XVII (10%); XVIII (10%)
XV	THF	—: 4; —	24	I (50%); XIX (50%)
XX	Hexane	TMEDA: 4; 2	24	XXI (90%)
XX[b]	Hexane	TMEDA: 4; 2	24	IV (8%); V (34%); XXII (26%); XXIII (26%)
XXIV	Hexane	TMEDA: 4; 2	24	XXV (55%); XXVIII (20%); XXVI (13%); XXVII (6.5%)
XXIV	Hexane	TMEDA: 4; 1	24	XXV (85%)
V[b]	THF	*i*-Pr_2NLi: 1; —	1	V (25%); XXII (50%); XXIII (25%)
XXX	Hexane	TMEDA: 4; 2	24	XXXI (90%)
XXX	Hexane	TMEDA: 4; 1	24	XXXI (90%)
XXX[b]	Hexane	TMEDA: 4; 1	24	VI (7.5%); XXXIII (24.5%); XXXIV (18%); XXXV (38%)

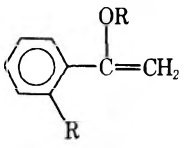
[a] Ratio 1, between BuLi considered as a monomer, and the substrate; ratio 2, between BuLi and TMEDA. [b] Alkylation with methyl bromide was performed instead of silylation.



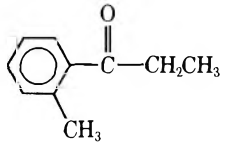
XIX



XX



XXI



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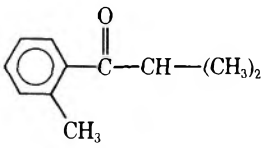

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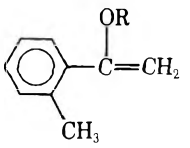

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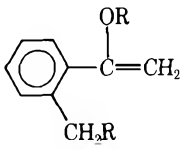

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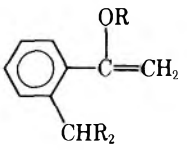
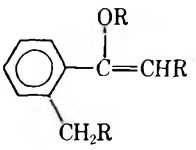


XXVI



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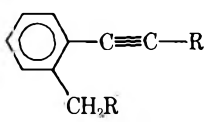

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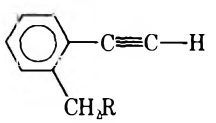
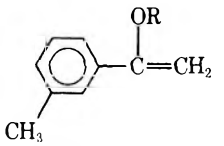
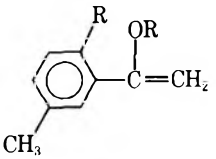


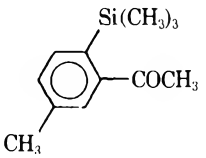
XXIX



XXX



XXXI



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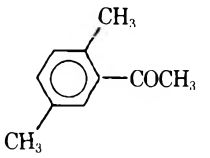

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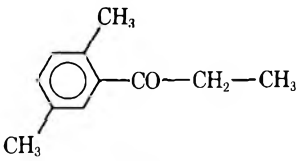

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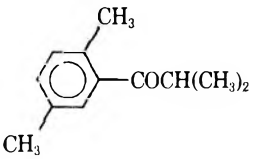
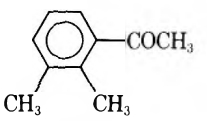


XXXV



XXXVI

of these ketones were resolved in the presence of $Eu(fod)_3$, and in all of them the signals of the aromatic protons consisted of a singlet shifted to low field (1 H) and an AB quartet (2 H) in the usual aromatic range. The other possible isomeric products, e.g., 2,3-dimethylacetophenone (XXXVI), would have shown an entirely different pattern in the NMR spectrum.

Metalation of XXXb in ether made it possible to follow its transformation into the enolate XXXa, and, after the addition of TMEDA, the further lithiation to XXXIa. In the first stage, the signals of the enolate appeared: aromatic at 6.78–7.24 (m), $=CH_2$ at 3.91 (s) and 3.62 (s), and the methyl at 2.11 ppm (s). These signals disappeared on further metalation, giving place

to an interesting pattern in the aromatic range: two doublets each of 1 H at 7.70 and at 6.66 ppm (J = 6 Hz), and a singlet (1 H) at 7.14 ppm. This spectrum confirmed the structure XXXIa, in which one proton ortho to the lithium is shifted to lower field[6] 7.70, and coupled with its neighbouring proton at 6.66 ppm. The proton between the enolate and the methyl appears as a singlet. Meta coupling was observed by broadening of the singlet and the higher field doublet.

Metalation with lithium diisopropylamide of an o-methyl in benzamides was reported.[7] However, no such metalation could be performed by us in the case of the enolates studied here.

Discussion

The lithium enolates of aryl methyl ketones undergo further metalation in ether–TMEDA, despite the negative charge of the side chain, which is also partially delocalized into the aromatic ring. Abstraction of two additional protons with organolithium compounds is observed in hexane–TMEDA. These metalations are strongly directed to the position ortho to the enolate, with a methyl at this position being metalated preferentially to the carbon ortho in the ring. These enolates therefore enter the class of directing groups in the metalation like amides[7-10] or benzylamines.[11-14] Chelation is probably the driving force for ortho metalation. The observation that abstraction of an additional proton occurs at the carbon of the side chain α to the carbonyl is of great interest. This is the first case observed for dimetalation of a methyl α to the carbonyl. Metalation is also observed in the p-, but not at the m-methyl.

We have therefore an additional directing effect to that for metalationat the ortho position. This effect discriminates between the m- and p-methyls, and we ascribe it to the preference shown by conjugated systems to introduce additional charges on the same set of starred carbons, conserving in that manner the charge alternation that was present in the initial odd alternating ion. This can occur when a proton is abstracted from a p- but not a m-methyl. The same charge alternation is maintained after an additional abstraction of a proton from the carbon α to the carbonyl, or from the o-methyl in preference to that from the ortho carbon. The preference for creating polyanions by proton abstraction in such a manner as to create conjugated systems with charge alternation was observed previously in olefins leading to trimethylenemethane dianions,[15] to allyl dianion,[16] add to propargylic di-[17] and trianions.[18] In the last case, proton abstraction was shown to occur three times consecutively from the same carbon rather than from the other propargylic position that would have led to a more even charge distribution.

The influence of chelation and its dependence on the solvent is illustrated by the preferential metalation of the enolate of 4-methylacetophenone at the ortho position in hexane–TMEDA and at the p-methyl in THF. It was observed before[19] that TMEDA solvates lithium salts of delocalized carbanions very strongly externally to a solvated tight ion pair, but THF can produce solvent separated ion pairs. The cation in the solvent separated ion pair is obviously less effective in chelation, and the electronic effects, that prefer charge alternation, are therefore determining in THF the position of proton abstraction. The coordination of the cation in the tight ion pair with one molecule of TMEDA only, thus leaving a site on the lithium free for chelation, may be an additional reason for the difference between the chelating efficiency of lithium in the presence of TMEDA and THF. In THF solution all the available sites on the lithium cation of an ion pair are probably coordinated with this ligand. The chelation through a separated ion pair in THF is sufficient to prefer metalation at the o- to that at the p-methyl, since in both reactions an ion with charge alternation is formed. However, the metalation rate at the p- relative to the o-methyl is larger in THF that in hexane–TMEDA, where tight ion pairs are present.

Steric effects intervene also in the metalation promoted by chelation. The attack on the enolate of 3-methylacetophenone by butyllithium takes place exclusively at the ortho position away from the ring methyl.

A charge in a π-conjugated system not only does not prevent the addition of further charges to this system, if the charge is introduced on the same set of starred atoms,[3,17,18,20] but makes it sometimes easier than the introduction of the first charge. Abstraction of a proton to create a carbon–metal σ bond that is perpendicular to the π system containing a charge is not prevented. It is of interest hat the presence of such a carbon–metal bond in aryllithium compounds interferes not only with further metalation by abstraction of protons of the ring and the formation of additional σ carbon–lithium bonds in the same plane as the first one, but also with the introduction of charges into the perpendicular π system,[21] if the C–Li bond is on a carbon belonging to the unstarred set.

The conjugation between the enolate group and the ortho or para benzylic methylenes in the polyanions is of the crossed-conjugation type. This kind of conjugation was found to be more stable than the linear one in the polyanions, e.g., trimethylenemethane dianion[15,20] relative to butadiene dianion or m-xylylene dianion relative to its para isomer.[3,5]

Experimental Section

NMR spectra of all compounds except the lithium derivatives were recorded in CCl_4 on a Varian T60 apparatus using Me_4Si as an internal standard. Gas chromatographic separations were performed on a Varian Aerograph A-90-P-3. Ir spectra were recorded on a Perkin-Elmer 337, and uv spectra on Unicam SP 800A spectrophotometers. Analyses were performed by Mrs. M. Goldstein of the Microanalytical Laboratory of the Hebrew University.

2,4,6-Trimethylacetophenone, 4-methylacetophenone, 3-methylacetophenone, 2-methylacetophenone, and acetophenone were commercial samples (Aldrich) that were tested by us by GLC.

The enol silyl ethers were prepared by the procedure recommended by Stork[4] using sodium hydride, but better yields were obtained when lithium diisopropylamide[22] was used as the base for proton abstraction. The first but not the second procedure failed with m-methylacetophenone.

An example for the general procedure for preparation of the enol silyl ethers is given for m-methylacetophenone.

Butyllithium (35 ml, 1.5 M) was added dropwise to 6.5 ml of diisopropylamine in 20 ml of dry THF under an inert atmosphere and cooled to 0 °C in an ice bath; then 5 g of VI was added. After the addition was complete, the mixture was left for 30–60 min at 0 °C; then 5.5 g of trimethylchlorosilane was added. After 30 min the reaction mixture was filtered. The organic phase was washed rapidly with water and an aqueous solution of sodium bicarbonate. After evaporation of the solvent, the residue was distilled at 110–120 °C (25 mm), yield 6.5 g (84%) of [1-(m-methylstyryl)oxy]trimethylsilane (XXX): NMR δ 7.08–7.05 (m, 4 H, ArH), 4.85 (s, 1 H, =CH), 4.38 (s, 1 H, =CH), 2.40 (s, 3 H, $ArCH_3$), 0.28 [s, 9 H, $OSi(CH_3)_3$]. Anal. Calcd for $C_{12}H_{18}SiO$: C, 69.9; H, 8.7. Found: C, 69.61; H, 8.68. Ir 850, 1020, 1250, 1310, 1490, 1590, 1600, 1620 cm^{-1}. The other enol silyl ether derivatives were obtained by this procedure.

[1′-(2,4,6-Trimethylstyryl)oxy]trimethylsilane (XIII): NMR δ 6.68 (s, 2 H, ArH), 4.54 (s, 1 H, =CH), 4.11 (s, 1 H, =CH), 2.34 (s, 3 H, $ArCH_3$), 0.28 [s, 9 H, $OSi(CH_3)_3$]; m/e 162 [$M^+ - Si(CH_3)_3$].

[1-(p-Methylstyryl)oxy]trimethylsilane (XV): NMR δ 7.01 (d, J = 8 Hz, 2 H, ArH), 7.38 (d, J = 8 Hz, 2 H, ArH), 4.75 (d, J = 2 Hz, 1 H, =CH), 4.35 (d, J = 2 Hz, 1 H, =CH), 2.35 (s, 3 H, $ArCH_3$), 0.21 [s, 9 H, $OSi(CH_3)_3$]. Anal. Calcd for $C_{12}H_{18}SiO$: C, 69.9; H, 8.7. Found: 69.7, H, 8.9. Ir 850, 1020, 1250, 1620 cm^{-1}.

[1-(Phenylvinyl)oxy]trimethylsilane (XX): NMR δ 7.61–7.15 (m, 5 H, ArH), 4.83 (d, J = 2 Hz, 1 H, =CH), 4.36 (d, J = 2 Hz, 1 H, =CH), 0.25 [s, 9 H, $OSi(CH_3)_3$]. Anal. Calcd for $C_{11}H_{16}OSi$: C, 68.7; H, 8.3. Found: C, 68.90; H, 8.64, Ir 850, 1010, 1120, 1250, 1320, 1620 cm^{-1}.

[1′-(2-Methylstyryl)oxy]trimethylsilane (XXIV): NMR δ 7.08–7.05 (m, 4 H, ArH), 4.85 (d, J = 2 Hz, 1 H, =CH), 4.38 (d, J = 2 Hz, 1 H, =CH), 2.40 (s, 3 H, $ArCH_3$), 0.28 [s, 9 H, $OSi(CH_3)_3$]. Anal. Calcd for

$C_{12}H_{18}SiO$: C, 69.9; H, 8.7. Found: C, 69.80; H, 8.86. Ir 850, 1020, 1090, 1140, 1250, 1270, 1310, 1620 cm^{-1}.

Metalation. All metalations were carried out by a standard procedure. An example for XXX is given. To 13 ml of 1.5 M butyllithium in hexane under an inert atmosphere and cooled to −20 to −30 °C, 2.6 ml of TMEDA was added, and then 1 g of XXX. The reaction mixture was left at room temperature for 24 h, then cooled to 0 °C in an ice bath and 5 g of trimethylchlorosilane was added. The reaction mixture was left at room temperature for several hours, then filtered and the organic solution washed rapidly with water. The solvent was evaporated and the product in the residue (1.4 g) separated by preparative GLC at 180 °C on a 2 m × 0.25 in. column of 15% SE-30 on Chromosorb W, mesh size 60/80. The following products of metalation and subsequent silylatiion were obtained in this manner.

[1-(2′-Trimethylsilylmethylene-4′,6′-dimethylsytryl)oxy]trimethylsilane (VII): NMR δ 6.64 (brs, 2 H, ArH), 4.54 (s, 1 H, =CH), 4.11 (s, 1 H, =CH), 2.28 (s, 6 H, $ArCH_3$), 2.21 (s, 2 H, $ArCH_2Si$), 0.18 [s, 9 H, $OSi(CH_3)_3$], −0.03 [s, 9 H, $CH_2Si(CH_3)_3$]; *m/e* 234 [M^+ − $Si(CH_3)_3$]; ir 850, 1050, 1080, 1170, 1250, 1300, 1600, 1620 cm^{-1}. Anal. Calcd for $C_{17}H_{30}OSi_2$: C, 66.3; H, 9.8. Found: C, 66.38; H, 9.96.

[1-Bis(2′,6′-trimethylsilylmethylene)-4-methylstyryl)oxy]trimethylsilane (VIII): NMR δ 6.51 (s, 2 H, ArH), 4.47 (s, 1 H, =CH), 4.07 (s, 1 H, =CH), 2.21 (s, 3 H, $ArCH_3$), 2.14 (s, 2 H, $ArCH_2Si$), 0.21 [s, 9 H, $OSi(CH_3)_3$], −0.06 [s, 9 H, $CH_2Si(CH_3)_3$]; *m/e* 306 [M^+ − $Si(CH_3)_3$]; ir 850, 1050, 1075, 1160, 1250, 1300, 1620 cm^{-1}. Anal. Calcd for $C_{20}H_{38}OSi_3$: C, 63.4; H, 10. Found: C, 63.42; H, 10.33.

[1-(2′-Trimethylsilyl-4′-methylstyryl)oxy]trimethylsilane (XVI): NMR δ 7.14 (s, 1 H, ArH), 4.32 (brs, 2 H =CH_2), 2.34 (s, 3 H, $ArCH_3$), 0.31 [s, 1 H, $ArSi(CH_3)_3$], 0.21 [s, 9 H, $OSi(CH_3)_3$]; ir 845, 1255, 1260, 1260 cm^{-1}. Anal. Calcd for $C_{15}H_{26}OSi_2$: C, 64.7; H, 9.36. Found: C, 64.65; H, 9.27.

1-(Trimethylsiloxy)-2-(trimethylsilyl)-1-(2′-trimethylsilyl-4′-methylphenyl)ethylene (XVII): NMR δ 7.09 (s, 1 H, ArH), 6.93 (s, 2 H, ArH), 4.41 (s, 1 H, =CH), 2.37 (s, 3 H, $ArCH_3$), 0.30 [s, 9 H, $ArSi(CH_3)_3$], 0.14 [s, 9 H, $OSi(CH_3)_3$], −0.06 [s, 9 H, $=CSi(CH_3)_3$].

[1-(2′-Trimethylsilyl-4′-trimethylsilylmethylenestyryl)oxy]trimethylsilane (XVIII): NMR δ 6.7–6.9 (m, 3 H, ArH), 4.26 (s, 2 H, $=CH_2$), 2.0 [s, 2 H, $CH_2Si(CH_3)_3$], 0.30 [s, 9 H, $ArSi(CH_3)_3$], 0.22 [s, 9 H, $OSi(CH_3)_3$], 0.04 [s, 9 H, $ArCH_2Si(CH_3)_3$].

[1-(2′-Trimethylsilylstyryl)oxy]trimethylsilane (XXI): NMR δ 7.44–7.24 (m, 1 H, ArH), 7.03–7.08 (m, 3 H, ArH), 4.38 (brs, 2 H, $=CH_2$), 0.31 [s, 9 H, $ArSi(CH_3)_3$], 0.21 [s, 9 H, $OSi(CH_3)_3$]; ir 840, 1130, 1260, 1620 cm^{-1}. Anal. Calcd for $C_{14}H_{24}OSi_2$: C, 63.6; H, 9.09. Found: C, 64.31; H, 9.64.

[1-(2′-Trimethylsilylmethylenestyryl)oxy]trimethylsilane (XXV): NMR δ 6.98 (m, 4 H, ArH), 4.41 (s, 1 H, =CH), 4.28 (s, 1 H, =CH), 2.25 (s, 2 H, $ArCH_2Si$), 0.11 [s, 9 H, $OSi(CH_3)_3$], −0.05 [s, 9 H, $ArCHSi(CH_3)_3$]; ir 850, 1015, 1110, 1250, 1310, 1620 cm^{-1}. Anal. Calcd for $C_{15}H_{26}OSi_2$: C, 64.7; H, 9.36. Found: C, 65.1; H, 9.4.

[1-(2′,2′-Bis(trimethylsilylmethylenestyryl)oxy]trimethylsilane (XXVI): NMR δ 6.71–6.81 (m, 4 H, ArH), 4.25 (s, 1 H, =CH), 4.08 (s, 1 H, =CH), 1.98 [s, 1 H, $ArCH(Si)_2$], 0.15 [s, 9 H, $OSi(CH_3)_3$], −0.01 [s, 18 H, $ArCH(Si(CH_3)_3)_2$].

1-(Trimethylsiloxy)-2-(trimethylsilyl)-1-(2′-trimethylsilylmethylene)styrene (XXVII): NMR δ 6.85–6.98 (m, 4 H, ArH), 4.45 (s, 1 H, =CH), 2.21 (s, 2 H, $ArCH_2Si$), 0.15 [s, 9 H, $OSi(CH_3)_3$], −0.01 [s, 9 H, $ArCH_2Si(CH_3)_3$], −0.05 [s, 9 H, $=CSi(CH_3)_3$].

1-(2′-Trimethylsilymethylenephenyl)-2-(trimethylsilyl)acetylene (XXVIII): NMR δ 6.98–7.2 (m, 4 H, ArH), 2.26 (s, 2 H, $ArCH_2Si$), 0.2 [s, 9 H, $=CSi(CH_3)_3$], 0.0 [s, 9 H, $ArCH_2Si(CH_3)_3$]; ir C≡C 2160 cm^{-1}.

[1-(2′-Trimethylsilyl-5′-methylstyryl)oxy]trimethylsilane (XXXI): NMR δ 7.35 (d, *J* = 6 Hz, 1 H, ArH), 6.96 (d, 1 H, ArH), 7.05 (s, 1 H, ArH), 4.38 (brs, 2 H, $=CH_2$), 2.34 (s, 3 H, $ArCH_3$), 0.21 [s, 9 H, $OSi(CH_3)_3$], 0.24 [s, 9 H, $ArSi(CH_3)_3$]; ir 860, 1020, 1265, 1320 cm^{-1}. Anal. Calcd for $C_{15}H_{26}OSi_2$: C, 64.7; H, 9.3. Found: C, 64.81; H, 9.33.

The hydrolysis of the enol silyl ethers to the corresponding ketones was carried out with *p*-toluenesulfonic acid in an aqueou methanolic solution.[4]

2-Trimethylsilylmethylene-4,6-dimethylacetophenone (X): NMR δ 6.63 (m, 2 H. ArH), 2.31 (s, 3 H, $COCH_3$), 2.23 (s, 3 H, $ArCH_3$), 2.15 (s, 3 H, $ArCH_3$), 1.88 (s, 2 H, $ArCH_2Si$), −0.03 [s, 9 H, $ArCH_2Si(CH_3)_3$]; *m/e* 234 (M^+); ir 850, 1250, 1350, 1700 cm^{-1}. Anal. Calcd for $C_{14}H_{22}OSi$: C, 71.8; H, 9.4. Found: C, 71.99; H, 9.38.

2,6-Bis(trimethylsilylmethylene)-4-methylacetophenone (XI): NMR δ 6.51 (s, 2 H, ArH), 2.35 (s, 3 H, $COCH_3$), 2.27 (s, 3 H, $ArCH_3$), 1.88 (s, 4 H, $ArCH_2Si$), −0.03 [s, 18 H, $Ar[CH_2Si(CH_3)]_2$]; *m/e* 306 (M^+); ir 850, 1150, 1250, 1350, 1420, 1695 cm^{-1}.

2,4-Bis(trimethylsilylmethylene)-6-methylacetophenone (XII): NMR δ 6.51 (m, 2 H, ArH), 2.38 (s, 3 H, $COCH_3$), 2.21 (s, 3 H, $ArCH_3$), 1.98 (s, 2 H, $ArCH_2Si$), 1.91 (s, 2 H, $ArCH_2Si$), 0.02 [s, 9 H, $Si(CH_3)_3$], 0.0 [s, 9 H, $Si(CH_3)_3$]; ir 850, 1160, 1250 1350, 1420, 1690 cm^{-1}; *m/e* 306 (M^+).

Reaction with Methyl Bromide. The metalation mixture was cooled in an acetone–dry ice bath and gaseous methyl bromide was bubbled through the solution for 10 min. The reaction mixture was brought to room temperature and left for several hours. Water was then added, and the organic layer was separated and washed with aqueous 5% hydrochloric acid and with aqueous sodium bicarbonate. The solvent was evaporated and the products in the residue (1.1 g) separated by GLC at 145 ° C on a 2 m × 0.25 in. column of 15% SE-30 on Chromosorb W. The products of metalation and subsequent alkylation of acetophenone were separated preparatively at 155 °C on a 5 m × 0.25 in. column of 20% Carbowax 20m on Chromosorb W, total yield 75%.

2,5-Dimethylacetophenone (XXXIII): NMR δ 7.41 (s, 1 H, ArH), 7.08 (s, 2 H, ArH), 2.3 (s, 3 H, $ArCH_3$), 2.45 (s, 3 H, $ArCH_3$), 2.48 (s, 3 H, $COCH_3$).

2,5-Dimethylpropiophenone (XXXIV): NMR δ 7.38 (s, 1 H, ArH), 7.06 (s, 2 H, ArH), 2.31 (s, 3 H, $ArCH_3$), 2.38 (s, 3 H, $ArCH_3$), 2.8 (q, 2 H, $COCH_2$), 1.15 (t, 3 H, CH_2CH_3).

2,5-Dimethylisobutyrophenone (XXXV): NMR δ 7.28 (s, 1 H, ArH), 7.11 (s, 2 H, ArH), 2.38 (s, 6 H, $ArCH_3$), 3.31 [quintet, 1 H, $CH(CH_3)_2$], 1.13 [d, 6 H, $(CH_3)_3CH$].

2-Methylacetophenone (V): NMR data were compared with a commercial sample (Aldrich).

2-Methylpropiophenone (XXII): NMR δ 7.41–7.61 (m, 1 H, ArH), 7.21 (m, 3 H, ArH), 2.45 (s, 3 H, $ArCH_3$), 2.8 (q, *J* = 6 Hz, 2 H, CH_2CO), 1.19 (t, 3 H, CH_3CH_2).

2-Methylisobutyrophenone (XXIII): NMR δ 7.41–7.61 (m, 1 H, ArH), 7.21 (m, 3 H, ArH), 2.4 (s, 3 H, $ArCH_3$), 3.3 [quintet, 1 H, $CH(CH_3)_2$], 1.16 [d, *J* = 6 Hz, 6 H, $(CH_3)_2CH$].

Metalation with Butyllithium in THF. Hexane was evaporated in vacuo from 16.5 ml (24.7 mmol) of a 1.5 M solution of butyllithium in hexane. The residue was cooled in an acetone–dry ice bath and15 ml of dry THF was added. The temperature was brought to 0 °C by changing the dry ice–acetone bath to an ice bath and 1 g of II was added. (The same procedure was used for XV.) Subsequent silylation and isolation of products was performed by the same procedure as described before, but only ketones were isolated from THF.

2,6-Dimethyl-4-(trimethylsilylmethylene) acetophenone (XIVb); NMR δ 6.4 (s, 2 H, ArH), 2.3 (s, 3 H, $COCH_3$), 2.13 (s. 6 H, $ArCH_3$), 1.93 (s, 2 H, $ArCH_2Si$), 0.0 [s, 9 H, $CH_2Si(CH_3)_3$].

4-(Trimethylsilylmethylene)acetophenone (XIXb): NMR δ 7.86 (d, *J* = 8 Hz, 2 H, ArH), 7.06 (d, *J* = 8 Hz, 2 H, ArH), 2.53 (s, 3 H, $COCH_3$), 2.2 (s, 2 H, $ArCH_2Si$), 0.0 [s, 9 H, $ArCH_2Si(CH_3)_3$]; *m/e* 206 (M^+); ir 1680 cm^{-1} (C=O).

The NMR spectra of XIIIa, VIIa, XXXa, and XXXIa were recorded by carrying out the metalation of II and XXXb, respectively, in NMR tubes. The metalation was also performed with BuLi in ether in the presence of TMEDA. Under this procedure it was possible to use catalytic amounts of TMEDA and to overcome the difficulties caused by precipitates formed when catalytic amounts of TMEDA in hexane were used. Chemical shifts have been determined relative to added Me_4Si.

The shift reagent used was $Eu(fod)_3$, i.e., tris(6,6,7,7,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium. Small portions of this shift reagent were added to CCl_4 solutions of the samples in NMR tubes until well-resolved spectra were obtained, and addition of further catalytic amounts had no significant influence on the spectra. (Excess must be avoided so as not to cause considerable line broadening.)

Registry No.—II, 1667-01-2; V, 577-16-2; VI, 585-74-0; VIIb, 59796-73-5; VIIIb, 59790-43-1; Xb, 59790-44-2; XIb, 59790-45-3; XIIb, 59790-46-4; XIIIb, 59790-47-5; XIVb, 59790-48-6; XVb, 54731-27-0; XVI, 59790-49-7; XVII, 59790-50-0; XVIII, 59790-51-1; XIXb, 1833-48-3; XXb, 13735-81-4; XXIb, 59790-52-2; XXII, 2040-14-4; XXIII, 2040-21-3; XXIVb, 59790-53-3; XXVb, 59790-54-4; XXVIb, 59790-55-5; XXVIIb, 59790-56-6; XXVIIIb, 59790-57-7; XXXb, 59790-58-8; XXXIb, 59790-59-9; XXXIII, 2142-73-6; XXXIV, 35031-52-8; XXXV, 5445-46-5; trimethylchlorosilane, 75-77-4.

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Solvent and Substituent Effects upon the n → π* Transition of Aliphatic Carboxylic Acids and Esters

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The near-ultraviolet spectra of 13 aliphatic carboxylic acids, 13 ethyl esters, and 16 alkyl acetates were determined for solutions in *n*-hexane, acetonitrile, and water. The carbonyl n → π* transition for these compounds was found in the vicinity of 206 nm under hydrogen-bonding conditions, and around 212 nm in the absence of hydrogen bonding. The spectra of the carboxylic acids in acetonitrile solution showed that the carboxyl group is not involved in hydrogen bonding in this solvent. The absorption band of alkyl acetates was red shifted by increasing bulkiness of the *O*-alkyl group. The values of ϵ_{max} ranged from 40 to 100 and were determined principally by the electron-donating abilities of the *C*-alkyl groups, for both acids and esters. The spectra of these compounds as neat liquids showed a very weak transition ($\epsilon_{max} \simeq 10^{-2}$) in the vicinity of 275 nm.

The electronic absorption spectra of saturated aliphatic carboxylic acids and their alkyl esters display three absorption bands. The best known of these bands is the transition observed between 200 and 220 nm, with a molar absorptivity of 50–60.[1] A variety of arguments have been used to assign this band to the carbonyl n → π* transition of both the acids[2,3] and the esters.[4] In agreement with this assignment, this band in the spectra of esters is blue shifted with increasing solvent polarity.[5] Variation of either the *C*-alkyl or the *O*-alkyl group in the ester structure produces variations in the transition energy which appear to be more closely related to the overall conformation of the molecule than to variation of the electrical effects of these substituents.[5,6]

The n → π* absorption band is superimposed upon the end absorption of a much stronger band with its peak in the vacuum ultraviolet. This absorption band has been studied by Nagakura and his co-workers,[7,8] who found peaks in the range 155–165 nm, with molar absorptivities from 2500 to 4200, in the spectra of the vapors of formic and acetic acids, and of ethyl acetate. Theoretical considerations led these authors to the conclusion that this band is of mixed character, involving intramolecular charge transfer from the singly bonded oxygen to the carbonyl group, combined with a smaller contribution from the π → π* transition of the carbonyl.[8]

In 1931, Hartleb published a study of the absorption spectra of neat liquid carboxylic acids.[9] This study showed the presence of a shoulder on the end absorption, at 270–280 nm. The molar absorptivity at this shoulder was of the order of magnitude of 10^{-2}. The only ester which was examined in the study, tributyrin, failed to show this shoulder, which led Hartleb to the conclusion that the shoulder was due to an absorption band of the carboxylate anion. Since the spectra of salts of carboxylic acids do not show an absorption band in the vicinity of this shoulder, this interpretation is not tenable. No further mention of this shoulder has appeared in the literature.

Although Closson and co-workers[5,6] made an extensive examination of solvent and substituent effects upon the spectra of aliphatic esters, no comparable study of the spectra of the corresponding acids has been described. Since the hydrogen bonding and steric interactions in carboxylic acids are quite different from those of esters, it is to be expected that solvent and substituent variation will have different effects upon the n → π* transition of acids than upon this transition of esters. In order to examine these effects, we have undertaken the measurement of the spectra of a number of carboxylic acids and their esters in three different solvents. These solvents were *n*-hexane, as a representative nonpolar solvent, acetonitrile, as a representative polar aprotic solvent, and water, as a representative polar hydrogen-bonding solvent. With supplies of these carboxylic acids and their esters available, it was also convenient to examine the spectra of these compounds as neat liquids, in the region of the shoulder described by Hartleb.[9]

Results and Discussion

The near-ultraviolet absorption spectra of 13 aliphatic carboxylic acids (Table I), 13 ethyl esters (Table II), and 16 alkyl acetates (Table III) were determined for solutions in *n*-hexane, acetonitrile, and water, and for neat liquids. All of the measurements were made with the samples thermostated at 20.0 °C,[10] in 1-cm rectangular cells. The wavelengths of the peaks, λ_{max}, were reproducible within ±0.3 nm; and the molar absorptivities, ϵ_{max}, of these peaks for the solution spectra were reproducible within ±8. Since the excitation energies are proportional to the wavenumbers of the peaks, $\bar{\nu}_{max}$, these latter values expressed in kilokaysers have been calculated, and are recorded in the tables.

Table I. Ultraviolet Absorption Spectra of Alkanoic Acids, RCO_2H, at 20.0 °C

		Neat liquid			In *n*-hexane			In acetonitrile			In water		
R	Registry no.	λ_{max}, nm	$\bar{\nu}_{max}$, kK	ϵ_{max}	λ_{max}, nm	$\bar{\nu}_{max}$, kK	ϵ_{max}	λ_{max}, nm	$\bar{\nu}_{max}$, kK	ϵ_{max}	λ_{max}, nm	$\bar{\nu}_{max}$, kK	ϵ_{max}
H	64-18-6	*a*			206.8	48.36	45.1	214.5	46.62	48.3	205.9	48.57	48.2
$Cl(CH_2)_2$	107-94-8	*b*			~208[c]	~48.1		*a*			~207[c]	~48.3	
CH_3	64-19-7	*a*			202.6	49.36	50.3	210.8	47.44	36.7	*a*		
C_2H_5	79-09-4	273.6	36.55	0.0184	204.6	48.88	57.8	211.4	47.30	37.6	202.8	49.31	52.4
n-C_3H_7	107-92-6	268.9	37.19	0.0522	205.1	48.76	59.3	213.1	46.93	43.5	203.8	49.07	51.2
i-C_4H_9	503-74-2	273.8	36.52	0.0455	206.8	48.36	68.4	213.8	46.77	45.4	204.9	48.80	63.8
n-C_4H_9	109-52-4	~275 [c]	~36.4		206.5	48.43	63.9	211.7	47.24	48.1	205.0	48.78	61.3
n-C_5H_{11}	142-62-1	*a*			205.6	48.64	68.7	213.0	46.95	46.0	202.1	49.48	63.7
Cyclohexyl	98-89-5	*a*			207.0	48.31	87.5	218.8	45.70	66.9	~208[c]	~48.1	
i-C_3H_7	79-31-2	270.2	37.01	0.0592	206.1	48.52	74.5	212.9	46.97	54.2	206.2	48.50	68.7
Cyclopentyl	3400-45-1	*a*			207.6	48.17	95.1	214.8	46.55	75.3	206.8	48.34	81.0
sec-C_4H_9	116-53-0	~277 [c]	~36.1		206.4	48.45	86.5	213.4	46.86	60.4	208.2	48.03	77.0
t-C_4H_9	75-98-9	*b*			207.9	48.10	99.1	213.9	46.75	68.1	208.7	47.92	84.4
Average[d]		271.6 ± 2.5	36.82 ± 0.33	0.0438 ± 0.0178	206.1 ± 1.5	48.53 ± 0.33	71.4 ± 17.5	213.5 ± 2.1	46.84 ± 0.45	52.5 ± 12.5	205.4 ± 2.2	48.68 ± 0.48	65.2 ± 12.6

[a] End absorption only. [b] Solid at 20.0 °C. [c] Shoulder. [d] ± One standard deviation; calculated only for peaks.

Table II. Ultraviolet Absorption Spectra of Ethyl Alkanoates, $RCO_2C_2H_5$, at 20.0 °C

		Neat liquid			In *n*-hexane			In acetonitrile			In water		
R	Registry no.	λ_{max}, nm	$\bar{\nu}_{max}$, kK	ϵ_{max}	λ_{max}, nm	$\bar{\nu}_{max}$, kK	ϵ_{max}	λ_{max}, nm	$\bar{\nu}_{max}$, kK	ϵ_{max}	λ_{max}, nm	$\bar{\nu}_{max}$, kK	ϵ_{max}
H	109-94-4	*a*			215.6	46.38	78.9	213.6	46.82	68.5	208.1	48.05	73.3
$Cl(CH_2)_2$	623-71-2	271.9	36.78	0.0956	212.8	46.99	58.3	211.2	47.35	58.1	202.6	49.36	65.6
CH_3	141-78-6	*a*			210.5	47.51	58.4	209.0	47.85	58.1	202.9	49.29	62.7
C_2H_5	105-37-3	~282 [b]	~35.50		208.0	48.08	67.3	208.1	48.05	65.3	204.3	48.95	77.6
n-C_3H_7	105-54-4	281.7	35.50	0.0208	213.3	46.88	66.2	212.4	47.08	63.8	206.2	48.50	74.3
i-C_4H_9	108-64-5	~272 [b]	~36.8		208.3	48.01	69.0	208.2	48.03	77.6	205.4	48.69	85.8
n-C_4H_9	539-82-2	271.8	36.79	0.0501	212.4	47.08	65.3	211.8	47.21	67.2	205.9	48.57	73.0
n-C_5H_{11}	123-66-0	~284 [b]	~35.2		211.6	47.26	71.8	209.2	47.80	73.6	204.4	48.92	*c*
Cyclohexyl	3289-28-9	*a*			218.0	45.87	90.4	215.7	46.36	92.0	207.0	48.31	*c*
i-C_3H_7	97-62-1	279.3	35.80	0.0317	213.4	46.86	80.4	209.1	47.82	80.4	207.6	48.17	107
Cyclopentyl	5453-85-0	*a*			214.8	46.55	88.3	212.6	47.04	89.7	208.6	47.94	92.3
sec-C_4H_9	7452-79-1	~275 [b]	~36.4		214.0	46.73	77.1	212.2	47.13	90.3	207.9	48.10	102
t-C_4H_9	3938-95-2	*a*			215.0	46.51	101	214.3	46.66	95.0	208.1	48.05	96.7
Average[d]		276.2 ± 5.1	36.22 ± 0.67	0.0496 ± 0.0330	212.9 ± 2.8	46.98 ± 0.63	74.8 ± 12.8	211.3 ± 2.4	47.32 ± 0.55	75.4 ± 13.1	206.1 ± 2.0	48.53 ± 0.48	82.8 ± 14.9

[a] End absorption only. [b] Shoulder. [c] Saturated solution. [d] ± One standard deviation; calculated only for peaks.

The only spectra which showed fine structure were those of formic acid, ethyl formate, and methyl acetate. The fine structure blurred with increasing polarity of the medium and disappeared from the spectra of methyl acetate in polar solvents. The fine structures of the spectra of formic acid[11] and of alkyl formates[5] have been described elsewhere.

Only four compounds provided high enough concentrations in the vapor phase, under the conditions of these measurements, to give satisfactory results in the determination of the vapor spectra. These compounds were formic acid, λ_{max} 204.0 nm ($\bar{\nu}_{max}$ 49.02 kK); ethyl formate, λ_{max} 215.5 nm ($\bar{\nu}_{max}$ 46.40 kK); methyl acetate, λ_{max} 208.7 nm ($\bar{\nu}_{max}$ 47.92 kK); and ethyl acetate, λ_{max} 209.8 nm ($\bar{\nu}_{max}$ 47.66 kK). The red shifts of the spectra of these compounds in going from the vapor state to solutions in *n*-hexane are attributable to the dispersion effects of the solvent.[12] These effects for a nonpolar solvent with low dielectric constant, such as *n*-hexane, are generally sufficiently small, in comparison with dipole–dipole and hydrogen-bonding effects, that the spectra in this solvent may be taken as approximating the vapor spectrum for purposes of comparison with spectra for polar solvents.

Using a set of four methyl esters, Closson and Haug[5] described a correlation between the excitation energies, E_T, and the Taft polar substituent constants,[13] σ^*, for the *C*-alkyl groups of the esters. In order to facilitate search for such relationships, the data in Tables I–III were assembled in order of decreasing σ^* of the alkyl groups, that is, in order of increasing electron-donating ability. The wavenumbers of the excitations, $\bar{\nu}_{max}$, in kilokaysers, are directly proportional to the excitation energies, and can be converted to kilocalories per mole by multiplying by 2.859.[14] If the correlation of E_T with σ^* of the *C*-alkyl group actually existed, we would expect to see a gradual decline in the values of $\bar{\nu}_{max}$ from top to bottom in Tables I and II, and constancy of $\bar{\nu}_{max}$ in Table III. In fact, the variation of $\bar{\nu}_{max}$ for the carboxylic acids (Table I) and for the ethyl esters (Table II) is no greater than the variation for the alkyl acetates (Table III), as long as all measurements are made in the same solvent.

It has therefore been assumed that for each set of compounds $\bar{\nu}_{max}$ has a constant value for each solvent, and, further, that the two sets of esters can be considered as a single group for purposes of comparing solvent effects and for comparison with the carboxylic acids. By comparing the average values of the transition energy for a set of compounds in two different solvents, using only those compounds which show well-defined peaks in both solvents, we can achieve a measure of the solvent

Table III. Ultraviolet Absorption Spectra of Alkyl Acetates, CH_3CO_2R, at 20.0 °C

R	Registry no.	Neat liquid λ_{max}, nm	Neat liquid $\bar{\nu}_{max}$, kK	Neat liquid ϵ_{max}	In *n*-hexane λ_{max}, nm	In *n*-hexane $\bar{\nu}_{max}$, kK	In *n*-hexane ϵ_{max}	In acetonitrile λ_{max}, nm	In acetonitrile $\bar{\nu}_{max}$, kK	In acetonitrile ϵ_{max}	In water λ_{max}, nm	In water $\bar{\nu}_{max}$, kK	In water ϵ_{max}
$Cl(CH_2)_2$	542-58-5	*a*			209.9	47.64	57.7	207.9	48.10	55.4	203.0	49.26	58.3
CH_3	79-20-9	276.5	36.17	0.0989	210.2	47.57	54.6	206.5	48.43	63.4	202.7	49.33	55.3
C_2H_5	141-78-6	*a*			210.5	47.51	58.4	209.0	47.85	58.1	202.9	49.29	62.7
n-C_3H_7	109-60-4	273.5	36.56	0.0465	211.3	47.33	57.9	207.8	48.12	57.5	203.0	49.26	59.4
i-C_4H_9	110-19-0	*a*			211.1	47.37	60.5	207.0	48.31	65.5	201.3	49.68	59.5
i-C_5H_{11}	123-92-2	313.4	31.91	0.106	212.1	47.15	59.9	209.4	47.76	59.0	201.3	49.68	60.7
n-C_4H_9	628-63-7	*a*			210.5	47.51	60.6	208.5	47.96	56.9	202.3	49.43	61.9
n-C_5H_{11}	142-92-7	*a*			212.6	47.04	53.8	209.2	47.80	62.7	202.5	49.38	57.6
Cyclohexyl	622-45-7	~324 [b]	~30.9 [b]		211.7	47.24	65.0	210.2	47.57	63.9	~208 [b]	~48.1	
$C_2H_5CH(CH_3)CH_2$	624-41-9	*a*			211.6	47.26	57.2	208.7	47.92	54.2	*a*		
$(CH_3)_3CCH_2$	926-41-0	277.6	36.02	0.115	208.7	47.92	66.8	209.1	47.82	64.2	*a*		
i-C_3H_7	108-21-4	*a*			211.4	47.30	58.8	208.5	47.96	56.1	204.2	48.97	59.5
Cyclopentyl	933-05-1	296.9	33.68	0.0846	212.2	47.13	63.2	210.4	47.53	61.8	*a*		
sec-C_4H_9	105-46-4	~281 [b]	~35.6		212.2	47.13	65.2	210.9	47.42	63.8	204.1	49.00	61.1
t-C_4H_9	540-88-5	*a*			218.0	45.87	57.2	215.2	46.47	66.0	208.9	47.87	55.4
t-C_5H_{11}	926-41-0	*a*			215.9	46.32	63.1	213.7	46.79	67.0	210.0	47.62	57.1
Average [c]		287.6 ± 17.1	34.87 ± 2.00	± 0.0268	211.9 ± 2.3	47.21 ± 0.50	60.0 ± 3.8	209.5 ± 2.3	47.74 ± 0.51	61.0 ± 4.2	203.8 ± 2.8	49.06 ± 0.65	59.0 ± 2.4

[a] End absorption only. [b] Shoulder. [c] ± One standard deviation; calculated only for peaks.

effects upon the spectra. In the case of the esters, the overall average value of the blue shift from *n*-hexane to acetonitrile was 0.45 ± 0.27 kK, or 1.3 ± 0.8 kcal/mol.[15] Such a shift is in agreement for the effect of a polar solvent on an n → π* transition in the absence of hydrogen bonding.

Hydrogen-bonding effects must be considered in the case of water as the solvent and with the carboxylic acids, since the nonbonding pair of electrons of the carbonyl is the acceptor site for the hydrogen bond. Brealey and Kasha[16] have shown that the excitation energy of an n → π* transition in a hydrogen-bonding solvent includes the energy which must be added to break the hydrogen bond. In water this hydrogen-bond energy constitutes most of the energy difference of the blue shift from a nonpolar solvent. The overall average value of the blue shift for the esters in the current study was 1.71 ± 0.48 kK, or 4.9 ± 1.4 kcal/mol, for the difference between *n*-hexane and water.

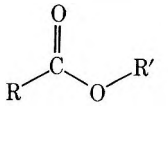
Carboxylic acids exist as hydrogen-bonded dimers in the vaper state and in solution in nonpolar solvents, as well as having the ability for hydrogen-bonding interaction with water. Comparison of the spectra of the acids with those of the esters shows that the spectra of the acids in *n*-hexane and in water are very similar to the spectra of the esters in water, that is, under hydrogen-bonding conditions. An unanticipated finding is noted, however, in the spectra of the acids in acetonitrile, which are similar to those of the esters in *n*-hexane. It must be concluded that the carboxylic acids are not involved in hydrogen-bonding interactions of any sort in acetonitrile. This conclusion is supported by nuclear magnetic resonance[17] and infrared[18] spectral studies of acetonitrile solutions of carboxylic acids. A study[19] of the vapor spectrum of acetic acid at elevated temperatures has shown a shift of λ_{max} from 200 nm for the dimer at 75 °C, to 210 nm at 200 °C, where acetic acid is almost entirely monomeric.[20] Reference to Table I shows 202.6 nm for the dimer in *n*-hexane, and 210.8 nm for the monomer in acetonitrile. These values are excellent agreements if one allows for the dispersion effects of the solvents. Similar solvent effects upon the π → π* transitions of three α,β-unsaturated acids have also been observed, and similarly interpreted.[21]

Using only data for acids that gave well-formed peaks in each pair of solvents, calculation of the blue shift from monomer in acetonitrile to dimer in hexane, and of the blue shift from acetonitrile to water, gave the same value for both shifts, 1.69 ± 0.35 kK, or 4.8 ± 1.0 kcal/mol, a remarkably good agreement with the value of the blue shift for esters. Using similar methods, Balasubramanian and Rao[22] have obtained a value of 4.8 kcal/mol for the energy of the hydrogen bond between acetone and water. Two conclusions must be made from this remarkable coincidence of values: first, for the systems examined here (though not necessarily under all conditions), water and carboxylic acids have comparable hydrogen-bond donating abilities; and, second, the nonbonding electrons of the singly bonded oxygen cannot be involved in either the hydrogen-bonding or the n → π* excitation of the acids and esters. The latter conclusion is further supported by protonation studies.[23] The infrared and Raman spectra of acetic acid in strong sulfuric acid solutions showed that the carboxyl is protonated on the carbonyl oxygen to give $CH_3C(OH)_2^+$, rather than the less symmetrical $CH_3(CO)OH_2^+$ ion which would result from the protonation of the singly bonded oxygen. This protonation of the carbonyl oxygen also suppressed the n → π* absorption band. In the current study, it was found that protonation of ethyl acetate by hydrochloric acid at concentrations as low as 0.1 N was sufficient to suppress the n → π* transition, leaving only end absorption.

Balasubramanian and Rao[22] found that the solvent-induced blue shifts of the n → π* transitions of methyl ketones, $RCOCH_3$, correlate fairly well with the σ* values for the alkyl groups, R, of these ketones. Despite the evidence that an electronically comparable transition is present in the absorption spectra of the acids and the esters, no such correlations could be detected in the spectral data for these compounds. The Taft σ* functions are measures solely of electronic influences of alkyl groups upon the carbonyl groups to which they are bonded. The failure of these functions to correlate with either the excitation energies or the solvent-induced changes in excitation energies means that other factors, in addition to the electronic effects of the *C*-alkyl groups, are significant in determining the experimental values of the excitation energies. Two such factors can be identified. The first of these is the increment of the experimental transition energy added by the end absorption of the 160-nm absorption band.

No rational correction for this end absorption can be made without a knowledge of the course and shape of this band deep into the vacuum ultraviolet for each compound and for the same experimental conditions. Such information is not experimentally accessible for spectra of solutions.

The second influencing factor is steric distortion of the chromophore away from a fully coplanar geometry. Since the n → π* transition of the carbonyl group is symmetry forbidden, some sort of small distortion of the group geometry, probably vibrational in origin, is necessary for the transition to be spectroscopically observable. Since the molar absorptivities of carboxylic acids and their esters are some five to six times larger than those of simple aldehydes and ketones, additional factors must be at work in the former compounds to enhance the probability of the transition. It has been shown[24] that acyclic esters prefer the s-trans conformation (1) to the s-cis (2). The studies of Closson and co-workers[6] with lactones



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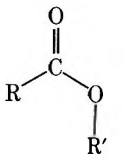

2

have shown that the s-cis conformation has a transition energy some 4 kcal/mol less than the s-trans. This difference is presumably largely due to the differences between the ground-state energies of the two conformations, with the s-trans conformation having the lower ground state energy. The preferred s-trans conformation places the *O*-alkyl group of the ester on the same side of the molecule as the carbonyl oxygen. The resulting steric interaction distorts the molecule out of coplanarity by an appreciable amount.[24] In the carboxylic acids, this distortion should be much smaller, but the generally accepted structure for the hydrogen-bonded dimer of these compounds requires that they also have the s-trans conformation in the dimeric state.

Increasing bulk of the *O*-alkyl group should increase the steric interaction of this group with the carbonyl oxygen, and result in further deviation from coplanarity in the ester group. This will necessarily result in a decline of resonance stabilization energy, and will increase the energy of the ground state. The presence of bulky *O*-alkyl groups should thus produce a decline in excitation energy, assuming that these steric factors do not similarly affect the excited state energy. A good example of this effect may be observed with the alkyl acetates (Table III). Using dipole moment data, Pinkus and Lin[25] have recently calculated the dihedral angles, or angles of twist about the C–O single bond, in four alkyl acetates to be methyl acetate, 31°; ethyl acetate, 38°; isopropyl acetate, 39°; and *tert*-butyl acetate, 45°. The excitation energies of these esters, in kilocalories per mole, for solutions in *n*-hexane, acetonitrile, and water, respectively, are methyl acetate, 136.0, 138.5, and 141.0; ethyl acetate, 135.8, 136.8, and 140.9; isopropyl acetate, 135.2, 136.7, and 140.0; and *tert*-butyl acetate, 131.1, 132.9, and 136.9. The steric effect in the *tert*-butyl acetate is large enough that resonance interaction in this molecule is largely inhibited. It would be interesting to learn how this inhibition affects the charge-transfer band in the vacuum ultraviolet.

Ethyl formate has a smaller excitation energy than most of the other ethyl esters (Table II). The data of Closson and Haug[5] show that methyl formate also has a lower excitation energy than other methyl esters, and that alkyl formates generally have smaller excitation energies than the corresponding alkyl acetates. If the inductive effect of the *C*-alkyl group, as measured by the σ* function, were the dominating factor in determining the excitation energy, we would expect to see larger excitation energies for the alkyl formates, rather than smaller ones. There is evidence[26] that the preferred conformation of alkyl formates may be s-cis rather than s-trans. Such a conformation certainly appears reasonable, since the hydrogen atom should offer less steric hindrance to the *O*-alkyl group than the carbonyl oxygen. The excitation energies of alkyl formates may thus not be electronically comparable with those of other esters as the result of a quite different geometry of charge distribution. It is interesting to note that the excitation energy of formic acid is similar to that of other carboxylic acids in *n*-hexane, but is considerably smaller in acetonitrile. In *n*-hexane, the formic acid should be locked into the s-trans conformation in the hydrogen-bonded dimer, but in the absence of hydrogen bonding in acetonitrile, each molecule is free to find its stablest conformation. In addition to these conformational effects, the excitation energies of formic acid and the formates are also lowered by the absence of *C*-alkyl hyperconjugation with the carbonyl group. The absence of this hyperconjugation, which raises the π* level, has been used to explain why the excitation energy of acetaldehyde is less than that of acetone.[27]

Examination of the standard deviations for the average molar absorptivity values in each of the tables reveals an interesting difference. The average of the standard deviations from the average of each set of ϵ_{max} values for carboxylic acids and ethyl esters is ±13.9, while the average for the alkyl acetates is only ±3.5, only one-fourth as much. Recalling that the estimated experimental error in measurement of ϵ_{max} was ±8, it must be concluded that ϵ_{max} can be considered constant for the alkyl acetates, but is variable for the carboxylic acids and their ethyl esters. Generalizing this conclusion leads to the prediction that, under comparable conditions of measurement, the value of the molar absorptivity is determined by the *C*-alkyl group, and the contributions of the *O*-alkyl group to its value are negligible. The data of Closson and Haug[5] for the molar absorptivities of six alkyl formates in isooctane, with an average value of 77 ± 4, support this conclusion.

Closer inspection of the data in Tables I and II shows that the ϵ_{max} values for each solvent increase rather regularly with increasing electron-donating ability of the *C*-alkyl group, in both the series of carboxylic acids and ethyl esters. Since this is the sequence of decreasing σ* values, it was of interest to determine if the ϵ_{max} values for these sets of compounds could be correlated with the ϵ_{max} values for the *C*-alkyl groups. We therefore assumed the simple straight-line relationship

$$\epsilon_{max} = \rho^*\sigma^* + \epsilon^0_{max}$$

and calculated the least-squares slopes ρ*, intercepts ϵ^0_{max}, and correlation coefficients *r*, using the points for seven alkyl groups: ethyl, *n*-propyl, isobutyl, *n*-butyl, isopropyl, *sec*-butyl, and *tert*-butyl. Three of the data sets yielded correlation coefficients which met Jaffé's criterion[28] for a "satisfactory" correlation, namely $r > 0.95$. These sets were for the carboxylic acids in *n*-hexane, with $\rho^* = -209 \pm 9$, $\epsilon^0_{max} = 38$, and $r = 0.977$; carboxylic acids in acetonitrile, with $\rho^* = -144 \pm 7$, $\epsilon^0_{max} = 27$, and $r = 0.974$; and ethyl esters in *n*-hexane, with $\rho^* = -173 \pm 9$, $\epsilon^0_{max} = 46$, and $r = 0.965$. The correlation coefficients for the other three data sets, carboxylic acids in water, ethyl esters in acetonitrile, and ethyl esters in water, were all less than 0.9, Jaffé's minimum limit for a "fair" correlation. It is not surprising that the correlations are better with the carboxylic acids than with the esters, considering the difference between steric effects in the two classes of compounds. It is also not surprising that the best correlations exist where the magnitude of interaction with the solvent is least. But it is surprising that these correlations exist at all. Their existence supports the conclusion that ϵ_{max} for carboxylic acids and their esters is determined mainly by the electrical effects of the *C*-alkyl group.

Since ethyl acetate was the reference compound in evaluation of the σ* values, the methyl group is automatically as-

signed a σ^* value of zero.[13] This leads to the expectation that the intercepts ϵ^0_{max} should equate with the ϵ_{max} values for acetic acid and ethyl acetate. Inspection of Tables I and II shows that the experimental ϵ_{max} values are significantly larger than the calculated ϵ^0_{max} values for these compounds. The sparse data for the only two available groups with positive σ^* values, $ClCH_2CH_2$ and H, suggest that the ϵ_{max} vs. σ^* curve may pass a minimum somewhere between $\sigma^* = -0.1$ and $\sigma^* = 0$, and show a positive slope for positive σ^* values. An alternate explanation is that the methyl group is actually more electron donating than is implied by the zero value for σ^* that is obtained when methyl is compared with itself; that is, the "real" value of σ^* for the methyl group should lie between −0.1 and 0.0.

A possible source of error which must be considered throughout these measurements is the effect of the rapid opening of the slits that occurs as the scan approaches the cutoff point of the instrument at 200 nm, especially in the 205–200-nm range.[5] Measurements of the slit widths for the three solvents were determined at 5-nm intervals between 215 and 200 nm and are recorded in the Experimental Section. The slit opening was serious only for *n*-hexane in the 200–205-nm range. Since, however, this affects only two spectra (acetic and propionic acids in *n*-hexane), we do not feel that the slit-opening effect has any seriously significant bearing on the experimental data or the general interpretation thereof.

The n → π^* transition of the carbonyl group is totally submerged when there is present in the molecule a stronger chromophore insulated from the carbonyl group, but with its λ_{max} near that of the carbonyl group. We examined the absorption spectra of phenylacetic and β-phenylpropionic acids and their ethyl esters, and of benzyl and β-phenethyl acetates. The spectra of these compounds were very similar to the spectra of toluene and ethylbenzene, with a very small blue shift of the λ_{max} values. This blue shift became smaller as the number of carbon atoms between the carbonyl group and the ring increased. The ϵ_{max} values were nearly identical with the values for the 205-nm band of the alkylbenzenes. Similar effects were observed for the 260-nm aromatic absorption band.

All of the acids and esters which are liquid at 20 °C showed evidence of an absorption band in the vicinity of the shoulder described by Hartleb[9] in the spectra of neat liquid fatty acids. In many cases this band was detectable only as a straightening out of the curvature of the end absorption, for which no specific λ_{max} value could be defined. In other cases there were shoulders similar to those described by Hartleb. A few cases gave very broad, low peaks in the vicinity of 275 nm.[29] Inspection of the data for alkyl acetates (Table III) shows that this peak is subject to red shifts by bulky *O*-alkyl groups, suggesting that the excitation energy is decreased by steric interaction between the *O*-alkyl group and the carbonyl oxygen. The extremely small molar absorptivity for this absorption band suggests that it is due to a singlet → triplet transition of the carbonyl group.

Experimental Section

The *n*-hexane used in these studies was Aldrich Gold Label spectrophotometric grade. The acetonitrile was Burdick and Jackson "distilled in glass" uv grade. The carboxylic acids and most of the esters were the highest purity grades commercially available. Four esters, ethyl α-methylbutyrate, ethyl cyclohexanecarboxylate, ethyl cyclopentanecarboxylate, and cyclopentyl acetate, were also synthesized in our laboratory, using standard esterification methods.

All absorption spectra were determined with a Cary Model 15 recording spectrophotometer, using a matched pair of 1-cm rectangular cells. Solutions were prepared using volumetric glassware calibrated for 20 °C, and the sample cell was thermostated at 20.0 ± 0.1 °C during measurement of all spectra.[10] Prior to each measurement, a baseline was established by a blank scan through the spectral region of interest, using solvent in both cells. The baseline absorbance at each peak was deducted from the absorbance at the peak. The resulting corrected absorbances were used for calculating absorptivities only if they fell within the range 0.2–0.9. The spectra were determined with a scale expansion of 1 nm per division of the chart paper. Slit widths were those automatically programmed by the instrument. These were for *n*-hexane 0.13 mm at 215 nm, 0.19 mm at 210 nm, 0.29 mm at 205 nm, and 0.51 mm at 200 nm; for acetonitrile, 0.12 mm at 215 nm, 0.14 mm at 210 nm, 0.20 mm at 205 nm, and 0.31 mm at 200 nm; and for water; 0.12 mm at 215 nm, 0.13 mm at 210 nm, 0.18 mm at 205 nm, and 0.24 mm at 200 nm.

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Some Transformations of DL-Phenylalanine Ortho Esters and *N*-Benzyloxycarbonyl-L-phenylalaninal[1]

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Glycine ortho esters have found a wide use[2] in the synthesis of glycyl derivatives of ribonucleosides,[2a,b] ribonucleotides,[2c] and ribooligonucleotides.[2d-h] The application of the ortho ester exchange method which provides the basis of the synthetic approach[2a] to the above mentioned compounds for amino acids other than glycine has been hampered for a long time by a lack of general method for the preparation of amino acid ortho esters.[3]

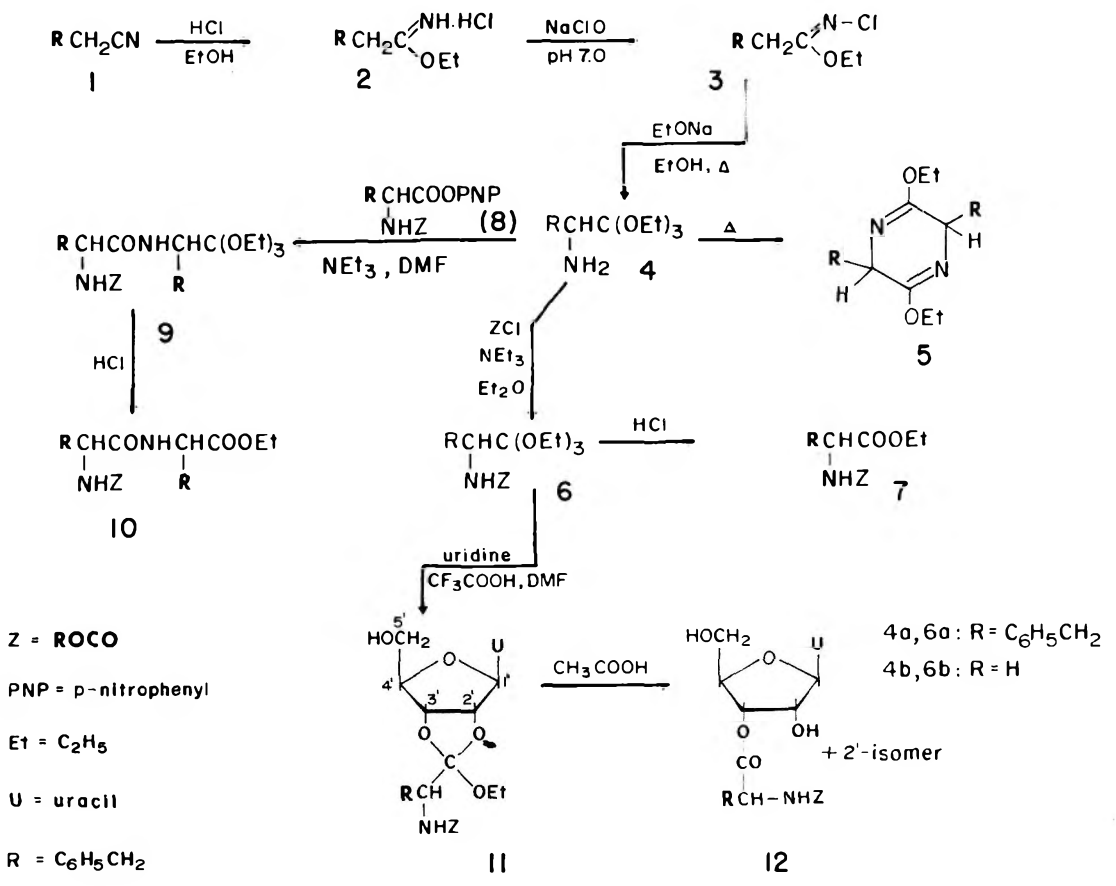
A brief report[4] describing a synthesis of some amino acid ortho esters has prompted us to investigate (a) N-protection of such derivatives, (b) synthesis of dipeptide ortho esters, and (c) synthesis of 2′(3′)-*O*-aminoacyl ribonucleosides via the corresponding cyclic ortho ester derivatives. The resuls from all three areas are the subject of this communication. In addition, a facile preparation of *N*-benzyloxycarbonyl-L-phenylalaninal dimethyl acetal (**17**) as well as the reaction of aldehyde **16** with adenosine in the presence of ethyl orthoformate is also described.

Ethyl DL-orthophenylalaninate (**4a**) was prepared as indicated in Scheme I (**1** → **2** → **3** → **4a**) according to a procedure described briefly for some other amino acid ortho esters.[4] Hydrocinnamonitrile (**1**) was converted in 98% yield to the corresponding imido ester hydrochloride[5] (**2**) which, in turn, was chlorinated[6] with aqueous NaClO at pH 7.0 to give an *N*-chloroimido ester (**3**) in 98% yield. The latter afforded the ortho ester **4a** by heating with sodium ethylate in ethanol for 2 h at 80 °C in 99% yield. Thus, the overall yield (**1** → **4a**) was 95%. The structure of **4a** was confirmed by ir which revealed a strong band at 1065 cm^{-1} indicating C–O–C grouping but absence of ester. NMR indicated the undistilled **4a** to be of a high (ca. 95%) purity. Distillation of **4a** afforded an analytical sample but led to an extensive decomposition. From the higher boiling fraction, a pyrazine derivative **5** was obtained and characterized by ir and NMR spectra. This observation contradicts the claim of the Soviet literature[7] that amino acid ortho esters as free bases are "very stable compounds and do not change even on long heating".

The reaction of ortho ester **4a** with benzyloxycarbonyl chloride in ether and in the presence of triethylamine gave ethyl *N*-benzyloxycarbonyl-DL-orthophenylalaninate (**6a**) in 66% yield. The same reaction was extended to the preparation of ethyl *N*-benzyloxycarbonylorthoglycinate[2a] (**6b**) from ortho ester[4] **4b** in 38% yield.

The structure of **6a** was confirmed by ir (urethane carbonyl band, strong C–O–C absorption) and NMR spectra. The latter showed the methyl protons of the ethoxy function as a sharp triplet; however, the signal for the methylene protons (quartet) was split (Figure 1), which was not the case in ethyl *N*-

Scheme I



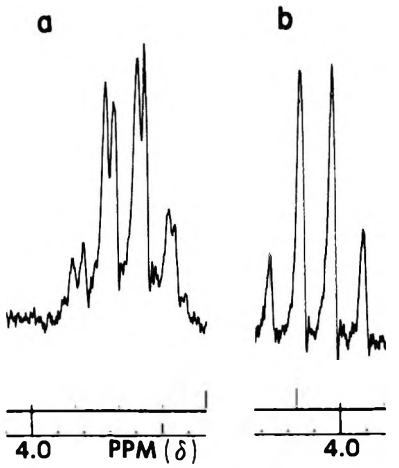
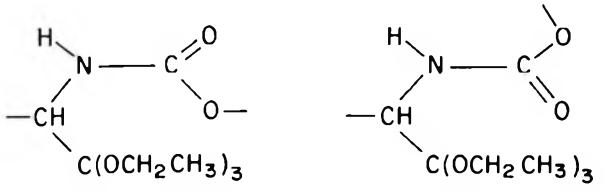


Figure 1. (a) Methylene proton signal of ethoxy group in ortho ester **6a**; (b) methylene proton signal of ethoxy group in ester **7**.

benzyloxycarbonylorthoglycinate (**6b**) or ethyl *N*-benzyloxycarbonyl-DL-phenylalaninate (**7**). The splitting pattern observed in our case (Figure 1) is also different from that described for some alicyclic ethyl esters.[8,9] The most likely explanation for the splitting is the assumption of *Z–E* isomerism of the urethane bond[10] (cf. formulas **13** and **14**). Additional



13 **14**

E-isomer **Z-isomer**

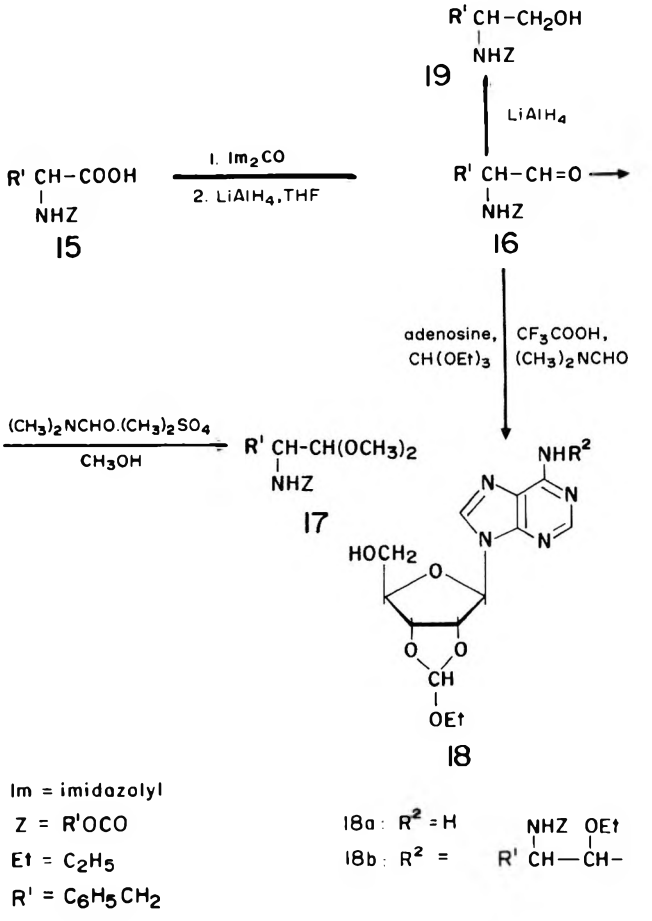
confirmation for the structure of **6a** derives from its hydrolysis with 10% HCl to the corresponding known[11] ester **7**.

The condensation of ortho ester **4a** with *N*-benzyloxycarbonyl-L-phenylalanine *p*-nitrophenyl ester[12] (**8**) in the presence of triethylamine in CH_2Cl_2 gave the dipeptide ortho ester **9** in 63% yield. The latter was characterized by spectral (ir and NMR) data which confirmed the presence of urethane and amide groups in addition to ethoxy functions. Compound **9** was hydrolyzed with 10% HCl to the corresponding dipeptide ester **10** whose structure was corroborated by NMR spectrum. Again, a secondary splitting of the methylene protons of the ethoxy group in **9** was observed although the resolution was lower than in the case of ortho ester **6a**. Thus, the situation is analogous to that noted with the urethane derivative **6a**. In addition to *Z–E* isomerism of the urethane grouping, a possibility of a similar isomerism can readily be visualized for **9** in view of the fact that the partial double bond character of the peptide bond is well established.[13] However, this case is more complex because **9** is a mixture of two diastereoisomers.

It is also of interest to utilize *N*-benzyloxycarbonyl ortho ester **6a** for the synthesis of 2′(3′)-*O*-phenylalanylribonucleosides. As shown previously, an ortho ester exchange reaction of ethyl *N*-benzyloxycarbonylorthoglycinate (**6b**) with ribonucleosides or ribonucleotides can be readily accomplished in dimethylformamide (DMF) using CH_3SO_3H[2a] or CF_3COOH[2c] as catalysts. In a model experiment with uridine (catalysis with CF_3COOH), compound **6a** afforded the expected 2′,3′-cyclic ortho ester **11** in 51% yield. The starting ortho ester **6a** is a racemate (DL mixture) and formation of the 2′,3′-cyclic ortho ester creates a new asymmetric center at the "ortho ester" carbon which presents the possibility of four diastereoisomers for compound **11**. TLC indicated, however, that such a mixture would be difficult to resolve. Compound **11** moved as a single spot.[14] Hydrolysis of **11** in dioxane–acetic acid–water (2:3:3) mixture gave 2′(3′)-*O*-(*N*-benzyloxycarbonyl)-DL-phenylalanyluridine[15] (**12**) in 95% yield which had the same mobility on TLC as the corresponding L-phenylalanyl derivative.[3a]

In connection with our experiments on the ortho ester exchange of **6a** with ribonucleosides, it was of interest to examine an analogous acetalation reaction of aldehyde **16**. *N*-Benzyloxycarbonyl-L-phenylalanine (**15**) was converted to the corresponding imidazolide which was reduced in situ with $LiAlH_4$ to aldehyde **16** in 50% yield following the procedure described for N^{α}-benzyloxycarbonyl-N^{ω}-nitroargininal.[16] In addition, *N*-benzyloxycarbonyl-L-phenylalaninol (**19**)[17,18] was also obtained (23% yield) as the final reduction product of aldehyde **16** (Scheme II). The ir spectrum of **16** showed dis-

Scheme II



tinctly separate aldehyde and urethane carbonyl bands. The assignments follow from the spectrum of acetal **17** which contains only a urethane carbonyl band. The NMR exhibited a typical low-field singlet of an aldehyde group. The fact that the optical rotation of **19** was slightly higher than that of an authentic sample[17,18] indicates that no racemization of the aldehyde **16** occurred during reaction with $LiAlH_4$. However, after isolation (chromatography on silica gel[19]) the aldehyde was almost completely (93%) racemized[19] as shown by $LiAlH_4$ reduction to alcohol **19** and comparing its rotation with optically pure L-compound. The reaction of **16** with dimethylformamide–dimethyl sulfate complex and methanol following the procedure[20] for acetalation of simple aliphatic aldehydes gave the corresponding acetal **17** in 60% yield.[21] Both the ir

and NMR spectra of **17** lack the bands characteristic of an aldehyde. It is of interest to note that the NMR spectrum of **17** exhibits two separate signals (singlets) for acetal methoxy groups. This finding probably reflects *Z*–*E* isomerism of the urethane bond[10] (cf. formulas **13** and **14**). A similar splitting of signals was observed with ortho ester **6a** (see Figure 1).

Acetalation of adenosine with aldehyde **16** in the presence of ethyl orthoformate and trifluroacetic acid as catalyst in DMF afforded only 2′,3′-*O*-ethoxymethyleneadenosine[22] (**18a**) in 73% yield in addition to the N,O mixed acetal **18b** obtained in 21% yield. The structure of the latter followed from analysis and uv max which is bathochromically shifted relative to **18a**. NMR shows the presence of two phenyl groups and two ethoxy functions. The absence of a free amino group was confirmed by the failure of **18b** to react with dimethylformamide dimethyl acetal.[23,24] In acid, compound **18b** is hydrolyzed[24] to adenosine 2′(3′)-formate and aldehyde **16**.

It is of interest to note that a similar reaction (formation of N,O mixed acetal derivative) was observed when adenosine was treated with *p*-nitrobenzaldehyde under similar conditions.[24] It appears therefore that alkoxycarbonium ions (see Scheme I, ref 24) derived from aldehydes carrying an electronegative substituent in the vicinity of aldehyde function are less reactive toward 2′,3′-cis diol grouping of adenosine than toward a weakly basic amino group of the adenine moiety. Contrariwise, the corresponding dialkoxycarbonium ions derived from analogous ortho esters [e.g., from ethyl *N*-benzyloxycarbonyl-DL-orthophenylalaninate (**6a**)] react smoothly with the 2′ and 3′ hydroxy groups of ribonucleosides (cf. compound **11**).

Experimental Section

General Methods. Evaporations were carried out in a Büchi rotary evaporator in vacuo at a bath temperature below 40 °C. Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Samples for analysis were dried at 10^{-3} mm over P_2O_5 at room temperature. Thin layer chromatography (TLC) was performed on 6 × 2 cm precoated silica gel F-254 aluminum foils (Merck, Darmstadt, Germany) in solvent S_1 (diethyl ether–petroleum ether, 1:1), S_2 (chloroform–methanol, 9:1), S_3 (chloroform–methanol, 4:1), S_4 ($CHCl_3$), and S_5 ($CHCl_3$–MeOH, 97:3). Preparative TLC and column chromatography were performed with silica gel 70–325 mesh ASTM (Merck, Darmstadt, Germany); for TLC 1% (w/w) fluorescent indicator, Lumilux Grün ZS Super (Riedel-De Haën AG, Seelze-Hannover, Germany) was added. Detection was performed in uv light (Mineralight) or with iodine vapors. Petroleum ether was of a 30–60 °C boiling range. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter. The ir spectra were measured in CCl_4 in a Perkin-Elmer Model 21 spectrometer. NMR spectra were obtained using a Varian A-60A spectrometer in CCl_4 or CD_3COCD_3, unless stated otherwise; $(CH_3)_4Si$ was used as an internal standard. Ethanol and DMF were dried with Linde molecular sieves. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ and stored over sodium wire. *N*-Benzyloxycarbonyl-L-phenylalanine was a product of Sigma Chemical Co., St. Louis, Mo. *N*-Benzyloxycarbonyl-L-phenylalanine *p*-nitrophenyl ester was prepared according to the literature.[12] Hydrocinnamonitrile was a product of Eastman Kodak Co., Rochester, N.Y.

Ethyl Hydrocinnamimidate Hydrochloride (2). The described procedure[5] was modified as follows. A solution of hydrocinnamonitrile [1, freshly distilled from P_2O_5 immediately before use, bp 98–100 °C (0.1 mm), 23.93 g, 0.182 mol] in ethanol (12.7 ml, 0.22 mol) was cooled in an ice bath and a slow stream of HCl was introduced directly from a tank with stirring to saturation. The resultant thick oil was kept overnight at 0 °C. The white, crystalline product **2** was filtered off after addition of dry ether (ca. 500 ml), and washed with ether and dried in vacuo over P_2O_5 and KOH in a desiccator: yield 38.41 g (98%); mp 144 °C dec (lit.[5] 130 °C); NMR (CD_3SOCD_3, sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard) δ 7.33 (s, 5, C_6H_5), 4.46 (q, 2, OCH_2), 1.32 (t, 3, CH_3).

Ethyl *N*-Chlorohydrocinnamimidate (3). The procedure described[6] for the preparation of ethyl *N*-chlorophenylacetimidate was followed. To the cooled (5 °C) solution of NaClO freshly made from NaOH (100 g, 2.5 mol) and chlorine (114.4 g, 1.61 mol) in water (800 ml) compound **2** was added portionwise with stirring (32.1 g, 0.15 mol) at 0–10 °C (ice–salt bath was used). It is imperative to keep the pH of the NaClO solution at 7.0 (pH meter) during the addition of hydrochloride **2** to avoid concomitant hydrolysis to the corresponding ester. The mixture was then stirred for 30 min, petroleum ether (100 ml) was then added, and the layers were separated. The aqueous portion was extracted with petroleum ether, and the combined extracts were dried ($MgSO_4$) and evaporated to give **3** as a colorless oil: 31.04 g (98%); $n^{30}D$ 1.5210; ir no absorptionat 1650–1800 (absence of CO ester) and 3200–4000 (absence of NH), 1600 cm^{-1} (strong, C=N—Cl, cf. ref 6); NMR (CCl_4) δ 7.17 (s, 5, C_6H_5), 4.09 (q, 2, OCH_2), 2.84 (s, 4, CH_2), 1.20 (t. 3, CH_3).

Ethyl DL-Orthophenylalaninate (4a) and 2,5-Dibenzyl-3,6-diethoxy-2,5-dihydropyrazine (5). The procedure[4] for preparation of amino acid ortho esters was extended to the phenylalanine derivative **4a**. The solution of compound **3** (21.17 g, 0.1 mol) in ethanol (50 ml) was added dropwise with stirring and external ice cooling to 1.25 M sodium ethylate (freshly prepared from sodium, 2.88 g, 0.125 mol, and 100 ml of ethanol). The solution was stirred for 1.5 h at 30–40 °C (bath temperature, NaCl started to precipitate) and 2 h at 80 °C. The reaction mixture was kept overnight at room temperature, poured into water (250 ml), and extracted with dichloromethane (3 × 100 ml). Combined organic layers were dried ($MgSO_4$) and evaporated to give **4a** as a yellow, rumlike smelling oil: $n^{28}D$ 1.4790; 26.46 g (99%); ir no absorption between 1650 and 1800 (absence of CO ester), 1065 cm^{-1} (strong, C–O–C); NMR (CCl_4) δ 7.13 (s, 5, C_6H_5), 3.65 (q, 6, OCH_2), 3.03 (m, 2, CH_2) 2.35 (q, 1, CH), 1.13 (t, 11, CH_3 overlapped with NH_2, after addition of D_2O the triplet became symmetric and it integrated for 9 protons). This product was sufficiently pure (ca. 95%) to be used in subsequent steps (preparation of **6a** and **9**) without further purification. Distillation of this product at 107–110 °C (0.25 mm) afforded ortho ester **4a** in two fractions (5.32 g, 20%). The second fraction ($n^{27}D$ 1.4813) was analyzed.

Anal. Calcd for $C_{15}H_{25}NO_3$ (267.4): C, 67.38; H, 9.43; N, 5.24. Found: C, 67.30; H, 9.27; N, 5.48.

Continued distillation afforded an additional fraction (2.1 g) of **4a** contaminated, according to ir, with **5**. The last fraction (thick syrup, $n^{25}D$ 1.5469), which was analyzed, was dissolved in petroleum ether and the solution cooled to −20 °C to give **5** (0.975 g, 5.6%): mp[25] 40–100 °C; ir 1703 cm^{-1} (C=N); NMR (CCl_4) δ 7.05 (m, 10, C_6H_5), 4.07 (m, 4, CH_2 of C_2H_5O), 1.23 (m, 6, CH_3 of C_2H_5O).[25]

Anal. Calcd for $C_{22}H_{26}N_2O_2 \cdot \frac{1}{4}H_2O$ (355.0): C, 74.44; H, 7.53; N, 7.89. Found: C, 74.50; H, 7.35; N, 8.15.

Ethyl *N*-Benzyloxycarbonyl-DL-orthophenylalaninate (6a). A solution of benzyloxycarbonyl chloride (7.5 g, 0.044 mol) in dry ether (200 ml) was added dropwise with stirring and external ice cooling to a mixture of ortho ester **4a** (10.68 g, 0.04 mol), triethylamine (12 ml, 0.12 mol), and dry ether (200 ml) during 40 min. The stirring continued for 1 h at 0 °C and after addition of ethanol (10 ml) for 30 min at room temperature. The precipitate (riethylamine hydrochloride) was filtered off and washed with ether and the filtrate was extracted with water (150 ml). Dried ($MgSO_4$) ether layer was evaporated and the resultant solid crystallized from petroleum ether (40 ml) at 0 °C to give 10.49 g (66%) of ortho ester derivative **6**: mp 77–79 °C; ir 3500 (NH), 1735 (CO, urethane), 1512, 1520 (amide II band of urethane plus aromatics), 1058 cm^{-1} (C–O–C); NMR (CCl_4) δ 7.15 (2 s, 10, C_6H_5), 4.9 (s, 2, CH_2 of $C_6H_5CH_2O$), 3.65 (d of q, 6, CH_2 of C_2H_5O), 2.8 (m, 2, CH_2), 1 13 (t, 9, CH_3 of C_2H_5O).

Anal. Calcd for $C_{23}H_{31}NO_5$ (401.5): C, 68.80; H, 7.78; N, 3.49. Found: C, 68.98; H, 7.90; N, 3.48.

Ethyl *N*-Benzyloxycarbonylorthoglycinate (6b). The procedure described for ortho ester **6a** was followed starting from ethyl orthoglycinate[4] **4b** (12.63 g, 0.071 mol) to give, after crystallization from petroleum ether, the *N*-benzyloxycarbonyl derivative **6b** (11.82 g, 38%), mp 35–40 °C (lit.[2a] 38–40 °C), which was identical with an authentic specimen:[2a] NMR (CCl_4) δ 7.19 (s, 5, C_6H_5), 4.98 (d, 2, CH_2 of $C_6H_5CH_2O$), 3.50 (q, 6, CH_2 of C_2H_5O, partially overlapped with CH_2 of the glycine portion), 3.32 (d, 2, CH_2 of glycine, partially overlapped with CH_2 of C_2H_5O).

Ethyl *N*-Benzyloxycarbonyl-DL-phenylalaninate (7). A solution of ortho ester **6a** (0.2 g, 0.5 mmol) in CH_2Cl_2 (20 ml) was stirred with 10% HCl (10 ml) for 30 min at room temperature. The layers were then separated, and the CH_2Cl_2 portion was washed with water (2 × 10 ml) and saturated solution of $NaHCO_3$ (10 ml). The dried ($MgSO_4$) organic phase was evaporated to a syrup which was dissolved in ether (5 ml). Petroleum ether (5 ml) was added and the mixture containing a syrupy precipitate was kept overnight at −20 °C whereupon it crystallized. Evaporation in vacuo gave crystalline ester **7**: mp 77–79 °C (lit.[11] 77–79 °C); mixture melting point with ortho ester **6a** was 65

°C; 0.13 g (80%); NMR (CCl_4) δ 7.25 and 7.14 (2 s, 10, C_6H_5), 5.03 (s, 2, CH_2 of $C_6H_5CH_2O$), 4.53 (m, 1, CH), 4.09 (q, 2, CH_2 of C_2H_5O), 1.17 (t, 3, CH_3 of C_2H_5O).

Ethyl *N*-Benzyloxycarbonyl-L-phenylalanyl-DL-orthophenylalaninate (9). The cooled solution of ortho ester **4a** (0.536 g, 2 mmol) and triethylamine (0.202 g, 2 mmol) in dichloromethane (10 ml) was treated with *p*-nitrophenyl ester[12] 8 (0.925 g, 2.2 mmol) in dichloromethane (10 ml). The reaction mixture was kept for 5 h at room temperature, whereupon it was extracted with a saturated solution of $NaHCO_3$ (3 × 10 ml) and NH_4OH (dilute 1:1, 3 × 10 ml). The organic layer was dried ($MgSO_4$) and evaporated to give a solid which as filtered after addition of ethanol: 0.69 g (63%), homogeneous on TLC (S_1); mp 114–118 °C was unchanged after recrystallization from cyclohexane; $[\alpha]^{24}D$ −27.4° (c 0.5, acetone); ir (KBr) 3370 (NH), 1705 (CO, urethane), 1660 (CO, amide), 1553, 1543 cm^{-1} (amide II bands of urethane and peptide bond and aromatics); NMR (CD_3COCD_3) δ ca. 7.22 (m, 15, C_6H_5), 4.95 (s, 2, CH_2 of $C_6H_5CH_2O$), 3.63 (poorly resolved d of q, 6, CH_2 of C_2H_5O), 1.08 (t, 9, CH_3).

Anal. Calcd for $C_{32}H_{40}N_2O_6$ (548.7): C, 70.05; H, 7.35; N, 5.11. Found: C, 70.07; H, 7.38; N, 5.13.

Ethyl *N*-Benzyloxycarbonyl-L-phenylalanyl-DL-phenylalaninate (10). A solution of dipeptide ortho ester **9** (70 mg, 0.13 mmol) in CH_2Cl_2 (10 ml) was stirred with 10% HCl (10 ml) for 30 min at room temperature. The layers were separated, the aqueous one was extracted with CH_2Cl_2 (10 ml), and the combined organic portions were washed with a saturated solution of $NaHCO_3$ (10 ml) and water (10 ml). The dried ($MgSO_4$) solution was evaporated, leaving a white solid **10**, mp 100–103 °C, TLC (S_1) homogeneous and different (slower) from ortho ester **9**. Crystallization from benzene–cyclohexane (2:1) gave 25 mg (40%) of material:[26] mp 128–130 °C; $[\alpha]^{24}D$ + 1.75° (c 0.91, ethyl acetate); NMR (CD_3COCD_3) δ 7.27 and 7.20 (2 s, 15, C_6H_5), 4.98 (s, 2, CH_2 of $C_6H_5CH_2O$), 4.55 (m, 2, CH), 4.09 (q, 2, CH_2 of C_2H_5O), 1.31 (t, 3, CH_3 of C_2H_5O).

Reaction of Uridine with Ortho Ester 6a. A solution of uridine (0.12 g, 0.5 mmol), ortho ester **6a** (0.4 g, 1 mmol), and CF_3COOH (5 drops) in DMF (5 ml) was kept for 15 h at room temperature. Triethylamine (0.5 ml) was then added, the solution was evaporated at 0.1 mm, and the residue was partitioned between CH_2Cl_2 (20 ml) and saturated $NaHCO_3$ (10 ml).The aqueous layer was extracted with CH_2Cl_2 (10 ml), and the combined organic portions were dried ($MgSO_4$) and evaporated. The syrupy residue was chromatographed on one 20 × 20 cm 2-mm thick layer of Stahl's silica gel GF-254 in solvent S_2 (0.1 ml of triethylamine/100 ml). The major slower moving uv-absorbing band was eluted with the 4:1 mixture of the same solvents and the eluate was evaporated to give a syrup. Trituration with ether–petroleum ether afforded 2′,3′-cyclic ortho ester **11** as an amorphous solid, 0.14 g (51%), homogeneous on TLC (S_2, S_3), uv max (ethanol) 260 nm (ε 8700), min 230 (ε 1800).

Anal. Calcd for $C_{28}H_{31}N_3O_9$ (553.6): C, 60.75; H, 5.65; N, 7.59. Found: C, 60.61; H, 5.90; N, 7.33.

2′(3′)-*O*-(*N*-Benzyloxycarbonyl-DL-phenylalanyl)uridine (12). A solution of 2′,3′-cyclic ortho ester **11** (83 mg, 0.15 mmol) in dioxane–acetic acid–water (2:3:3) mixture (4 ml) was kept for 22 h at room temperature. The solution was then lyophilized, the residue dissolved in $CHCl_3$, and ether–petroleum ether added to precipitate **12** as an amorphous powder, 77 mg (95%); the mobility on TLC (S_2, S_3) was identical with that of an authentic sample[3a] of the corresponding L-phenylalanyl derivative.

***N*-Benzyloxycarbonyl-L-phenylalaninal (16) and *N*-Benzyloxycarbonyl-L-phenylalaninol (19).** A solution of *N*-benzyloxycarbonyl-L-phenylalanine (**15**, 7 g, 0.023 mol) in tetrahydrofuran (45 ml) was cooled to 10 °C and *N,N′*-carbonyldiimidazole (4 g, 0.025 mol) was added. The resulting mixture was stirred for 20 min at 10 °C, then cooled to −20 °C and a solution of $LiAlH_4$ (1.9 g, 0.050 mol) in tetrahydrofuran (80 ml) was added dropwise over a period of 30 min. The stirring of the reaction mixture then continued for 15 min at −20 °C whereupon 2 M HCl (80 ml) was added. Evaporation in vacuo gave a solid which was extracted with chloroform (total 350 ml). The combined extracts were washed with water (100 ml), dried ($MgSO_4$), and evaporated. The residue was dissolved in chloroform (10 ml) and the solution was put on the top of the column made from silica gel (120 g, 3 × 30 cm). Elution with chloroform (250 ml) after evaporation gave a crystalline solid which was crystallized from ether–petroleum ether (1:2) to afford aldehyde **16** (3.3 g, 50%): mp 76–77 °C; $[\alpha]^{22}D$ −1.8° (c 0.45, $CHCl_3$);[19] ir (KBr) 3370 (NH), 1736 (CO, aldehyde), 1683 cm^{-1} (CO, urethane); NMR ($CDCl_3$) δ 9.35 (s, 1, CH=O), 7.31–6.94 (m, 10, C_6H_5), 5.03 (s, 2, CH_2 of benzyloxycarbonyl), 4.37 (q, 1, CH), 3.04 (d, 2, CH_2).

Anal. Calcd for $C_{17}H_{17}NO_3$ (283.3): C, 72.07; H, 6.05; N, 4.94. Found: C, 71.91; H, 6.08; N, 4.87.

Further elution with chloroform (100 ml) gave *N*-benzyloxycarbonyl-L-phenylalaninol (**19**, 1.53 g, 23%), mp 92–92.5 °C (lit.[17,18] 90–92 and 90 °C, respectively), $[\alpha]^{22}D$ −45.9° [lit.[17] −41.5° (c 1.4, ethanol)], $[\alpha]^{22}D$ −44.6° [lit.[18] −42° (c 2.0 methanol)].

The reduction of aldehyde **16** in a standard fashion (see above) with $LiAlH_4$ gave alcohol **19**, mp 76–77 °C, $[\alpha]^{22}D$ −3.4° (c 1.4, ethanol), ir corresponded to that of optically pure **19**.

***N*-Benzyloxycarbonyl-L-phenylalaninal Dimethyl Acetal (17).** Aldehyde **16** (0.4 g, 1.4 mmol) was added portionwise to a mixture of dimethylformamide dimethyl sulfate complex[28] (0.31 g, 1.55 mmol) and anhydrous methanol (65 mg, 2 mmol) at room temperature with stirring which then continued for 2.5 h. The mixture was kept overnight, and the crystallized product was washed with petroleum ether and recrystallized from petroleum ether–ether (1:1) to give acetal **17** (0.28 g, 60%): mp 58–60 °C; $[\alpha]^{22}D$ −8.4° (c 1.22, $CHCl_3$); ir (KBr) 3350 cm^{-1} (NH), 1690 (CO, urethane), 1550 (amide II band, urethane); NMR ($CDCl_3$) δ 7.25 and 7.16 (two s, 10, C_6H_5), 5.00 (s, 2, CH_2 of benzyloxycarbonyl), 4.08 (m, 2, CH), 3.41 and 3.35 (two s, 6, OCH_3), 2.85 (m, 2, CH_2).

Anal. Calcd for $C_{19}H_{23}NO_4$ (329.4): C, 69.28; H, 7.04; N, 4.25. Found: C, 69.20; H, 7.10; N, 4.17.

Reaction of Adenosine, Aldehyde 16, and Ethyl Orthoformate. A solution of aldehyde **16** (0.4 g, 1.4 mmol), ethyl orthoformate (0.46 g, 3.1 mmol), adenosine (0.376 g, 1.4 mmol), and trifluoroacetic acid (0.24 g, 2.1 mmol) in DMF (10 ml) was kept at room temperature for 39 h. Triethylamine was then added to adjust pH to 8–9 (indicator paper) and the volatile components were evaporated at 0.1 mm and room temperature. The residue was chromatographed on two loose layers of silica gel (35 × 15 cm, 3 mm thick) in solvent S_5 containing 0.2% of triethylamine (double development). The faster moving band was eluted with the solvent and evaporated to give amorphous product **18b** (0.185 g, 21%): TLC (S_2) homogeneous; uv max (ethanol) 265 nm (ε 16 500), min 228 (2100); NMR (CD_3COCD_3 + D_2O) δ 8.15 (s, 2, H_8 + H_2), 7.13 (m, 10, C_6H_5), 6.35 (d, 1, J = 3.5 Hz, $H_{1'}$), 1.10 and 1.42 (two t, CH_3 of C_2H_5O).

Anal. Calcd for $C_{32}H_{38}N_6O_8$ (634.7): C, 60.55; H, 6.04; N, 13.24. Found: C, 60.41; H, 6.17; N, 13.13.

Elution of the slower moving band with solvent S_2 containing 0.2% of triethylamine gave 2′,3′-*O*-ethoxymethyleneadenosine (**18a**, 0.33 g, 73%) identical with an authentic sample[22] (TLC, uv, and melting point).

Attempted Reaction of 18b with Dimethylformamide Dimethyl Acetal. A solution of compound **18b** (2 mg) and dimethylformamide dimethyl acetal (0.05 ml) in DMF (0.2 ml) was kept for 16 h at room temperature.[23] After evaporation the uv spectrum of the residue (ethanol) was identical with that of starting material **18b**.

Hydrolysis of Compound 18b. A solution of **18b** (5 mg) in 80% formic acid (0.5 ml) was kept at room temperature for 30 min. A sample of the mixture was chromatographed (TLC) in solvents S_4 and S_5 along with authentic samples of **18b**, adenosine 2′(3′)-*O*-formate prepared in situ from **18a** by the same procedure,[24] and aldehyde **16**.

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Registry No.—**1**, 645-59-0; **2**, 52353-64-7; **3**, 59830-53-4; **4a**, 59830-54-5; **4b**, 24595-61-7; **5**, 59830-55-6; **6a**, 59830-56-7; **6b**, 13347-35-8; **7**, 3588-57-6; **8**, 2578-86-1; **9**, 59830-57-8; **10**, 59830-58-9; **11**, 59830-59-0; **15**, 1161-13-3; **16**, 59830-60-3; **17**, 59830-61-4; **18b**, 59830-62-5; NaClO, 7681-52-9; sodium ethylate, 141-52-6; benzyloxycarbonyl chloride, 501-53-1; uridine, 58-96-8; *N,N′*-carbonyldiimidazole, 530-62-1; dimethylformamide, 68-12-2; adenosine, 58-61-7; ethyl orthoformate, 122-51-0.

References and Notes

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Orientation of the Nitrogen Lone-Pair Electrons in Cannivonine

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The structure of cannivonine b (1) has been reasonably established using ^1H NMR spectra recorded in the presence of shift reagents.[1-3] The cannivonine b is a tricyclic alkaloid having a 1-cyclohexen-3-ol ring fixed on the azabicyclo-[2.2.2]octane skeleton. Such a tricyclic compound can undergo syn–anti equilibration (Scheme I).

In the presence of the shift reagents, syn oriented nitrogen lone-pair electrons contribute to the formation of the eight-coordinate two donor atoms complex that involves O and N.[3] Recently Morishima and Yoshikawa[4] have found that the nitrogen lone pair of *N*-methyl-2-azabicyclo[2.2.2]oct-5-ene (and its dihydro derivative) is oriented in an anti position.

The NMR spectra, ^1H and ^{13}C, recorded in the presence of nickel bisacetylacetonate do not show the orientation of the metal relative to the double bond. The CNDO–MO calculations, carried out by the same authors, confirmed the preferential anti position of the nitrogen lone pair.[5,6] However, for cannivonine b, acetylacetonate can easily lie between the nitrogen and oxygen atoms and force the nitrogen lone pair into syn orientation (endo using Morishima nomenclature).

The syn orientation of the nitrogen lone pair is deduced from the ^{13}C NMR spectra of cannivonine (Table I).

The acetylacetonate relative induced shift of β carbons, with respect to the lone pair, is bigger if the lone pair is oriented trans (anti-coplanar) to this carbon. However, the gauche or eclipsed orientation shows a rather small contact shift (Scheme II). There are four carbons atoms β to the nitrogen lone pair (C-4, C-8, C-10, and C-11) and two β to the oxygen lone pairs (C-5 and C-7). Thus, the large C-10 relative induced shift of −1.38 is now understandable compared with the C-11, C-8, or C-4 induced shifts.

The oxygen atom has lone pairs oriented in such a manner that at the same time they are trans and eclipsed to C-5 and C-7. As a result, an average (~0.4) relative induced shift is observed.[7]

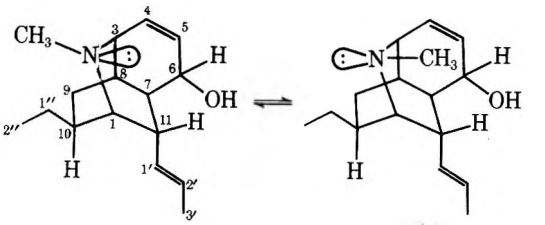
Finally, examination of steric repulsion in the 1-syn and 1-anti conformers shows that the syn conformers is effectively more stable. The interaction of 10-ethyl–NCH_3 and H-9β–NCH_3 in the syn conformer is smaller than the total interac-

Table I. Ni(acac)$_2$ Induced ^{13}C Contact Shifts for 1 [a]

C	δ_C	Relative induced shift
1	52.17	+1.00
NCH_3	43.81	+1.62
3	56.24	+1.40
4	129.73	−0.52
5	131.34	−0.44
6	65.51	+0.84
7	25.40	+0.40
8	26.87	−0.33
9	25.65	+0.02
10	24.92	−1.38
11	25.17	−0.41
1′	130.71	+0.08
2′	121.37	−0.17
3′	13.41	+0.14
1″	25.02	+0.08
2″	12.10	0.00

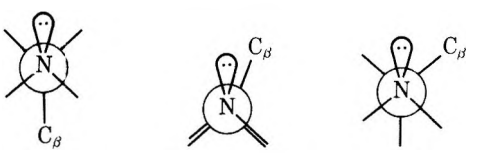
[a] Identification from off-resonance ^1H; see Experimental Section for details of calculations.

Scheme I



syn-1 *anti*-1

Scheme II



trans anti-coplanar eclipsed gauche

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tion of the cyclohexene part–NCH_3 in the anti conformer. Since the lone pair electrons of the nitrogen atom have such an important effect on the β carbon situated in the anti-coplanar position, this effect could be used in the investigation by C-13 spectroscopy of the preferential orientation of the nonbonded electrons in different cyclic amines.

Experimental Section

The cannivonine b (1) sample was isolated as previously described.[1] Nickel bisacetylacetonate (Aldrich Chemical Co.) was dried under reduced pressure for 24 h at the temperature of boiling acetone. The ^{13}C NMR spectra were obtained on Brucker HF-X-10 and Jeolco FT spectrometers (22.6 and 25.1 MHz, respectively) with an internal lock ^2H. The δ_C were measured in parts per million using Me_4Si as a standard. Solutions of 1 (10.0%) in $CDCl_3$ in standard tubes (10 mm or 8 mm) at a temperature of 25 ± 1 °C were used. The $Ni(acac)_2$ relative induced shifts for all carbons were measured from the slopes of linear plots of observed ^{13}C contact shifts vs. concentration of acetylacetonate (induced ^{13}C contact shifts in hertz plotted vs. concentration of $Ni(acac)_2$ expressed in millimoles). The "true" shift of 2.20 ppm was observed for 0.025 mol of $Ni(acac)_2$ for C-1 and was normalized to unity.

Acknowledgment. The author thanks the National Research Council of Canada for a small research grant.

Registry No.—1, 52340-94-0.

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Configuration of the Photoisomers of Benzylideneanilines

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Benzylideneanilines (ArCH=NAr′) are formally related to stilbenes (ArCH=CHAr′) and azobenzenes (ArN=NAr′), but are different from the latter two in the respect that *Z* (cis) and *E* (trans) isomers have not been isolated. It was reported that the irradiation of a solution of benzylideneaniline at low temperature converts it reversibly to a photoisomer of different uv absorption,[1a] but no concrete evidence as to its structure has been presented although a *Z* structure has been assigned to the photoisomer of 4,4′-dichlorobenzylideneaniline on the basis of dipole moment measurements.[2]

We have determined the uv spectra of photoisomers of many substituted benzylideneanilines in an EPA matrix (ether–isopentane–ethanol) at −196 °C and showed that the imino arene ring of the photoisomer is about 90° rotated from the ArCH=N– plane around the N–Ar′ bond.[3] However, it was not possible to determine whether or not the photoisomer has a *Z* structure.

As described in our previous paper,[3] the photoisomers are stable in a matrix at −196 °C for a long period and stable for several hours in solutions (EPA, methylcyclohexane, or acetone) at −72 °C. Therefore, the configuration of the photoisomers was studied by determining ^1H NMR spectra in acetone-d_6. Since this photoisomerization is complete only in dilute concentrations (~10^{-3} M), spectra were determined by use of a Fourier transform instrument (accumulation, 500–1000 sweeps). When the photoisomers produced at −196 or −72 °C were warmed to room temperature, the ^1H NMR and uv spectra showed that the photoisomers were completely converted back to the original *E* isomers. This change can be reproduced many times.

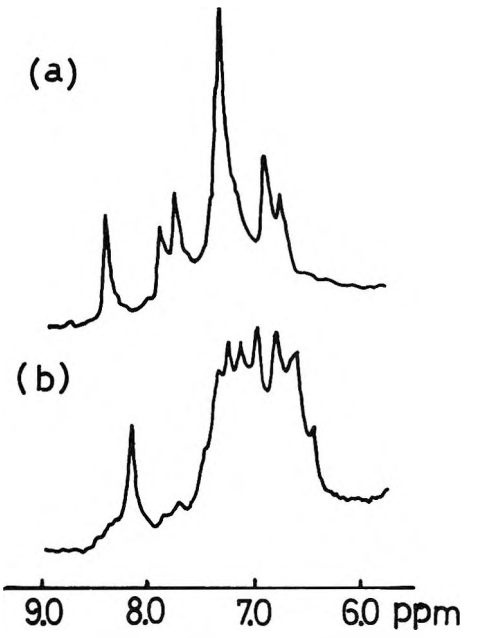
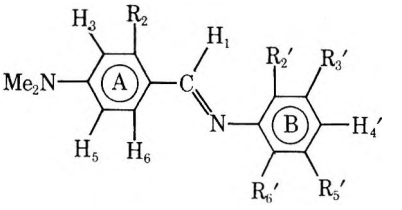
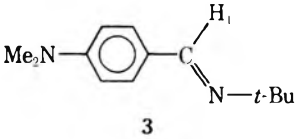


Figure 1. NMR spectra of (a) 1 and (b) its photoisomer 1a.

p-Dimethylaminobenzylideneaniline (1) and its methyl



1, $R_2 = R_2' = R_3' = R_5' = R_6' = H$
2, $R_2' = R_6' = Me$; $R_2 = R_3' = R_5' = H$
4, $R_2 = R_2' = R_6' = H$; $R_3' = R_5' = Me$
5, $R_2 = Me$; $R_2' = R_3' = R_5' = R_6' = H$



3

derivatives were chosen for our study because they have strong absorption maxima at wavelengths greater than 300 nm, and are almost completely converted to their photoisomers upon irradiation in acetone-d_6 solutions with a high-pressure mercury lamp. In order to ascertain the assignments of aromatic NMR absorptions, some derivatives of 1 deuterated at suitable positions were synthesized and their spectra were determined.

Results and Discussion

Figure 1a is the NMR spectrum of 1 in acetone-d_6 at −75 °C; H_1 (s, 8.41 ppm from internal Me_4Si); H_2 and H_6 (q, 7.85 ppm); H_3 and H_5 (q, 6.84 ppm); other ArH (m, ca. 7.4 ppm). Figure 1b is the NMR spectrum of the photoisomer of 1 (1a),

Table I. Chemical Shifts of Benzylideneanilines and Their Photoisomers[a]

	δ				Δδ	δ		Δδ	δ		Δδ	δ		Δδ
	1	1-2′,4′,6′-d_3	1a	1a-2′,4′,6′-d_3	(1 − 1a)	2	2a	(2 − 2a)	4	4a	(4 − 4a)	5	5a	(5 − 5a)
H_1	8.41	8.41	8.21	8.21	0.20	8.15	8.37	−0.22	8.42	8.18	0.24	8.63	8.53	0.10
H_2	7.85	7.85		7.09	0.76	7.87[b]	7.03[b]	0.8	7.88[c]	7.13[c]	0.24			
H_6												8.03[d]	6.65[d]	1.38
H_3	6.84	6.84		6.59	0.25	*e*	6.58[b]		6.8[c]	6.58[c]	0.2	6.64	6.63	0.01
H_5												6.71[d]	6.20[d]	0.51
$H_2′,H_6′$	7.4								6.86	6.39	0.47	7.31	6.82	0.49
$H_3′,H_5′$	7.4	7.44		7.42	0.02	e	7.03					7.42	7.32	0.10
$H_4′$	7.4					*e*			6.8			?	?	

[a] Downfield shift from internal Me_4Si in acetone-d_6 in parts per million. [b] $J_{H_2,H_3} = J_{H_5,H_6} = 8.79$ Hz (quartet). [c] $J_{H_2,H_3} = J_{H_5,H_6} = 8.79$ Hz (quartet). [d] $J_{H_5,H_6} = 8.79$ Hz (quartet). [e] 7.08–6.96.

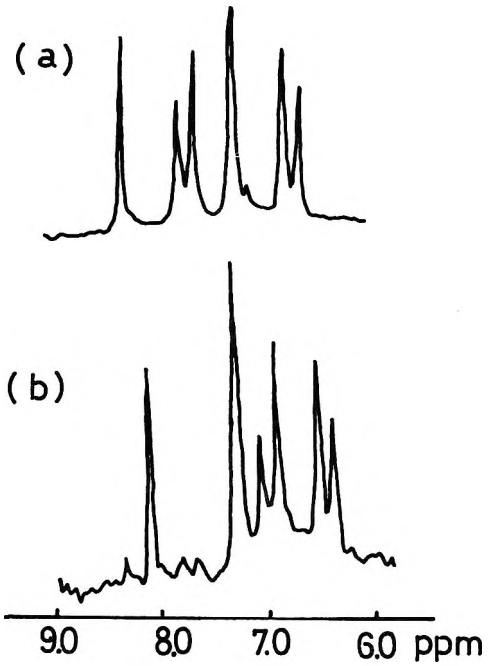


Figure 2. NMR spectra of (a) 1-2′,4′,6′-d_3 and (b) its photoisomer.

in which the absorption of H_1 is shifted to higher field (8.21 ppm). In order to assign other aromatic absorptions, 2′,4′,6′-trideuterated 1 was prepared, and its NMR spectrum and that of its photoisomer were determined (Figure 2). The chemical shifts of 1 and 2′,4′,6′-trideuterated 1 and their photoisomers are compared in Table I.

The absorptions of H_2, H_6, H_3, and H_5 are AA′BB′ type quartets, and this shows that ring A freely rotates around the Ar–C bond within the NMR time scale: $J_{H_2,H_3} = J_{H_5,H_6} = 8.79$ Hz. In the NMR spectrum of 1-2′,4′,6′-d_3, $H_3′$ and $H_5′$ are equivalent, and this can be interpreted in two ways: ring B also rapidly rotates around the Ar–N bond, or as proposed in our previous paper[3] the stable conformation of **1a** has ring B about 90° rotated around the Ar–N bond. The data shown in Table I can be reasonably explained if one assumes that **1a** has the *Z* structure shown in Figure 3. Although the possibility of the rapid rotation of ring B in **1a** cannot be rejected from the NMR data alone, examination of its molecular model suggests that it is unlikely, since its uv spectrum shows that ring A and the CH=N– group lie in the same plane.

In the case of *cis*-stilbenes no such twist of ring B has been invoked. One of the factors for stabilizing this twisted conformation for the photoisomers of benzylideneanilines must be the conjugation between the lone pair of the imino nitrogen and ring B. An x-ray analysis showed that ring B of benzylideneaniline (*E* isomer) itself is rotated by about 50° from the PhCH=N– plane.[4]

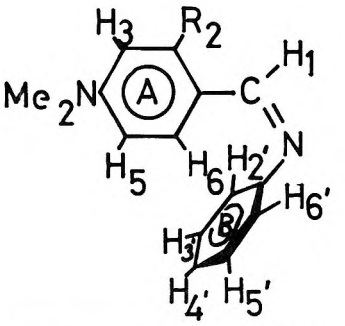


Figure 3. Structures proposed for photoisomers **1a** and **5a**: **1a**, R_2 = H; **5a**, R_2 = ME.

Although ring B in **1** is probably rotated around the Ar–N bond to some extent from the ArCH=N– plane,[5] H_1 must be strongly shifted to a lower field by the paramagnetic deshielding of the ring current. In accordance with such estimation, the methine proton H_1 of *p*-$Me_2NC_6H_4CH$=N-*t*-Bu (**3**) (to be discussed later) absorbs at 8.21 ppm at −75 °C in acetone-d_6. If **1a** has the *Z* structure shown above, the H_1 should not be affected by the ring current of ring B; the upfield shift (0.20 ppm) observed is quite reasonable.

The significant changes in H_2 and H_6 (0.75 ppm) can be ascribed to the diamagnetic shielding by ring B. If **1a** has the *Z* structure, H_2 and H_6 may be situated right above ring B, and such diamagnetic shielding is expected. H_3 and H_5 must be affected similarly by such diamagnetic shielding, but owing to the greater distance from ring B the upfield shift observed was smaller (0.25 ppm).

The comparison of the NMR spectra of 4-dimethylaminobenzylidene-2′,6′-dimethylaniline (**2**) and its photoisomer (**2a**) shown in Table I further supports our assignment of **1a** to the *Z* structure. **2** has an *E* structure as to the C=N bond, but because of the steric repulsion between 2′,6′-methyls and H_1 the ring B is greatly rotated around the Ar–N bond from the ArCH=N– plane. This can be readily understood from its molecular model, but is also further supported from the fact that the uv spectrum of **2** is quite similar to those of *p*-$Me_2NC_6H_4CH$=N-*t*-Bu (**3**) and **1a**. Therefore, H_1 of **2** is affected by the diamagnetic shielding effect of ring B and the downfield shift upon irradiation (0.22 ppm) can be ascribed to the loss of such diamagnetic shielding in H_1 of *Z*-structured **2a**. The upfield shift (0.8 ppm) of H_2 and H_6 upon irradiation is about the same as that observed in the case of **1** to **1a**.

Then, in order to clarify the changes in the absorptions of $H_2′$ and $H_6′$, the NMR spectra of 4-dimethylaminobenzylidene-3′,5′-dimethylaniline (**4**) and its photoisomer (**4a**) were

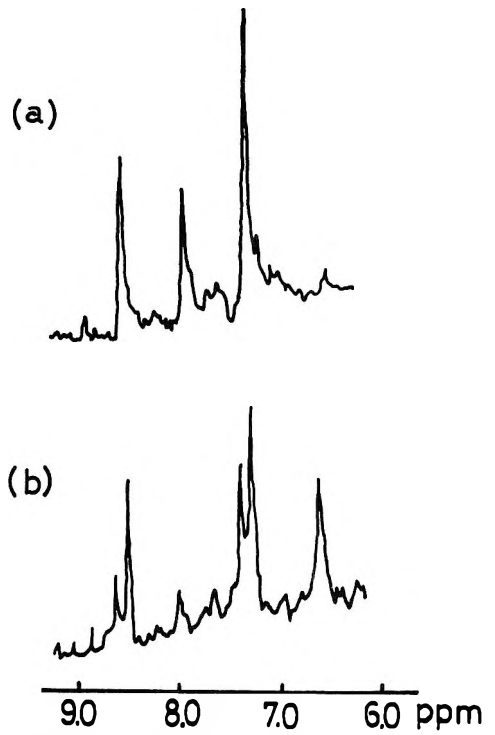


Figure 4. NMR spectra of (a) **5**-*3,5,2′,4′,6′-d*$_5$ and (b) its photoisomer (because of incomplete isomerization, a weak signal of the original azomethine signal is observed.)

investigated. The magnitude of the upfield shift in H_1 (0.24 ppm) upon irradiation is about the same as that observed in the case of **1**. The large upfield shift in H_2 and H_6 (0.75 ppm) upon irradiation is comparable to those observed in the case of **1** and **2**. The comparison of the NMR spectra of **4** and **4a** shows that the absorptions of H_2' and H_6' of ring B suffer an upfield shift of 0.47 ppm. This upfield shift can be explained as follows. The paramagnetic deshielding due to the ring current of the C=N bond affects the H_2' and H_6' in **4**, but not the H_2' and H_6' in **4a**, which has a twisted *Z* structure as shown in the case of **1a**. H_2' and H_6' are greatly rotated out of the ArCH=N– plane.

In **1**, **2**, **4**, or their photoisomers, ring A rotates around the Ar–C bond rapidly within the NMR time scale. Therefore, the upfield shift observed in the absorptions of H_2 and H_6 of **1** and **4** upon irradiation must be the average of the shifts of the H_6 affected by the diamagnetic shielding from the ring B and the H_2 not affected by such shielding. If the rotation of ring A around the Ar–C bond could be restricted, the real upfield shift in H_6 upon irradiation would be shown. Therefore, the changes in the NMR spectra of 2-methyl-4-dimethylaminobenzylideneaniline (**5**), its 2′,4′,6′-trideuterio derivative, and 3,5,2′,4′,6′-pentadeuterio derivative upon irradiation were investigated. If the photoisomer of **5** has a *Z* structure shown in Figure 3, the 2-methyl group should be situated far from ring B. Figure 4 shows the NMR spectra of **5**-*3,5,2′,4′,6′-d*$_5$ and its photoisomer.

The absorption of H_6 suffers a large upfield shift of 1.38 ppm, which is approximately twice the upfield shift observed in the H_2 and H_6 in **1**, **2**, or **4** (0.75 ppm) in accordance with our expectation. The upfield shift in H_5 (0.51 ppm) is also about two times that observed in the H_3 and H_5 in **1** or **4** (0.2–0.25 ppm). This is reasonable because H_5 in **5** is not equivalent with H_3 owing to the restriction of the rotation. The structure of **5a** postulated is consistent with the fact that the absorption of the H_3 was not shifted upon the photoisomerization. The upfield shift in H_2' and H_6' (0.49 ppm) is comparable to that observed in **4** (0.47 ppm), and this can be explained in terms of the loss of the paramagnetic deshielding by the C=N group upon isomerization.

Thus, the shifts observed in the absorptions of the methine proton and aromatic protons in **1**, **2**, **4**, and **5** upon irradiation can be rationalized if one assumes that the photoisomer has the *Z* structure and the ring B is rotated around the Ar–N bond from the ArCH=N plane by about 90°. Therefore, we may conclude that, as in the cases of stilbenes and azobenzenes, benzylideneanilines do have *Z* isomers, which are stable only below −70 °C and consequently have not been isolated as such.

Experimental Section

Materials. Benzylideneanilines **1**, **2**, **4**, and **5** and their deuterated derivatives were prepared by heating equimolar mixtures of the corresponding aldehydes and amines without solvent at 150 °C for 10 h, and recrystallized several times from hexane. The melting points follow: **1**, 98–99 °C (lit.[7] 99–100.5 °C); **1**-*2′,4′,6′-d*$_3$, 97–100 °C; **2**, 68–69 °C; **4**, 68–70 °C; **5**, 83–85 °C; **5**-*2′,4′,6′-d*$_3$, 81.5–84 °C; **5**-*3,5,2′,4′,6′-d*$_5$, 81–83 °C. **2**, **4**, and **5** are new compounds, and their identities are supported by their satisfactory elemental analyses data and NMR spectra. **3** was prepared by heating *p*-dimethylaminobenzaldehyde and *tert*-butylamine at the boiling point of the amine for 48 h, and purified by vacuum distillation at 143–145 °C (7.5 mmHg).

4-Dimethylamino-2-methylbenzaldehyde, used for synthesizing **5**, was prepared from *m*-toluidine by methylation with methyl phosphate and formylation of the 3-methyl-*N*,*N*-dimethylaniline[8] with formaldehyde and *p*-dimethylaminonitrosobenzene according to the method of formylating *N*,*N*-dimethylaniline.[9]

2,4,6-Trideuterioaniline was prepared by refluxing anilinium chloride in D_2O[10] (the extent of exchange, over 95%). 2-Methyl-3,5-dideuterio-4-dimethylaminobenzaldehyde was prepared by refluxing 2-methyl-4-dimethylaminobenzaldehyde in excess D_2O and acetic acid (the extent of exchange, over 95%).

An acetone-d_6 solution of a benzylideneaniline in a Pyrex tube (10 mm) was cooled in a dry ice–acetone bath and irradiated through a quartz Dewar bottle with a 500-W high-pressure mercury lamp till about 100% isomerization (5–10 h). Then its ^1H NMR spectrum was immediately determined at −75 °C with a JEOL Fourier transform NMR spectrophotometer FX-60.

Registry No.—**1**, 1613-99-6; **1**-*2′,4′,6′-d*$_3$, 59812-52-1; **1a**, 40339-45-5; **1a**-*2′,4′,6′-d*$_3$, 59812-53-2; **2**, 59812-54-3; **2a**, 59812-55-4; **3**, 59812-56-5; **4**, 59812-57-6; **4a**, 59812-58-7; **5**, 59812-59-8; **5**-*3,5,2′,4′,6′-d*$_5$, 59812-60-1; **5a**, 59812-61-2; **5a**-*3,5,2′,4′,6′-d*$_5$, 59813-33-1; *p*-dimethylaminobenzaldehyde, 100-10-7; *tert*-butylamine, 75-64-9; 4-dimethylamino-2-methylbenzaldehyde, 1199-59-3; 2,4,6-trideuterioaniline, 7291-08-9; 2-methyl-3,5-dideuterio-4-dimethylaminobenzaldehyde, 59812-62-3.

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(5) The extent of rotation varies with the substituent, and the molecule of 4-nitrobenzylidene-4′-dimethylaminoaniline is almost planar with very little rotation.[6] An x-ray analysis of **1** has not been reported in the literature, but the angle of rotation of ring B in **1** can be estimated as about 40–50° since the wavelength of the absorption maximum in the uv spectrum of **1** (340 nm, in hexane) is greater than those in **2** or **3** (324 nm, in hexane), and this suggests considerable conjugation between ring B and the ArCH=N– system.
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Ring Expansion Reaction of 1,2-Dihydroquinolines to 1-Benzazepines. 2

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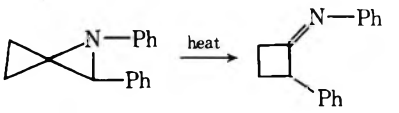
In a previous paper,[1] we reported a convenient synthetic method for the preparation of 1-benzazepines from 1,2-dihydroquinolines by the use of ethyl azidoformate. It was also revealed that the reaction proceeded by way of the intermediate 1,3-dialkyl-2-alkylidene-1,2-dihydroquinolines which were easily prepared by the treatment of 1,2,3-trialkylquinolinium chlorides with alkali. Successful employment of phenyl and benzoyl azides in the same ring expansion reaction is described in this paper with some mechanistic considerations.

When a mixture of 1,3-dimethyl-2-ethylidene-1,2-dihydroquinoline (**3**) with phenyl or benzoyl azide was heated at 110–120 °C, 1,3,4-trimethyl-2-phenylimino- (or benzoylimino-) 2,3-dihydro-1*H*-1-benzazepine (**4b** or **4c**) was produced in a good yield. Alkaline hydrolysis of **4b** or **4c** gave a high yield of 1,3,4-trimethyl-2-oxo-2,3-dihydro-1*H*-1-benzazepine (**5**) with elimination of aniline or benzamide. The yields are shown in Scheme I together with that previously reported for the case of ethyl azidoformate.[1]

compositions of the corresponding compounds **4a, 4b,** and **4c**. When **8a–c** were heated at 180 °C for 1 h, excellent yields of **4a–c** were obtained. These results together with the spectral data suggest that compounds **8** have the structures of 1,3-dimethyl-1,2-dihydroquinoline-2-spiro-2′-(1′-substituted 3′-methyl)aziridines. A similar thermal rearrangement of 1,2-diphenylazaspiro[2.2]pentane has been reported by Crandall et al.[4]



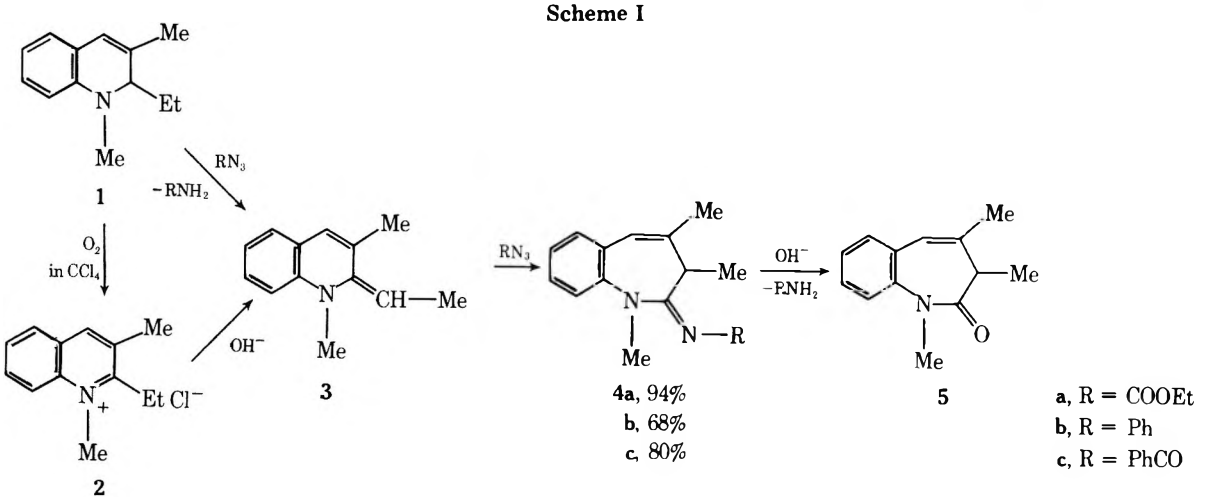
Because the aziridines **8** are stable at 120 °C, they are not intermediates in the thermal reaction of **3** with the azides. The azide addition via **6** and **7** may therefore be a more reasonable mechanism for the thermal reaction.

Experimental Section

NMR spectra were recorded using a JNM-MH-100 (JEOL) spectrometer with Me_4Si as internal standard. Ir spectra were taken on a IRA-2 (JASCO) spectrometer. Fractional distillation was accomplished by a Büchi GKR-5 Kugelrohr distillation apparatus. All procedures were carried out under a nitrogen atmosphere.

1,3,4-Trimethyl-2-phenylimino-2,3-dihydro-1*H*-1-benzazepine (4b). To a solution of 1,3-dimethyl-2-ethylquinolinium chloride[5] (**2**, 1.50 g, 6.8 mmol) in 10 ml of water was added 10 ml of 20% potassium hydroxide at 0–5 °C. 1,3-Dimethyl-2-ethylidene-1,2-dihydroquinoline

Scheme I

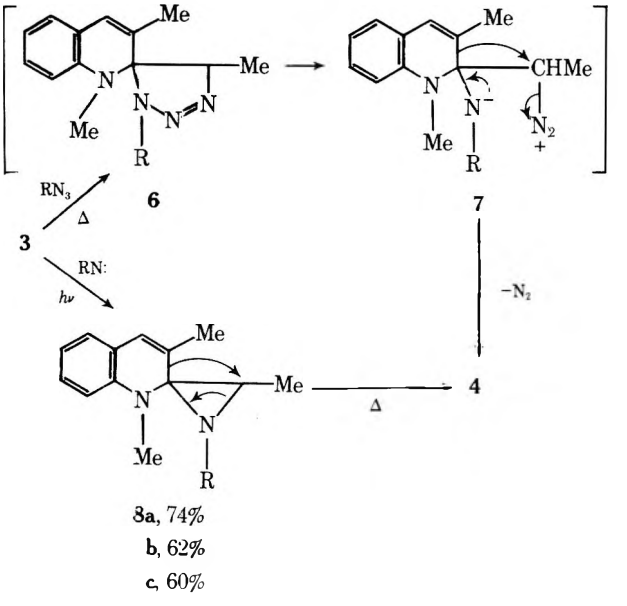


Compound **4b** was also obtained in 40% yield by the reaction of 1,3-dimethyl-2-ethyl-1,2-dihydroquinoline (**1**) with an excess of phenyl azide. However, a similar treatment of **1** with benzoyl azide gave no **4c** but phenyl isocyanate which is a thermal decomposition product of the azide.[2] This result would be attributable to the different thermal stabilities of azides employed.[2]

The half-life of the unimolecular decomposition of ethyl azidoformate to ethoxycarbonyl nitrene may be estimated to be 1–2 h at 120 °C based on Breslow's work.[3] The thermal reaction of **3** with azide may proceed either via a 1,3-dipolar addition process giving the triazoline **6** or via a cycloaddition process of a nitrene to give the aziridine **8** (Scheme II). Uv irradiation of a mixture of **3** and an azide at low temperature was expected to direct the reaction exclusively into the nitrene pathway.

A solution of **3** and an azide (ethyl azidoformate, phenyl azide, or benzoyl azide) in petroleum ether was thus irradiated with a high-pressure mercury lamp at 0–10 °C to give a yellow oil (**8a, 8b,** or **8c**), which could be distilled between 120 and 150 °C under reduced pressure without appreciable decomposition. The empirical formulas of these oils agreed with the

Scheme II



(3) was liberated immediately as a yellow oil, which was extracted with 40 ml of ligroin (bp 110–120 °C). To the boiling ligroin solution was added dropwise 1.61 g (13.5 mmol) of phenyl azide and the mixture was refluxed for 3 h. Fractional distillation of the reaction mixture gave 1.28 g (68%) of **4b**: bp 152–156 °C (0.03 mm); NMR ($CDCl_3$) δ 0.76 (d, 3, J = 7.5 Hz, C-3 CH_3), 1.78 (s, 3, C-4 CH_3), 3.49 (s, 3, NCH_3), 3.49 (q, 1, J = 7.5 Hz, C-3 H), 6.31 (s, 1, C-5 H), and 6.63–7.30 (m, 9, aromatic H).

Anal. Calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.38; H, 7.30; N, 10.31.

1,3,4-Trimethyl-2-benzoylimino-2,3-dihydro-1*H*-1-benzazepine (4c). In a similar manner as described above for **4b**, **3** prepared from **2** (1.00 g, 4.5 mmol) was treated with benzoyl azide (1.29 g, 8.8 mmol) to give 1.10 g (80%) of **4c**: bp 158–162 °C (0.03 mm); NMR ($CDCl_3$) δ 0.81 (d, 3, J = 7.0 Hz, C-3 CH_3), 1.98 (s, 3, C-4 CH_3), 3.52 (s, 3, NCH_3), 3.82 (q, 1, J = 7.0 Hz, C-3 H), 6.38 (s, 1, C-5 H), and 6.80–8.20 (m, 9, aromatic H).

Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.63; H, 6.73; N, 9.25.

Hydrolysis of 4b or 4c. A solution of **4b** (550 mg, 2.0 mmol) in 5% potassium hydroxide in 50% ethanol (20 ml) was refluxed for 12 h. After removal of the ethanol, the aqueous solution was extracted with chloroform. The extract was washed with water, dried, and concentrated. Fractional distillation of the residue gave 65 mg (35%) of aniline and 362 mg (90%) of **5**, bp 105–109 °C (0.03 mm) [lit.[1] bp 103–105 °C (0.025 mm)].

In a similar manner, **4c** (257 mg, 0.84 mmol) gave 49 mg (48%) of benzamide and 158 mg (93%) of **5**.

1,3-Dimethyl-1,2-dihydroquinoline-2-spiro-2′-(1′-ethoxycarbonyl-3′-methyl)aziridine (8a). Ethyl azidoformate 0.96 g, 9.0 mmol) was added to a solution of **3** [prepared from 1.00 g (4.5 mmol) of **2**] in 40 ml of petroleum ether. The mixture was irradiated with a high-pressure mercury lamp (100 W) at 0–10 °C for 6 h. The solvent was removed under reduced pressure. Distillation of the residue gave 832 mg (74%) of **8a**: bp 118–125 °C (0.03 mm); ir (neat) 1708 cm^{-1}; NMR ($CDCl_3$) δ 0.86 (d, 3, J = 7.5 Hz, C-3′ CH_3), 1.37 (t, 3, J = 7.0 Hz, ethoxy CH_3), 2.16 (s, 3, C-3 CH_3), 3.14 (s, 3, NCH_3), 4.07 (q, 1, J = 7.5 Hz, C-3′ H), 4.32 (q, 2, J = 7.0 Hz, ethoxy CH_2), and 6.83–7.40 (m, 5, C-4 and aromatic H).

Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.32; H, 7.41; N, 10.34.

1,3-Dimethyl-1,2-dihydroquinoline-2-spiro-2′-(1′-phenyl-3′-methyl)aziridine (8b). In a similar manner as described for **8a**, a solution of **3** [prepared from 1.00 g (4.5 mmol) of **2**] and phenyl azide (1.08 g, 8.4 mmol) in petroleum ether was treated giving 772 mg (62%) of **8b**: bp 125–132 °C (0.03 mm); NMR ($CDCl_3$) δ 1.36 (d, 3, J = 7.5 Hz, C-3′ CH_3), 1.72 (s, 3, C-3 CH_3), 2.36 (s, 3, NCH_3), 4.28 (q, 1, J = 7. Hz, C-3′ H), and 6.40–7.48 (m, 10, C-4 and aromatic H).

Anal. Calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.43; H, 7.29; N, 10.28.

1,3-Dimethyl-1,2-dihydroquinoline-2-spiro-2′-(1′-benzoyl-3′-methyl)aziridine (8c). In a similar manner as described above for **8a**, treatment of **3** [prepared from 1.00 g (4.5 mmol) of **2**] with benzoyl azide (1.33 g, 8.4 mmol) gave 821 mg (60%) of **8c**: bp 143–149 °C (0.04 mm); ir (neat) 1660 cm^{-1}; NMR ($CDCl_3$) δ 0.82 (d, 3, J = 7.5 Hz, C-3′ CH_3), 2.23 (s, 3, C-3 CH_3), 2.98 (s, 3, NCH_3), 4.03 (q, 1, J = 7.5 Hz C-3′ H), and 6.73–8.05 (m, 10, C-4 and aromatic H).

Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.74; H, 6.64; N, 9.23.

Thermal Rearrangement of 8a, 8b, and 8c to 4a, 4b, and 4c. Five hundred milligrams of **8a**, **8b**, or **8c** was sealed in a glass tube under reduced pressure and heated at 180 °C for 1 h. Distillation of the reactant gave 450 mg (90%) of **4a** [bp 138–142 °C (0.07 mm), lit.[1] bp 130–132 °C (0.03 mm)], 490 mg (98%) of **4b**, or 457 mg (91%) of **4c**. They were identified by spectroscopic comparisons with authentic samples obtained by the thermal reaction of **3** with ethyl azidoformate,[1] phenyl azide, or benzoyl azide, respectively.

Reaction of 1,3-Dimethyl-2-ethyl-1,2-dihydroquinoline[5] (1) with Phenyl Azide or Benzoyl Azide. Phenyl azide (4.76 g, 40 mmol) was added dropwise to a boiling solution of **1** (1.87 g, 10 mmol) in 20 ml of ligroin (bp 110–120 °C). The mixture was heated at reflux for 6 h. Fractional distillation of the reaction mixture was repeated to give 1.11 g (40%) of **4b**, which was identified with an authentic sample prepared by the thermal reaction of **3** with phenyl azide.

A similar treatment of **1** (1.87 g, 10 mmol) with benzoyl azide (5.88 g, 40 mmol) gave 3.82 g (80%) of phenyl isocyanate and 1.83 g (98%) of **1**.

Registry No.—**1**, 51904-95-1; **2**, 55539-76-9; **3**, 57091-72-2; **4b**, 59181-48-5; **4c**, 59183-03-5; **5**, 57091-65-3; **8a**, 59181-49-6; **8b**, 59813-04-6; **8c**, 59181-51-0; phenyl azide, 622-37-7; benzoyl azide, 582-61-6; ethyl azidoformate, 817-87-8.

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A General Method for the Synthesis of Reactive α,β-Unsaturated Diazomethyl Ketones: Allenyl Diazomethyl Ketone and Vinyl Diazomethyl Ketone[1]

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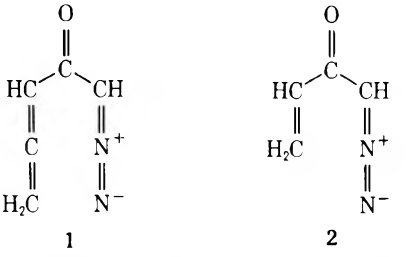
In the course of our photochemical studies, we required two unknown α,β-unsaturated diazomethyl ketones, allenyl diazomethyl ketone (**1**) and vinyl diazomethyl ketone (**2**).

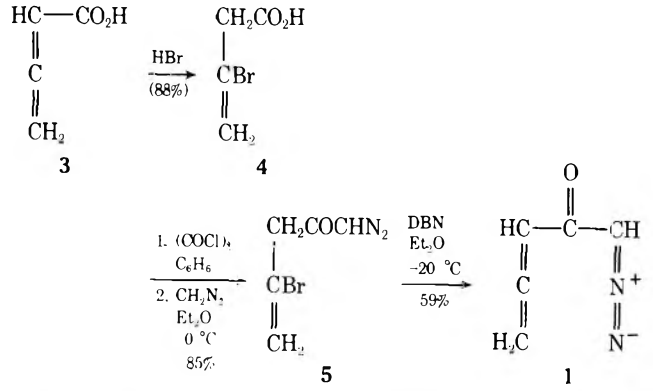


1 **2**

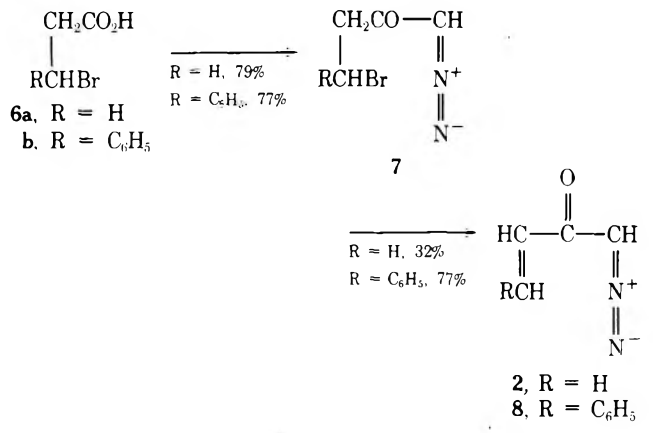
Synthesis of α,β-unsaturated diazomethyl ketones poses special problems. The Arndt–Eistert reaction of diazomethane with α,β-unsaturated acid chlorides does not compete effectively with the cycloaddition of diazomethane to the conjugated double bond.[2,3] The normal Arndt–Eistert reaction prevails only in a few highly substituted α,β-unsaturated acid chlorides.[3-6] Alternative procedures based on diazo transfer,[2,7] tosylhydrazone anion decomposition,[8] and the modified Forster[9] reaction have been developed for certain α,β-unsaturated diazo ketones. We wish to describe a facile method for the conversion of α,β-unsaturated carboxylic acids to the corresponding α,β-unsaturated diazomethyl ketones which is applicable to the synthesis of even the most reactive α,β-unsaturated diazomethyl ketones. The method uses a protected double bond in the Arndt–Eistert reaction and takes advantage of the stability of diazomethyl ketones in base in the regeneration of the double bond.

Addition of hydrogen bromide to 2,3-butadienoic acid (**3**)[10] gives 3-bromo-3-butenoic acid (**4**). Successive treatment of **4** with oxalyl chloride and diazomethane gives **5** which on treatment with DBN (1,5-diazabicyclo[4.3.0]non-5-ene)[11] in ether at −20 °C gives allenyl diazomethyl ketone (**1**). The maximum yield of allenyl diazomethyl ketone (**1**) was obtained when **5** was treated with 1 equiv of DBN in ether at −20 °C followed by warming to room temperature over 20 min. Use of potassium *tert*-butoxide in ether gave a lower yield of **1**.

A similar sequence starting from 3-bromopropionic acid (**6a**) gives vinyl diazomethyl ketone (**2**) via **7a**. Vinyl diazomethyl ketone proved to be very reactive at room temperature. It forms a glassy solid in 30 min at room temperature even in



the absence of light and oxygen. The utility of our method for substituted vinyl diazomethyl ketones is illustrated by the



synthesis of the previously described 1-diazo-4-phenyl-3-buten-2-one (8)[7,9] from commercially available 3-bromo-3-phenylpropionic acid.

Experimental Section

3-Bromo-3-butenoic Acid (4). Anhydrous hydrogen bromide was passed for 3 min into a stirred solution of **3**[10] (3.75 g, 0.0447 mol) in 150 ml of anhydrous ether at 0 °C. Removal of the solvent and excess acid under reduced pressure gave a solid residue, which when recrystallized from hexane gave **4** (6.5 g, 88%) as white platelets: mp 45.5–47 °C (lit.[12] mp 46–47 °C); ir ($CHCl_3$) 1720 (s, C=O), 1634 cm^{-1} (m, C=C); ^1H NMR ($CDCl_3$) δ 3.54 (d, 2 H, J = 1 Hz, CH_2), 5.64 (d, 1 H, J = 2 Hz, vinyl H), 5.78 (m, 1 H, vinyl H); molecular ion m/e 164 and 166.

Anal. Calcd for $C_4H_5BrO_2$: C, 29.12; H, 3.05; Br, 48.43. Found: C, 29.33; H, 3.10; Br, 48.22.

4-Bromo-1-diazo-4-penten-2-one (5). A solution of **4** (3.30 g, 0.02 mol) and oxalyl chloride (2.8 g, 0.022 mol) in benzene (12 ml) was stirred at 38 °C until the ir spectrum of the solution showed no acid carbonyl bond (12–14 h). About 20% of the solvent was removed under vacuum, and the solution was added rapidly to a vigorously stirred solution of diazomethane (2.0 g, 0.048 mol) in 170 ml of ether at 0 °C. After 10 min of stirring, removal of the ether under reduced pressure at 0 °C gave an orange liquid. Distillation in a cold finger still at 0.1 mm with pot temperature 50–75 °C gave **5** (3.21 g, 85%) as a yellow liquid: ir ($CHCl_3$) 2110 (s, C=N_2), 1642 (s, C=O), 1360 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 3.48 (d, 1 H, J < 1 Hz, CH_2), 5.48 (s, 1 H, CHN_2), 5.66 (d, 1 H, J = 2 Hz, vinyl H), 5.80 (m, 1 H, vinyl H); no molecular ion observable, fragment ion m/e 147 and 149 (loss of CHN_2).[13]

4-Bromo-1-diazo-2-butanone (7a). 3-Bromopropanoic acid (4.59 g, 0.03 mol) was reacted by the procedure described for the preparation of **5**. The product was distilled in a short-path still to give **7a** (4.2 g, 79%) as a yellow liquid: bp 43 °C (0.03 mm); ir ($CHCl_3$) 2112 (s, C=N_2), 1640 (s, C=O), 1375 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 2.88 (t, 2 H, J = 6 Hz, CH_2), 3.58 (t, 2 H, J = 6 Hz, CH_2), 5.36 (s, 1 H, CHN_2), splitting is observable in each peak of the triplets; molecular ion m/e 175.9591 (calcd for $C_4H_5BrN_2O$, 175.9586).[13]

4-Bromo-1-diazo-4-phenyl-2-butanone (7b). 3-Bromo-3-phenylpropanoic acid (5.73 g, 0.025 mol) was reacted by the procedure described for the preparation of **5**, except that the acid chloride was formed at 50 °C. The product, a yellow solid, when recrystallized from 1/6 benzene/hexane gave **7b** (4.87 g, 77%) as light yellow needles: mp 68.5–70 °C; ir ($CHCl_3$) 2110 (s, C=N_2), 1642 (s, C=O), 1378 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 3.14 (d, 1 H, J = 6 Hz, CH_2), 3.22 (d, 1 H, J = 8 Hz, CH_2), 5.21 (s, 1 H, CHN_2), 5.41 (d of d, 1 H, J = 8 and 6 Hz, CH), 7.32 (broad s, 5 H, phenyl); molecular ion m/e 252 and 254.

Anal. Calcd for $C_{10}H_9BrN_2O$: C, 47.45; H, 3.58; Br, 31.57; N, 11.09. Found: C, 47.76, H, 3.57; Br, 31.72; N, 11.04.

1-Dizao-3,4-pentadien-2-one (1). A solution of **5** (0.672 g, 0.0035 mol) and hydroquinone (0.02 g) in 40 ml of anhydrous ether was cooled to −20 °C under N_2. With vigorous stirring, freshly distilled DBN (0.435 g, 0.0035 mol) was added dropwise over 1 min. A precipitate formed immediately. The solution was warmed to room temperature over 20 min and filtered, and the solvent was removed under vacuum at 0 °C giving a yellow liquid. The flask containing the liquid was immediately connected to a U-tube leading to a vacuum pump. With the tube at 15 °C the system was evaporated to 0.1 mm, and the flask was warmed over 15 min to 70 °C. The product (**1**, 0.224 g, 59%) was collected as a yellow liquid: ir ($CHCl_3$) 2112 (s, C=N_2), 1968 and 1935 (m, C=C=C), 1620 (s, C=O), 1368 cm^{-1} (s); ^1H NMR δ 5.20 (broad d, 2 H, J = 7 Hz, allenyl CH_2), 5.52 (s, 1 H, CHN_2), 5.71 (d of d, 1 H, J = 7 and 8 Hz, allenyl CH) (the allenyl ^1H NMR pattern is similar to that of **3**); molecular ion (**1**) m/e 108.0331 (calcd for $C_5H_4N_2O$, 108.0324).[13] The product (1) could be kept for a few days at −30 °C. Allenyl diazomethyl ketone (1, 0.025 g) could be chromatographed on activity III alumina (2.0 g) with rapid elution by 20% benzene in pentane (75% recovery). Alumina of greater activity entirely decomposed 1.

1-Diazo-3-buten-2-one (2). Reaction of **7a** (1.33 g, 0.0075 mol) and DBN (0.930 g, 0.0075 mol) by the method used to prepare 1 gave, upon removal of solvent, a yellow liquid. This liquid was immediately transferred to a 5-ml pear-shaped flask fitted with a N_2 capillary ebullator and connected through a cold trap to a vacuum pump. The system was protected from light. The trap was cooled to −7 °C, the system evacuated to 0.1 mm, and the flask warmed over 10 min to 35 °C. The product (**2**, 0.23 g, 32%) was collected as a yellow liquid: ir ($CHCl_3$) 2100 (s, C=N_2), 1645 (s, C=C), 1610 (s, C=O), 1348 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 5.34 (s, 1, CHN_2), 5.56 (d of d, 1 H, J = 5 and 7 Hz, vinyl CH), 6.22, 6.19, and 6.11 (m, 2 H, vinyl CH_2) (the vinyl CH_2 pattern is interpretable as two doublets, with their upfield peaks superimposed; the olefin ^1H NMR pattern is similar to that of 3-buten-2-one); molecular ion (**2**) m/e 96.0326 (calcd for $C_4H_4N_2O$, 96.0324).[13] The product (**2**) decomposed significantly in 2 days when stored at −30 ° C.

1-Diazo-4-phenyl-3-butene-2-one (8). Reaction of **7b** (1.52 g, 0.006, mol) and DBN (0.758 g, 0.0061 mol) using the procedure for the preparation of **2** gave, on removal of solvent, a yellow solid, which when recrystallized from hexane gave **8** (0.79 g, 77%) as yellow needles: mp 66.5–68.5 °C (lit.[9] mp 68–69 °C); ir ($CHCl_3$) 2102 (C=N_2), 1642 (C=C), 1592 cm^{-1} (C=O).

Acknowledgment. This research was supported by Grant HD09279 from the National Institute for Child Health and Human Development.

Registry No.—**1**, 59813-08-0; **2**, 59813-09-1; **3**, 5732-10-5; **4**, 21031-45-8; **5**, 59813-10-4; **6a**, 590-92-1; **6b**, 15463-91-9; **7a**, 59813-11-5; **7b**, 59813-12-6; **8**, 24265-71-2; oxalyl chloride, 79-37-8; diazomethane, 334-88-3; DBN, 3001-72-7.

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(13) Elemental analysis was not possible because the product was not sufficiently stable at room temperature.

Selective Reduction of α,β-Unsaturated Esters, Nitriles, and Nitro Compounds with Sodium Cyanoborohydride

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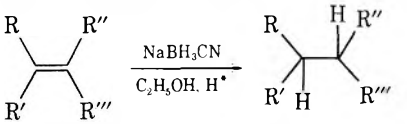
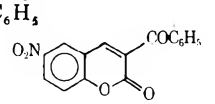
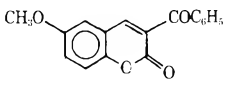
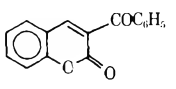
Our interest in the selective reducing properties of cyanoborohydride coupled with the recent attention accorded the reduction of α,β-unsaturated systems[1] prompts this report of the capability of cyanoborohydride for the facile and selective reduction of certain conjugated double bonds to the corresponding saturated derivatives.

The reduction of alkenes conjugated with strong electron-withdrawing groups such as esters,[5] nitriles,[5] sulfonate esters,[6] or nitro groups[7] has been observed with borohydrides or lithium aluminum hydride.[8] Thus, α,β-unsaturated esters are reduced by borohydride to the saturated derivatives if an additional cyano or ester is located at the α position.[5] Furthermore, conjugated cyano esters are often reduced to the saturated cyano alcohols.[5d,e] The highly electronegative cyano group evidently renders the normally resistant carbethoxy substituent electrophilic enough to suffer attack by borohydride. Recently, lithium tri-sec-butylborohydride (L-Selectride) at low temperatures has been found to effectively reduce conjugated carbonyl compounds, including esters, to the saturated derivatives,[9] Finally, Dittmer[6a] has reported reduction of the double bond in the strained ring thiete 1,1-dioxide with borohydride; acetylenic sulfones, however, apparently are reduced clearly to trans α,β-unsaturated sulfones.[6b]

Sodium cyanoborohydride is such an extremely nonaggressive reducing agent that even normally sensitive groups such as aldehydes and ketones are effectively reduced only when the electrophilicity of the carbonyl is increased by protonation.[4,10] Even under acidic conditions, however, other carbonyl derivatives, including esters, acids, and amides, remain unmolested. We envisioned that the reactivity of carbon–carbon double bonds of α,β-unsaturated carbonyl systems might be susceptible to activation by protonation and consequently enable the selective conversion of such systems to the saturated derivatives without affecting other functional groups. This note describes the successful realization of this conception using $NaBH_3CN$ in acidic ethanol at ambient temperature. The general procedure utilized was mild and convenient. The substrate, a 10% mole excess of $NaBH_3CN$, and a small quantity of bromocresol green were stirred in ethanol and concentrated HCl added dropwise until the solution was acidic as indicated by a color change to yellow.

Table I. Selective Reduction of Conjugated Alkenes with Sodium Cyanoborohydride[a]



Registry no. (alkene)	Entry	R	R′	R″	R‴	Time, h	% yield[b] (GLC)	Registry no. (product)
5292-53-5	1	C_6H_5	H	$CO_2C_2H_5$	$CO_2C_2H_5$	1.0	(90)	607-81-8
	2	C_6H_5	H	$CO_2C_2H_5$	$CO_2C_2H_5$	4.0	85	
	3	C_6H_5	H	$CO_2C_2H_5$	$CO_2C_2H_5$	2.0[c]	(69)	
17422-56-9	4	o-$NO_2C_6H_5$	H	$CO_2C_2H_5$	$CO_2C_2H_5$	1.0	78	59803-35-9
22399-00-4	5	p-$NO_2C_6H_5$	H	$CO_2C_2H_5$	$CO_2C_2H_5$	0.75	98	7598-70-1
6331-45-9	6	m-$NO_2C_6H_5$	H	$CO_2C_2H_5$	$CO_2C_2H_5$	1.0	84	59803-36-0
22511-22-4	7	p-$CH_3CONHC_6H_5$	H	$CO_2C_2H_5$	$CO_2C_2H_5$	2.5	80	59803-37-1
59803-31-5	8	m-CNC_6H_5	H	$CO_2C_2H_5$	$CO_2C_2H_5$	1.0	84	59803-38-2
2025-40-3		C_6H_5	H	$CO_2C_2H_5$	CN	1.0	67	6731-58-4
18925-00-3	9	m-$NO_2C_6H_5$	H	$CO_2C_2H_5$	CN	1.0	82	59803-39-3
6629-53-4	10	p-$CH_3CONHC_6H_5$	H	$CO_2C_2H_5$	CN	1.0	80	59803-40-6
59803-32-6	11	o-BrC_6H_5	H	$CO_2C_2H_5$	CN	1.0	88	59803-41-7
7324-89-2	12	2,4-di-ClC_6H_5	H	$CO_2C_2H_5$	CN	1.0	99[d]	59803-42-8
709-79-5	13	C_6H_5	H	$CONH_2$	CN	1.5	72	7216-46-8
705-60-2	14	C_6H_5	H	NO_2	CH_3	1.0	67	17322-34-8
6802-75-1	15	CH_3	CH_3	$CO_2C_2H_5$	$CO_2C_2H_5$	5.0	31[e]	759-36-4
103-36-6	16	C_6H_5	H	H	$CO_2C_2H_5$	1.0	0[f]	2021-28-5
59803-33-7	17					1.5	86	59803-43-9
59803-34-8	18					1.5	81	59803-44-0
1846-74-8	19					4.0	57	7216-47-9

[a] The reductions were conducted at ambient temperature as 0.4 M solutions of the compound in ethanol using a 10% mole excess of $NaBH_3CN$. Bromocresol green was employed as an indicator and the solutions were acidified with concentrated HCl. [b] Isolated yields, purified by distillation or recrystallization. GLC yields are corrected for detector response and utilized an internal standard. All known compounds corresponded to literature descriptions. New compounds gave satisfactory elemental analyses copies of which have been provided to the Editor (exception, entry 10). [c] No acid used. [d] Reaction was conducted in methanol; yield of crude product. [e] 69% recovery of starting material. [f] 93% recovery of starting material.

Additional HCl was added as required to maintain the solution acidity. After an appropriate time period, usually 1 h, the products were isolated by dilution with water followed by filtration or extraction with ether. Table I presents results for a variety of structural types. As evident, the method appears suitable for conjugated derivatives which are activated by a nitro group (entry 14) or by two α-positioned electron-withdrawing substituents including ester, cyano, lactone, ketone, or amide in varying combinations. Singly substituted double bonds as in ethyl cinnamate (entry 16) are resistant and aryl substitution enhances the reduction rate (entry 15). The method is quite selective in that other functional groups are unaffected including amido (entries 7, 10, 13), aromatic and aliphatic nitro (entries 4–6, 9, 14, 17) or cyano (entries 8–13) moieties, esters (entries 1–12, 15, 16), lactones (entries 17–19), or aryl ketones (entries 17–19). Furthermore, in contrast to analogous reductions with $NaBH_4$,[5d,e] cyano esters are not further reduced to the corresponding cyano alcohols. The use of acid, although not essential, results in higher yields (compare entries 1 and 3), ostensibly by rapid protonation of initially produced stable α carbanions before side reactions can intervene. This is evidenced by the relatively high yield of 1-methyl-2-phenylnitroethane obtained (entry 14) compared to previous investigations[7a,b] coupled with the absence of dimeric Michael products which are concomitantly produced with other hydride reagents.[7a,11]

Experimental Section

Materials. $NaBH_3CN$ was obtained from Aldrich Chemical Co. and used without purification. Starting materials were either obtained commercially or prepared by standard procedures.[12] All new compounds gave satisfactory elemental analysis and showed spectral (ir and NMR) data consistant with the structures. Elemental analyses were provided by Chemalytics, Inc., Tempe, Ariz., copies of which have been provided the Editor.

General Reduction Procedure. The general procedure utilized is presented in the text and is described below for the reduction of 6-nitro-3-benzoylcoumarin.

6-Nitro-3-benzoyl-3,4-dihydrocoumarin. A slurry of 6-nitro-3-benzoylcoumarin (2.95 g, 10 mmol), $NaBH_3CN$ (0.69 g, 11 mmol), and a small amount of bromocresol green indicator in 25 ml of ethanol was magnetically stirred while concentrated HCl was added dropwise until the color changed to yellow. Periodically, additional HCl was added in order to maintain the yellow color. After 1.5 h the reaction mixture was diluted with ca. 150 ml of water and cooled and the resulting while needles were filtered and dried under vacuum (2.54 g, 86%). The ir and NMR indicated complete reduction of the double bond.

Anal. Calcd for $C_{16}H_{11}NO_5$: C, 64.65; H, 3.73. Found: C, 64.70; H, 3.55.

Acknowledgment. The authors thank the donors of the Petroleum Research Fund, administrated by the American Chemical Society, for partial support of this work.

Registry No.—$NaBH_3CN$, 25895-60-7.

References and Notes

(1) Recent studies include the successful reduction of conjugated ketones to the corresponding saturated derivatives with potassium tri-sec-butylborohydride,[2a] various Cu(I) H complexes,[2b-e] hydrosilanerhodium(I) complexes,[2f] and ferrocene–HCl.[2g] Tetrahydroaluminate,[2h] borohydride,[3] and cyanoborohydride[4] are less discriminate and carbonyl reduction competes favorably in most cases.

(2) (a) B. Ganem, *J. Org. Chem.*, **40**, 146 (1975); (b) S. Masamune, G. S. Bates, and P. E. Georghian, *J. Am. Chem. Soc.*, **96**, 3686 (1974); (c) R. K. Boeckman, Jr., and R. Michalak, *ibid.*, **96**, 1623 (1974); (d) M. F. Semmelhack and R. D. Stauffer, *J. Org. Chem.*, **40**, 3619 (1975); (e) E. C. Ashby and J. J. Lim, *Tetrahedron Lett.*, 4453 (1975); (f) I. Ojima and T. Kogure, *ibid.*, 5035 (1972); (g) K. Yamakawa and M. Moroe, *J. Organomet. Chem.*, **50**, C43 (1973); (h) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **70**, 3738 (1948).

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(4) Cyanoborohydride apparently affords reduction of conjugated alkenes only when the system is cyclic; cf (a) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971); (b) R. O. Hutchins and D. Kandasamy, *J. Org. Chem.*, **40**, 2530 (1975); (c) M.-H. Boutique, R. Jacquesy, and Y. Petit, *Bull. Soc. Chim. Fr.*, **11**, 3062 (1973); (d) C. V. Grudzinskas and M. J. Weiss, *Tetrahedron Lett.*, 141 (1973).

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(10) C. F. Lane, *Synthesis*, 135 (1975).

(11) The results further suggest the intriguing possibility of generating enolate ions in aprotic solvents with cyanoborohydrides which can subsequently be exploited for condensation or alkylation reactions.[9] This tactic is being actively pursued.

(12) (a) α,β-Unsaturated cyanoacetates: F. D. Popp, *J. Org. Chem.*, **25**, 646 (1960). (b) α,β-Unsaturated malonates: C. F. H. Allen and F. W. Spangler, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 377; *Org. Synth.*, **25**, 42 (1945). Benzoylcoumarins: ref 5b. α-Cyanocinnamamide: ref 5b.

Oxidation of Sterically Hindered Alcohols to Carbonyls with Dimethyl Sulfoxide–Trifluoroacetic Anhydride

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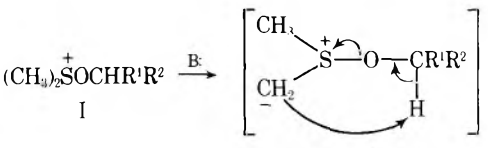
As an outgrowth of our earlier study of a new synthesis of iminosulfuranes,[1] we have investigated a new reagent for the oxidation of alcohols to aldehydes or ketones which appears to be generally useful, operationally simple, highly selective, and efficient.[2] This new reagent, dimethyl sulfoxide–trifluoroacetic anhydride (Me_2SO–TFAA), complements previous reagents[3-13] for the conversion of alcohols to dimethylalkoxysulfonium salt intermediates (I) which, on treatment with base under mild conditions, are rapidly converted to carbonyls in high yields (eq 1):



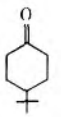
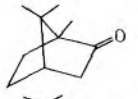
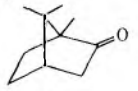
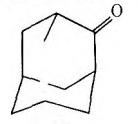
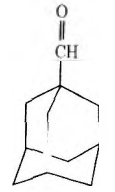
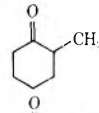
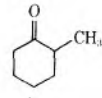
$$\longrightarrow (CH_3)_2S + R^1R^2C{=}O \quad (1)$$

R^1, R^2 = alkyl, aryl, aralkyl, H, alicyclic, etc.

None of the previous methods gives satisfactory results with all classes of primary and secondary alcohols. The new reagent, dimethyl sulfoxide–trifluoroacetic anhydride, now appears to be a most generally useful reagent for the facile conversion of primary and secondary alcohols to carbonyls in high to quantitative yields. In assessing the scope and limitations of this new reagent, the oxidation of some model sterically hindered alcohols was studied. In this note we are reporting the results obtained thus far.

Yields of carbonyls from hindered alcohols (>80–100%) are higher than those from previously studied unhindered alcohols and by-product formation is reduced (usually to <5%) (Table I). We find that (a) the more hindered the alcohol, the higher the yield and alcohols (**5, 6**) with bulky groups on both sides of the carbinol carbon give quantitative yields; (b) no difficulty is experienced in oxidizing primary and secondary

Table I

Alcohol	Carbonyl product	Procedure	Yield, % GLC	Yield, % DNP[a]	Yield, % Isolation
4-*tert*-Butylcyclohexanol (1) (mixture of cis and trans)		C	88	88	
2,2-Dimethyl-1-phenyl-propanyl (2)		A	97	95	
3,3-Dimethyl-2-butanol (3)		C		84	
2,2-Dimethyl-1-propanol (4)		C		81	
2,4-Dimethyl-3-pentanol (5)		C	100	42	86
2,6-Dimethylcyclohexanol (6) (mixture of isomers)		C	100	76	89
1-Borneol (7)		C	98	81	93
dl-Isoborneol (8)		A	93	85	88
8		C	88		
exo-Norborneol (9)		C	95	83	
Norborneol (10) (mixture of exo and endo)		C	96	85	
2-Adamantanol (11)[b]		C	96	95	
1-Adamantanemethanol (12)[c]		C		86	
2-Methylcyclohexanol (13) (mixture of cis and trans)		C	84	80	
trans-2-Methylcyclohexanol (14)		C	80	71	

[a] By isolation of the 2,4-dinitrophenylhydrazone. [b] Added as a solution in Me_2SO (10 ml)–CH_2Cl_2 (10 ml). [c] Additional CH_2Cl_2 (10 ml) was used in the reaction system to effect solution.

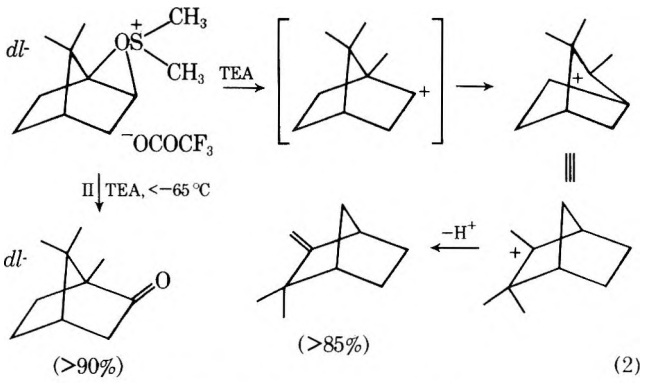
neopentyl-type alcohols (**2, 3, 4, 12**); (c) no substantial difference is noted in oxidizing both exo and endo hydroxyl groups (**7, 8, 9, 10, 13**); and (d) seemingly equally good results are obtained in the oxidation of both equatorial and axial hydroxyl groups (**1, 6, 13**).[1]

The literature is sparse on the oxidation of sterically hindered alcohols with the previously reported oxidizing reagents. Me_2SO–DCC and Me_2SO–SO_3 are reported to oxidize highly hindered hydroxyl groups reluctantly owing to the bulk of the initial adducts and hence are inert, for example, to axial 11β-hydroxyprogestrone.[4] Me_2SO–Ac_2O is often well suited for the oxidation of rather hindered alcohols; however, poor results were obtained in the oxidation of two hindered alcohols, 3,3-dimethyl-2-butanol (**3**)[14] and 2,2,3-trimethyl-2-butanol.[15]

In view of the excellent yields of carbonyls from the hindered alcohols studied thus far, Me_2SO–TFAA is clearly superior to the other reagents and is the reagent of choice for the oxidation of highly hindered alcohols. We believe that this is a consequence both of the smaller size of the Me_2SO–TFAA adduct and the outstanding leaving group property of trifluoroacetate ion.

In addition, the Me_2SO–TFAA reaction occurs instantaneously at very low temperature (<−50 °C) thus making it

possible to oxidize alcohols which form stable sulfonium salts *only* at low temperatures. The oxidation of *dl*-isoborneol is a good illustration of this point. The sulfonium salt (II) is solvolyzed at room temperature (or above) and camphene, the rearrangement–elimination product, is obtained when procedure C (room temperature addition of TEA) is employed. But *dl*-camphor, the anticipated oxidation product, can still be obtained in high yield by addition of TEA at low temperature (<−65 °C). The reaction course is depicted as follows (eq 2):



(2)

Experimental Section

Procedures for Oxidation of Alcohols. Procedure A. To a solution of dry Me_2SO (20 mmol) in distilled dry CH_2Cl_2 (10 ml) cooled below −65 °C with a dry ice–acetone bath, TFAA (15 mmol) in CH_2Cl_2 (5 ml) was added with efficient mechanical stirring in ca. 10 min. After 10 min below −65 °C, a solution of an alcohol (10 mmol) in CH_2Cl_2 (5–10 ml) was added to the mixture in ca. 10 min. The rate of addition of TFAA or alcohol was controlled to keep the temperature below −65 °C. The mixture was stirred below −65 °C for 30 min, followed by addition of TEA (4 ml) dropwise in ca. 10 min. The temperature was maintained below −65 °C until addition of TEA was complete. The cooling bath was then removed and the reaction mixture was allowed to warm up to room temperature (ca. 40 min), then washed with H_2O (20 ml) and the aqueous layer was backwashed with CH_2Cl_2 (5 ml). The combined organic solutions were subjected to GLC analysis as previously reported.[2]

Procedure C. This procedure was identical with procedure A through the addition of alcohol. Stirring was continued for an additional 5 min below −65 °C; the dry ice bath was removed and the stirred mixture was allowed to warm up to room temperature (ca. 40 min). After another 30 min of stirring, at room temperature, TEA (4 ml) was added dropwise (ca. 10 min) at room temperature. The remainder of the workup was the same as in procedure A.

2,4-Dinitrophenylhydrazones.[2] The precipitate was filtered, washed, and dried. Ir and melting point were compared with those of authentic samples.

Isolation of Carbonyls. Ether was added to the reaction mixture which was then washed with dilute HCl, Na_2CO_3, and H_2O in succession. The organic layer was dried over magnesium sulfate and, after evaporation of solvent, a crude product was obtained as a residue. The pure product was isolated either by distillation or short-column chromatography on silical gel with petroleum ether/CH_2Cl_2 as eluent. Physical characteristics (ir, NMR, melting point) were compared with those of authentic samples of carbonyls.

Acknowledgment. This investigation was supported by Grant No. CA-07803 and 12227, awarded by the National Cancer Institute, DHEW, and the Samuel S. Fels Fund.

Registry No.—*cis*-**1**, 937-05-3; *trans*-**1**, 21862-63-5; **2**, 3835-64-1; **3**, 464-07-3; **4**, 75-84-3; **5**, 600-36-2; **6**, 5337-72-4; **7**, 507-70-0; **8**, 24393-70-2; **9**, 497-37-0; *endo*-**10**, 497-36-9; **11**, 700-57-2; **12**, 770-71-8; *cis*-**13**, 7443-70-1; **14**, 7443-52-9; 4-*tert*-butylcyclohexanone DNP, 54532-12-6; 2,2-dimethyl-1-phenyl-1-propanone DNP, 59830-27-2; 3,3-dimethyl-2-butanone DNP, 964-53-4; 2,2-dimethylpropanol DNP, 13608-36-1; 2,4-dimethyl-3-pentanone DNP, 7153-35-7; 2,6-dimethylcyclohexanone DNP, 5074-27-1; 2-bornanone DNP, 2628-66-2; *dl*-2-bornanone DNP, 53567-66-1; camphene, 79-92-5; 2-norbornanone DNP, 3281-03-6; 2-adamantanone DNP, 10535-35-0; 1-adamantanecarboxaldehyde DNP, 18220-81-0; 2-methylcyclohexanone DNP, 5138-30-7.

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Ferrocenecarboxylic Acids from Substituted Ferrocenes. A Convenient and Versatile Oxidation Method[1]

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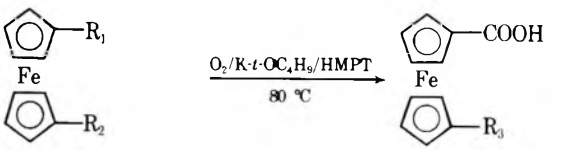
There are only very few examples known in which ferrocenecarboxylic acids can be prepared via side chain oxidation of ferrocenes. The oxidation is limited to ferrocenecarboxaldehydes[2] and acetylferrocenes[3,4] giving only low yields of carboxylic acids.

We now wish to report a convenient and versatile method for the oxidation of hydroxymethyl, formyl, acetyl, and *N,N*-dimethylaminomethyl substituted ferrocenes to ferrocenecarboxylic acids. The oxidation is performed with molecular oxygen at 80 °C in hexamethylphosphoric triamide (HMPT) as a solvent and in the presence of potassium *tert*-butoxide. The results which are summarized in Table I were obtained after a reaction time of 24 h by using 10 equiv of potassium *tert*-butoxide per equivalent of substituent to be oxidized. Lowering the amounts of base gave inferior yields and required longer reaction times.



1a, $R_1 = CH_2OH$; $R_2 = H$
b, $R_1 = CHO$; $R_2 = H$
c, $R_1 = COCH_3$; $R_2 = H$
d, $R_1 = CH_2N(CH_3)_2$; $R_2 = H$
e, $R_1 = R_2 = CH_2OH$
f, $R_1 = R_2 = CHO$
g, $R_1 = R_2 = COCH_3$

2a, $R_3 = H$
b, $R_3 = COOH$

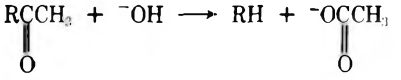
The oxidation reaction with hydroxymethyl, formyl, and acetyl substituted ferrocenes proceeded with almost quantitative conversions. The lower yields of ferrocenecarboxylic acids (**2a,b**) (see Table I) obtained from the oxidation of ac-

Table I. Ferrocenecarboxylic Acids via Oxygenation

Reaction	Yield,[a] %	Reaction	Yield,[a] %
1a → 2a	80	1e → 2b	83
1b → 2a	86	1f → 2b	86
1c → 2a	51	1g → 2a	34
1d → 2a	25	2b	17

[a] Satisfactory analytical and ir data were obtained.

etylferrocenes are due to a keto cleavage which acetylferrocenes partially can undergo in the presence of strong base.[5]



Thus, oxidation of **1c** gave 40% ferrocene and only 51% **2a**. The oxidation of **1g** yielded 26% ferrocene, 34% **2a**, and only 17% **2b**.

The high conversions of **1a–c** and **1e,f** are very surprising because the corresponding oxidation of mono- and dimethylferrocenes to ferrocenecarboxylic acids never yielded more than 25%.[6] As we could show the lower yields are due to an inhibiting effect caused by oxidation products of HMPT.[7]

Obviously this inhibiting effect does not exist during oxidation of hydroxymethyl, formyl, and acetyl substituted ferrocenes but seems to exist during oxidation of *N,N*-dimethylaminomethylferrocene (**1d**) which yielded only 25% of **2a**. This result leads to the assumption that oxidation products of *N,N*-dimethylamino groups, which are present in HMPT and in **1d**, may inhibit the base-catalyzed oxidation. The inhibiting effect is under further investigation.

Experimental Section

General Procedure. To a solution of freshly sublimed potassium *tert*-butoxide (150 mmol, for one substituent to be oxidized) in 110 ml of freshly distilled HMPT was added under inert atmosphere a solution of **1a–g** (15 mmol) in 20 ml of HMPT. After stirring for 30 min at room temperature dry oxygen was bubbled through the mixture which then was heated to 80 °C for 24 h. The reaction products were poured on ice, and the resulting alkaline solution was extracted with ether. The aqueous phase was acidified with dilute hydrochloric acid. Ferrocenecarboxylic acids **2a,b** precipitating upon acidification were filtered off and dried over phosphorus pentoxide. The acid solution was extracted with ether, and the compounds **2** were obtained after evaporation of the ether extracts. Recrystallization from ethanole was not necessary (**2a**, mp 202–204 °C, lit.[2] mp 205–210 °C; **2b**, mp 250 °C dec, lit.[3b] mp 250 °C dec). Mixtures from **2a** and **2b**, obtained from the oxidation of 1,1′-diacetylferrocene, can be separated by extraction with hot benzene, in which the monocarboxylic acid is soluble.

Registry No.—**1a**, 1273-86-5; **1b**, 12093-10-6; **1c**, 1271-55-2; **1d**, 1271-86-9; **1e**, 1291-48-1; **1f**, 1271-48-3; **1g**, 1273-94-5; **2a**, 1271-42-7; **2b**, 1293-87-4.

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Hydrogenation of Cyclohexene Catalyzed by First Row Transition Metal Stearates

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Among the most unusual and promising catalysts for homogeneous hydrogenation of olefins and aromatics are the transition metal stearates reported by Tulupov.[1–4] A good brief summary can be found in James' book[5] and Tulupov has published on the kinetics and mechanism of the reaction[6] and on the interaction of the metals with cyclohexene[7] in addition to two reviews.[8] We have attempted to repeat some of Tulupov's work and failed.

Briefly, Tulupov reported the reduction of cyclohexene in ethanol by hydrogen at ca. 1 atm at room temperature in the presence of stearate salts of Ni(II), Cu(II), Co(II), Cr(III), Fe(III), Sc(III), Ti(IV), and Zn(II). He also reports the hydrogenation of benzene catalyzed by stearate salts of Ni(II), Co(II), Fe(III), and Pb(II). There is little precedent for these observations in the literature. It is well known that Cu(I) carboxylate salts catalyze the reduction of benzoquinone[9] in quinoline and this reaction has been studied by two groups.[10,11] Also Rh(II) acetate is known to catalyze the hydrogenation of olefins in a variety of solvents.[12] A number of salts reported as active in ethanol by Tulupov have been reported to be inactive in aqueous systems,[13] consistent with Tulupov's claim of inhibition by water. Neither the Rh(II) nor Cu(I) work serves as confirmation of Tulupov's reports since the Cu(I) system was run in a solvent very different from ethanol and Tupulov did not study any rhodium systems. A thorough literature search yielded no reports of attempts to repeat Tulupov's studies.

Results

A number of stearate salts were prepared using Koenig's procedure,[14] the same one used by Tulupov. After a number of washings, pure salts having acceptable analyses were obtained. When we attempted to dissolve the Ni(II) stearate in anhydrous ethanol (Tulupov[2] reports the solubility as 4.21×10^{-3} M/l.), the ethanol remained colorless and all the salt was recovered by filtration. Two very tiny crystals of Ni(II) stearate were placed in an Erlenmeyer flask with ca. 100 ml of ethanol and allowed to stand for 6 h with occasional shaking. They did not dissolve. Warming the flask until the Ni(II) stearate melted did not result in any room temperature solubility. Similar observations were made with Cu(II) stearate (reported[3] solubility 4.02×10^{-4} M/l.) except that we did note some small solubility in hot ethanol. Koenig[14] reports that these two salts are insoluble in methanol but soluble in amyl alcohol.

A number of attempts were made to hydrogenate cyclohexene and some of them are reported in Table I. All reactions were run in Parr hydrogenators in which other catalytic hydrogenations had successfully been carried out. In no case was any reaction observed. With reaction no. 7, assuming that Tulupov's[3] reported reaction rate in ethanol would be unchanged in isobutyl alcohol, we can calculate a pressure drop of ca. 5.3 psi under our reaction conditions. We could detect a pressure drop of ca. 0.2 psi. The reactions were run with commercial anhydrous ethanol and with ethanol dried by refluxing over Mg and distillation under dry N_2 onto molecular sieves (3A). Two different batches of sodium stearate were used. The cyclohexene gave only two peaks on gas chromatography; one, having a slightly larger retention time than

Table I. Attempted Catalytic Hydrogenation of Cyclohexene Using Tulupov's Catalysts

Rxn	"Catalyst"	Solvent	Temp, °C	H_2 pressure, psia	Rxn time, h	Pressure drop, psi
1	Ni(II) stearate	Hexanes	~23	37	48	0
2	Ni(II) stearate	Hexanes	60	38	60	0
3	$NiCl_2$	Ethanol	~23	45	37	0
4	$NiCl_2 \cdot 6H_2O$	Ethanol	~23	47	43	0
5	$NiCl_2$/stearic acid[2]	Ethanol	~23	45	36	0
6	$NiCl_2 \cdot 6H_2O$/stearic acid	Ethanol	~23	35	24	0
7	Cu(II) stearate	Isobutyl alcohol	50	38	28	0
8	$CoCl_2$	Ethanol	~23	46	67	0
9	$CoCl_2$/stearic acid	Ethanol	~23	47	36	0
10	Ni(II) stearate[a]	Hexanes	~23	49	42	0

[a] The olefin used was norbornene.

cyclohexene, had an area less than 0.1% of the cyclohexene peak area.

Discussion

We have been unable to reproduce Tulupov's reported reactions or catalyst solubilities. Since both $NiCl_2$ and stearic acid are quite soluble in ethanol, the reported solubility may be due to impure Ni(II) stearate contaminated with the compounds from which it is made. It does take extensive washing to remove these.

It is more difficult to explain our failure to hydrogenate cyclohexene. Obviously, neither the salts nor their precursors showed any catalytic activity. Since Tulupov observed reactivity with a variety of salts, and we with none, the place to look for the explanation is in those compounds common to all systems: the sodium stearate and cyclohexene. The use of two different batches of sodium stearate from two different manufacturers greatly reduces the probability that there was an inhibitor present. Likewise, use of a second olefin (norbornene, rxn 10) with the same results reduces the possibility of an inhibitor being present in the reactant. It is possible that something is present in Tulupov's stearic acid which is causing the reaction. Having been unable to obtain samples of catalyst from Tulupov, we are not able to investigate this aspect of the problem further. In any event, it is quite clear that all is not well with the reported use of transition metal stearate salts as homogeneous catalysts for olefin hydrogenation.

Experimental Section

Melting points were taken on a Mel-Temp apparatus and were uncorrected. Analytical gas chromatography utilized a Varian Aerograph Model 1400 instrument equipped with a flame ionization detector and using a 0.125 in. × 7 ft 5% SE-30 on 60–80 mesh Chromosorb W column. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Ethanol was dried by refluxing over magnesium and distillation under dry nitrogen onto molecular sieves (3A). Hexanes and isobutyl alcohol were dried over molecular sieves (3A).

Metal Stearates. Sodium stearate (13.5 g, Fischer) was dissolved in 900 ml of water and the mixture was heated and stirred until the solution was clear. The hot soap solution then was poured with vigorous stirring onto a solution containing 6 g of $NiSO_4 \cdot 6H_2O$ or 4 g of $CuSO_4$ in 600 ml of warm water. The precipitates were washed by decantation with water and dried in the air at 115 °C for 15 h. Nickel stearate was also made from the sodium stearate prepared from stearic acid (Emery) and sodium hydroxide.

Nickel(II) stearate: green solid; mp 100 °C; yield 84%. Anal. Calcd for $NiC_{36}H_{70}O_4$: C, 69.09; H, 11.34. Found: C, 69.77; H, 10.70.

Copper(II) stearate: light blue solid; mp 106–108 °C; yield 80%. Anal. Calcd for $CuC_{36}H_{70}O_4$: C, 68.56; H, 11.21. Found: C, 68.51; H, 11.66.

Attempted Catalytic Hydrogenation of Cyclohexene. To a stearate salt (~1 g) in ~110 ml of warm solvent was added 12 g of cyclohexene (Eastman Kodak). The solution was poured into a 500-ml hydrogenation bottle and the bottle was then mounted on a low-pressure Parr hydrogenator. Air was removed from the system by alternatively filling the system with hydrogen to 35 psi and venting it at least three times. The solution was shaken at ca. 3 atm hydrogen pressure. Similar procedure was also carried out for the hydrogenation of bicyclo[2.2.1]-2-heptene (Aldrich). The pressure of the system was monitored.

Acknowledgment. We are grateful to the Energy Research and Development Administration for support of this work.

Registry No.—Sodium stearate, 822-16-2; nickel(II) stearate, 2223-95-2; copper(II) stearate, 660-60-6; cyclohexene, 110-83-8; bicyclo[2.2.1]-2-heptene, 498-66-8.

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An Aberrant Rearrangement in the Reaction of 1,2-Dibromo-3,3-difluorocyclopropene with Anthracene[1]

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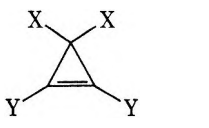
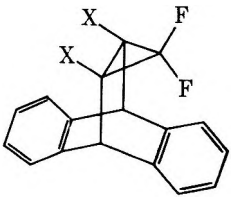
In an attempt to develop a rational synthesis of the as yet unknown, but potentially useful synthon 3,3-difluorocyclopropene (**1a**), we have examined the reaction of anthracene with 1,2-dibromo-3,3-difluorocyclopropene (**1b**).[2] It was anticipated that the [4 + 2] cycloadduct **2** would permit a classical approach to the elusive[3] cyclopropene (**1a**) via reductive

debromination and subsequent thermal cycloreversion of the dibenzohomobarrelene derivative **3**. We now report that contrary to expectations the reaction of anthracene with **1b** affords a rearranged adduct of a type previously unobserved in cycloadditions with tetrahalocyclopropenes.

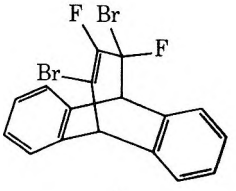
The reaction of anthracene with excess **1b** was carried out in carbon tetrachloride solution in a sealed tube at 120–130 °C until complete consumption (NMR) of anthracene (7 days). Chromatography and recrystallization of the reaction residue afforded a crystalline 1:1 adduct (40%) whose ^{19}F NMR spectrum immediately suggested a rearranged structure. Cycloadducts of **1b** typically show well-separated (15–40 ppm) AB quartets in their ^{19}F spectra centered at around 110–120 ppm (upfield from external $CFCl_3$).[4] By contrast the anthracence–**1b** adduct showed only a fluorine singlet at δ 47.0! The proton spectrum of this adduct consisted of two one-proton singlets at δ 5.27 and 5.11 for the bridgehead hydrogens, in addition to complex aromatic absorptions, suggesting an unsymmetrical structure for the adduct.



1a, Y = H; X = F
b, Y = Br; X = F



2, X = Br
3, X = H



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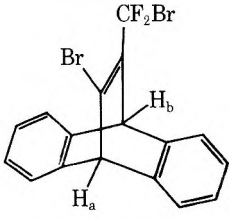

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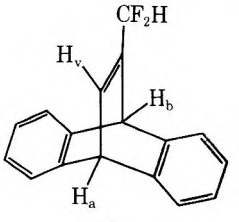

6

While the above spectral results clearly eliminate adduct **2** from further consideration, the ^{19}F data are equally inconsistent with the most obvious rearranged structure **4** which would be derived by electrocyclic ring opening with 1,2-fluorine migration. This mode of ring opening has been frequently observed for tetrahalocyclopropene adducts where at least one of the geminal halogens is chlorine[4,5] or bromine.[4a] However, owing to the low ionization propensity of the C–F bond all of the previous cycloadducts of 3,3-difluoro-substituted cyclopropenes have been observed to be thermally stable to electrocyclic ring-opening reactions.[4,6]

An alternative mode of ring opening involving rupture of one of the peripheral cyclopropane bonds of **2** could presumably lead to the dibenzobarralene derivative **5**, a structure consistent with the observation of a singlet in the fluorine spectrum. That **5** is indeed the structure of this unusual adduct is supported by spectral data for the tri-*n*-butyltin hydride debrominated adduct **6**. The 100-MHz ^1H NMR spectrum of **6** revealed a triplet centered at δ 6.1 with a coupling constant (J_{HF}) of 56 Hz while the fluorine spectrum showed a doublet of doublets at δ 117.1, J_{HF} = 56 and 4 Hz. These results are in complete keeping with the presence of a $-CF_2H$ grouping. The smaller doublet splitting (J_{HF} = 4 Hz) is assigned to allylic fluorine coupling to the vinyl proton (H_v) which is unfortunately obscured in the aromatic region of the proton spectrum. The bridgehead protons H_a and H_b are observed as a pair of doublets, $J_{H_aH_v}$ = 6 Hz and $J_{H_bH_v}$ = 2 Hz, at 5.16 and 5.30, respectively.[7] Final corroboration of structure is provided by the mass spectrum of **6**, which shows a base peak at *m/e* 203 corresponding to loss of the CF_2H radical.

Although diradical rupture of a peripheral cyclopropane bond of **2** followed by 1,2-bromine shift provides an adequate rationale for formation of **5**, we cannot at present rule out the possible rearrangement of **1b** to 1,3-dibromo-3,3-difluoropropyne under the forcing conditions of the reaction.[8] To our knowledge, however, such a rearrangement of a tetrahalocyclopropene, while not unreasonable, is unprecedented.

Experimental Section

Proton magnetic resonance spectra were recorded on Varian A-60A and Varian XL-100 spectrometers; chemical shifts are reported in parts per million downfield from internal Me_4Si. All ^{19}F NMR spectra were recorded on the XL-100 instrument at 94.1 MHz with chemical shifts reported in parts per million upfield from external $CFCl_3$. Infrared spectra were determined on a Perkin-Elmer Model 137 instrument as KBr wafers. Mass spectra were recorded on an AEI-MS 30 spectrometer at 70 eV. Elemental analyses were performed by Atlantic Microlabs, Inc., Atlanta, Ga.

1,2-Dibromo-3,3-difluorocyclopropene (**1b**) was prepared by a slight modification of the published procedure[2] using freshly sublimed antimony trifluoride.

Reaction of Anthracene with 1b. Anthracene (0.890 g, 5.00 mmol), 1,2-dibromo-3,3-difluorocyclopropene (**1b**, 1.75 g, 7.47 mmol), and 25 ml of carbon tetrachloride were placed in a Fischer-Porter tube which was capped and heated at 120 °C for 4 days. NMR analysis of the reaction mixture at this point indicated ca. 50% conversion of the anthracene. Additional **1b** (1.0 g) was added, the tube recapped, and heating resumed at 130 °C. After 3 days at this temperature the anthracene was completely consumed. The dark reaction mixture was concentrated and chromatographed on silica gel with benzene as elutant. Concentration of the first fraction gave 1.94 g (94%) of a oily brown solid which on crystallization from hexane afforded 0.823 g (39.9%) of hard brown crystals. Recrystallization from hexane afforded analytically pure **5**: mp 94–97 °C ν 1616, 1456, 1308, 1276, 1120, 990, 959, 864, 820, 742, 622 cm^{-1}; mass spectrum *m/e* (rel intensity) 414 (3.1), 412 (6.7), 410 (3.5), 334 (49.5), 332 (50.5), 252 (82.6), 202 (100), 200 (74.5), 179 (65.5), 150 (78.9), 127 (30.3), 111 (44.8); δ ($CDCl_3$) 7.5–6.8 (m, 8, aromatic), 5.27 (s, 1, H_b), 5.11 (s, 1, H_a); ϕ_{CFCl_3}($CDCl_3$) 47.01 (s, $-CF_2Br$).

Anal. Calcd for $C_{17}H_{10}Br_2F_2$: C, 49.55; H, 2.45; Br, 38.79. Found: C, 49.65; H, 2.51; Br, 38.96.

7-Difluoromethyldibenzotricyclo[2.2.2]octa-2,5,7-triene (6). A magnetically stirred mixture of tri-*n*-butyltin hydride (2.24 g, 7.68 mmol) and **5** (1.06 g, 2.56 mmol) containing a catalytic amount of di-*tert*-butyl peroxide was heated at 90 °C for 15 h. Chromatography of the reaction mixture on neutral alumina using benzene–hexane (1:1 v/v) as eluent followed by recrystallization from hexane afforded 0.245 g (37.3%) of a yellow solid. A second recrystallization from hexane–methanol gave 0.137 g of **6**, mp 137.5–138 °C as white flakes homogeneous to thin layer chromatography: ν 1640, 1452, 1368, 1320, 1288, 1059, 994, 738 cm^{-1}; mass spectrum *m/e* (rel intensity) 254 (54.6) 233 (6.6), 203 (100), 202 (63.5), 178 (12.7), 152 (3.2), 151 (3.3), 102 (5.0), 101 (8.5), 87 (3.2), 76 (3.2); δ (CCl_4, 100 MHz), 7.44–6.84 (m, 9, aromatic, H_v), 6.22 (t, J_{HF} = 56 Hz, $-CF_2H$), 5.30 (d, $J_{H_bH_v}$ = 2 Hz, 1, H_b), 5.16 (d, $J_{H_aH_v}$ = 6 Hz, 1, H_a), ϕ_{CFCl_3}($CDCl_3$) 117.1 (dd, J_{HF} = 56, J_{FH_v} = 4 Hz, 1, $-CF_2-$).

Anal. Calcd for $C_{17}H_{12}F_2$: C, 80.30; H, 4.76. Found: C, 80.40; H, 4.75.

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Registry No.—**1b**, 6262-46-0; **5**, 59790-60-2; **6**, 59790-61-3; anthracene, 120-12-7.

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(3) Initial attempts in our laboratory to directly generate **1a** from **1b** by reductive debromination have not met with success. Most surprising was the failure of tri-*n*-butyltin hydride to produce any volatile products on reaction with **1b** in mineral oil.
(4) (a) D. C. Law and S. W. Tobey, *J. Am. Chem. Soc.*, **90**, 2376 (1968); (b) related work described in ref 1.
(5) (a) R. M. Magid and S. E. Wilson, *J. Org. Chem.*, **36**, 1775 (1971); (b) M. A. Battiste, L. A. Kapicak, M. Mathew, and G. J. Palenik, *Chem. Commun.*, 1536 (1971); (c) M. A. Battiste and C. T. Sprouse, *Tetrahedron Lett.*, 4661 (1970).
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(7) (a) With exception of the broad triplet for the $-CF_2H$ proton the pattern of the proton spectrum and the coupling constants for the bridgehead protons H_a, H_b were almost identical with that observed for the model system 7-chiorodibenzobicyclo[2.2.2]octa-2,5,7-triene[7b] in deuteriobenzene [δ (C_6D_6, 60 MHz) 7.17–6.56 (m, 8, aromatic), 6.40 (dd, J = 2.3, 6.5 Hz, 1, vinyl), 4.82 (d, J = 2.3 Hz, 1, bridgehead), 4.50 (d, J = 6.5 Hz, 1, bridgehead); δ ($CDCl_3$) 7.38–6.75 (m, 8, aromatic), 6.68 (dd, J = 2.2, 6.4 Hz, 1, vinyl), 4.94 (overlapping doublets, 2, bridgeheads)]. (b) Prepared by the method of S. J. Cristol, R. Caple, R. M. Sequeira, and L. O. Smith, Jr., *J. Am. Chem. Soc.*, **87**, 5679 (1965).
(8) As pointed out by a referee, an alternative ionic pathway for rearrangement of **2** involving carbon–bromine ionization with simulaneous electrocyclic cleavage of a peripheral cyclopropane ring bond cannot be excluded on the basis of the limited data. While this mechanistic possibility should not be ignored, the lack of literature precedent for cyclopropyl to allyl conversions of bridgehead halides and the energetically unfavorable accumulation of positive charge at the $-CF_2$ carbon render it suspect in comparison with the postulated diradical mode of ring opening.

Carbonyl Insertion Reactions of Ethyl α-Trimethylsilyldiazoacetate. An Improved Route to Diazoacetate Aldol Products

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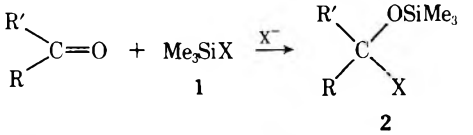
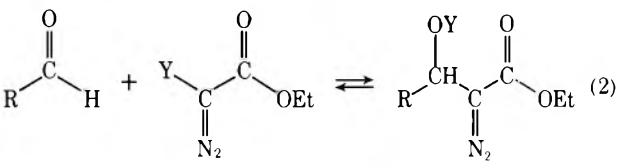
Interest in the carbonyl insertion[1] chemistry of organosilicon compounds has only recently developed in spite of the central role the carbonyl function plays in organic synthesis.[2–4] Of particular interest to us has been the generality of the anion-initiated carbonyl insertion process illustrated below (eq 1). To date we have demonstrated that the reaction of



(1)

trimethylsilyl cyanide (**1**, X = CN) with an extensive variety of aldehydes and ketones is readily initiated by both cyanide and fluoride ion.[2a,b] The only other silicon pseudohalide which has been found to react in an analogous fashion has been trimethylsilyl azide (**1**, X = N_3) which forms aldehyde adducts **2** (X = N_3; R′ = H) in excellent yields.[2b] Recently, we have found that thiosilanes **1** (X = SR), in the presence of anionic initiators, will also form aldehyde adducts **2** (X = SR) in excellent yields.[4a] As has recently been demonstrated, these organosilane–carbonyl adducts are valuable intermediates in chemical synthesis.[5,6]

We now wish to report that the carbonyl insertion reactions of ethyl α-trimethylsilyldiazoacetate (**3a**) can be effected (eq 2), and that the reaction is subject to specific anion initiation. Wenkert and McPherson have shown[7] that ethyl diazoacetate adds to aldehydes in the presence of a catalytic amount of sodium hydroxide. Unfortunately, the reaction affords an equilibrium mixture of the aldol product **4b** and starting



(2)

3 **4**

a, Y = $SiMe_3$; **b**, Y = H; **c**, Y = $SnMe_3$

materials where adduct formation is quite unfavorable for some aldehydes and most ketones. Based upon crude thermodynamic approximations, it was predicted that the silyldiazoacetate addition reactions (**3a** → **4a**) should be *more* exothermic than the analogous diazoacetate addition processes (**3b** → **4b**). These predictions have now been verified. The addition of **3a**[8] to both aromatic and aliphatic aldehydes occurs exothermically at room temperature in nearly quantitative yield when catalyzed by the potassium cyanide–18-crown-6 complex.[2b] For sensitive substrates (i.e., the isobutyraldehyde adduct), which were unstable to the heat generated by the reaction, solvents such as chloroform were used to moderate the temperature. Removal of the solvent at room temperature afforded essentially pure aldol adduct **4a**. Analytical samples were obtained by column chromatography on Florisil, *but partial hydrolysis of* **4a** *to the corresponding alcohol* **4b** *was usually observed.* Table I compares the chromatographed yields of the silyldiazo ester insertions with Wenkert's protiodiazo ester reactions where possible. Not only are the yields consistently higher, but the reaction conditions are nonaqueous and essentially neutral. Preliminary results indicate that even tigaldehyde survives the reaction to afford a moderate yield of the 1,2 adduct; no 1,4 adduct could be detected.

Less reactive carbonyl systems such as acetophenone, cyclohexanone, 3-pentanone, and 3-methyl-3-penten-2-one all failed to produce detectable adducts (by NMR). In hope of achieving a still more favorable equilibrium, the analogous reactions of ethyl α-trimethylstannyldiazoacetate[9] (**3c**) were examined, but 3-pentanone was inert to the reagent and hexanal was slowly polymerized.[10] Since the completion of our work, Schollkopf has shown that **3** (Y = Li, MgX) will add to both aldehydes and ketones under very carefully controlled conditions to afford the corresponding aldol-type products in high and moderate yields, respectively.[11] Both thermal and Lewis acid catalyzed reaction conditions failed to generate the aldol adducts **4** from either the silyl or stannyldiazo esters **3a** or **3c**. This is in marked contrast to related carbonyl insertions by other organosilanes.[2–4]

The presumed mode of catalysis by anionic initiators such as cyanide ion (Scheme I) involves the generation of catalytic amount of diazo ester enolate **5** via either of the processes illustrated in eq 3 and 4 followed by carbonyl addition and subsequent silicon transfer steps to regenerate **5**. It is pre-

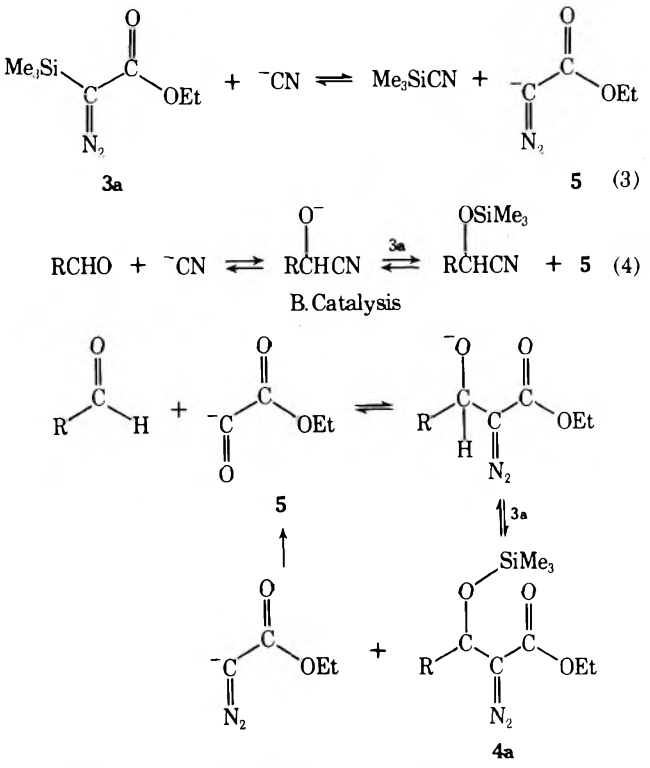
Table I. Carbonyl Addition Reactions of 3a (Eq 1)

RCH=O	Registry no.	% yield of 4a[a,b]	% yield of 4b[c]
$CH_3(CH_2)_4CHO$	66-25-1	86 (63:37)	68 (R = C_6H_{13})
$(CH_3)_2CHCHO$	78-84-2	93 (76:24)	80
C_6H_5CHO	100-52-7	86 (84:16)	60
p-ClC_6H_4CHO	104-88-1	93 (78:22)	25
p-$CH_3OC_6H_4CHO$	123-11-5	83 (100:0)	
$CH_3CH{=}\overset{CH_3}{\overset{\vert}{C}}CHO$	497-05-0	44 (100:0)	

[a] Calculated on isolated yields of adduct. [b] Values in parentheses refer to the ration of 4a:4b isolated from chromatography. Prior to chromatography only 4a was present. [c] Yields for the base-catalyzed addition of 3b to illustrated aldehydes (ref 7).

Scheme I

A. Initiation



B. Catalysis

sumed that fluoride ion would also serve as an efficient initiation catalyst.

In conclusion, the use of silyldiazo ester **3b** as a masked carbon nucleophile in carbonyl addition reactions establishes a valuable precedent for the design of related masked carbon nucleophiles. The extremely mild catalytic conditions under which these insertions occur make them particularly valuable in organic synthesis. In the present case not only is a carbon–carbon bond formed, but the β-hydroxy-α-diazocarbonyl function created is of practical interest.[7,11,12]

Experimental Section

Ethyl 2-Diazo-3-trimethylsiloxy-3-phenylpropionate (4a, R = C_6H_5). To a nitrogen-blanketed solution of 0.176 g (1.66 mmol) of freshly distilled benzaldehyde and 0.308 g (1.66 mmol) of ethyl 2-trimethylsilyl-2-diazoacetate (**3a**)[8] in 2 ml of chloroform was added 0.005 g (a catalytic amount) of 18-crown-6–potassium cyanide complex.[2b] The solution warmed instantly upon the addition of the catalyst. The yellow solution was stirred at ambient temperature for 1.75 h whereupon the solvent was removed at reduced pressure and the yellow oil was chromatographed on 50 g of Florisil eluting with 1% ether in hexane. This eluent afforded 0.348 g (72%) of product **4a** (R = C_6H_5) as a clear yellow oil. The eluting solvent was changed to 1:1 ether–hexane and 0.0955 g (14%) of the clear yellow alcohol **4b** (R = C_6H_5) was obtained. The trimethylsiloxy adduct had the following properties: ir (neat) 2100 (C=N_2), 1695 (–CO_2Et), and 1255 cm^{-1} ($SiCH_3$); NMR (CCl_4) 7.33 (s, 5, aryl H), 5.38 (s, 1, $OCHC_6H_5$), 4.28 (q, 2, J = 7.0 Hz, OCH_2), 1.33 (t, 3, J = 7.0 Hz, CH_2CH_3), 0.18 ppm (s, 9, $SiCH_3$).

Anal. Calcd for $C_{14}H_{20}N_2O_3Si$: C, 57.51; H, 6.89. Found: C, 57.31; H, 6.71.

Ethyl 2-Diazo-3-trimethylsiloxy-3-(4-methoxyphenyl)propionate (4a, R = p-$CH_3OC_6H_4$). The addition was carried out in 83% by the general method described above: ir (neat) 2090 (C=N_2), 1685 (CO_2Et), and 1245 cm^{-1} ($SiCH_3$); NMR (CCl_4) δ 7.31 (d, 2, J = 9 Hz, OC=C–CH), 6.84 (d, 2, J = 9 Hz, OC=CH), 5.78 (s, 1, CHOSi), 4.25 (q, 2, J = 7 Hz, OCH_2), 3.77 (s, 3, OCH_3), 1.30 (t, 3, J = 7 Hz, CH_2CH_3), 0.15 (s, 9, $SiCH_3$).

Anal. Calcd for $C_{15}H_{22}N_2O_4Si$: C, 55.87; H, 6.88. Found: C, 56.08; H, 6.95.

Ethyl 2-Diazo-3-trimethylsiloxy-3-(4-chlorophenyl)propanoate (4a, R = p-ClC_6H_4). The addition was carried out according to the general method described above in 73% yield along with 20% of the corresponding alcohol **4b**: ir (neat) 2105 (C=N_2), 1695 (CO_2Et), and 1250 cm^{-1} ($SiCH_3$); NMR ($CDCl_3$) δ 7.32 (s, 4, aryl H), 5.82 (s, 1, $OCHC_6H_4Cl$), 4.25 (q, 2, J = 7.0 Hz, OCH_2), 1.27 (t, 3, J = 7.0 Hz, CH_2CH_3), and 0.12 (s, 9, $SiCH_3$).

Anal. Calcd for $C_{14}H_{19}ClN_2O_3Si$: C, 51.45; H, 5.86. Found: C, 52.05; H, 5.71.

Ethyl 2-Diazo-3-trimethylsiloxyoctanoate (4a, R = n-C_5H_{11}). Following the general procedure the adduct was obtained in 54% yield by the general method described above along with 32% of the corresponding alcohol **4b**: ir (neat) 2085 (C=N_2), 1690 (–CO_2Et), and 1254 cm^{-1} ($SiCH_3$); NMR (CCl_4) δ 4.54 (t, 1, J = 6 Hz, CHOSi), 4.18 (q, 2, J = 7 Hz, OCH_2), 0.06 (s, 9, Si=CH_3).

Anal. Calcd for $C_{13}H_{26}N_2O_3Si$: C, 54.51; H, 9.15. Found: C, 54.67; H, 9.22.

Ethyl 2-Diazo-3-trimethylsiloxy-4-methylpentanoate (4a, R = i-C_3H_7). Following the general procedure the adduct was obtained in 71% yield by the general method described above along with a 22% yield of the corresponding alcohol **4b**: ir (neat) 2100 (C=N_2), 1695 (–CO_2Et), and 1280 cm^{-1} ($SiCH_3$); NMR (CCl_4) δ 4.20 (d, 1, J = 7.0 Hz, CHOSi), 4.16 (q, 2, J = 7 Hz, OCH_2), 1.73 [m, 1, $CH(CH_3)_2$], 1.25 (t, 3, J = 7 Hz, CH_3CHCH_3), 0.07 (s, 9, $SiCH_3$).

Anal. Calcd for $C_{11}H_{22}N_2O_3Si$: C, 51.13; H, 8.58. Found: C, 51.16; H, 8.45.

Ethyl 2-Diazo-3-trimethylsiloxy-4-methyl-(*E*)-4-hexenoate [4a, R = $C(CH_3)$=$CHCH_3$]. The adduct was prepared in 44% yield by the general method described above: ir (neat) 2100 (C=N_2), 1695 (–CO_2Et), and 1250 cm^{-1} ($SiCH_3$); NMR (CCl_4) δ 5.64 (q, 1, J = 7 Hz, CH_3CH=C), 4.93 (s, 1, CHOSi), 4.20 (q, 2, J = 7 Hz, OCH_2), 1.65 (d, 3, J = 7 Hz, CH_3CH=C), 1.58 (s, 3, CH_3C=CH), 1.28 (t, 3, J = 7 Hz, OCH_2CH_3), and 0.12 (s, 9, $SiCH_3$). Combustion analysis was not obtained owing to the unstable nature of the adduct.

Acknowledgment. Research support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

Registry No.—**3a**, 17145-48-1; **4a** (R = C_6H_5), 59840-31-2; **4a** (R = p-$CH_3OC_6H_4$), 59840-32-3; **4a** (R = p-ClC_6H_4), 59840-33-4; **4a** (R = n-C_5H_{11}), 59840-34-5; **4a** (R = i-C_3H_7), 59840-35-6; **4a** [R = $C(CH_3)$=$CHCH_3$], 59840-36-7.

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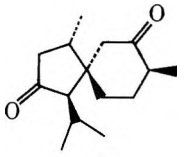
Carbonyl Homologation with α Substitution. A New Approach to Spiroannelation

Summary. A novel approach is described for the geminal alkylation of a ketone carbonyl group to give a quaternary carbon atom bearing substituents suitably functionalized for the *direct* spiroannelation of a cyclohexenone ring.

Sir: Within the past few years, a wide variety of natural products belonging to the several classes of spiro sesquiterpenes have been discovered. Representative examples of these classes include acorone (an acorane) (**1**),[1] β-vetivone (a vetispirane) (**2**),[2] and α-chamigrene (a chamigrane) (**3**).[3] Since



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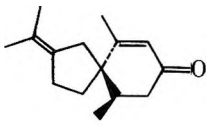

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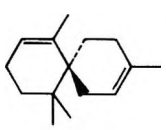
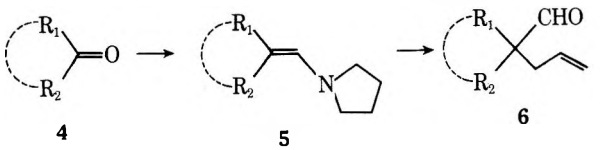


3

these compounds, along with other members of their respective classes, exhibit a diversity of both skeletal and functional variations, there has been a demand for efficient, general methods for the construction of substituted spirocyclic systems.[4,5] However, many recent approaches toward spiroannelation may be characterized as multistep procedures which are frequently limited in scope because they are designed for the synthesis of specific spiro sesquiterpenes.[1-3,6]

Owing to its synthetic utility, the carbonyl group has evolved as one of the most important and readily accessible functional groups in organic chemistry. Thus, a synthetic procedure for the transformation of a carbonyl group into a quaternary carbon center possessing substituents suitably functionalized for subsequent spiroannelation operations would be especially desirable. We now wish to report an efficient procedure for the direct conversion of ketones into 4,4-disubstituted 2-cyclohexen-1-ones. Application of this approach to cyclic ketones affords a facile method for the construction of spirocyclic ring systems. Furthermore, the newly formed six-membered ring possesses an α,β-unsaturated ketone which may be exploited by subsequent condensation or addition reactions to introduce additional substituents and functional groups.

We recently described the utility of diethyl pyrrolidinomethylphosphonate as a reagent for the conversion of ketones **4** into the pyrrolidine enamines of the homologous α-disubstituted aldehydes **5**.[7] Treatment of these enamines with allyl bromide gave α-allyl dialkylaldehydes **6** in good yields (eq 1). Although the newly introduced alkyl appendages of **6**

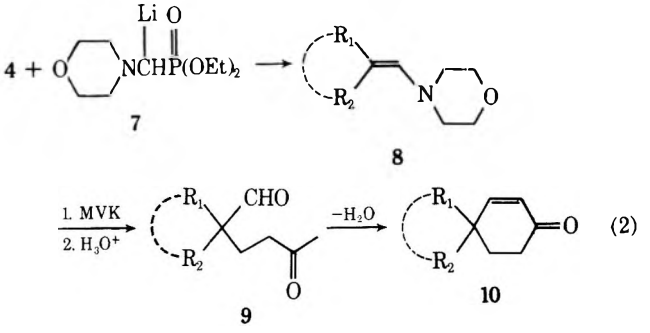


(1)

4 **5** **6**

can be modified for eventual cyclization to spirocyclic systems, the procedure requires extensive functional group manipulation.[5d] A method for introducing geminal substituents suitably functionalized for direct elaboration to cyclic compounds would have obvious advantages. For example, the introduction of a 3-oxobutyl group would afford a 1,5-dicarbonyl compound which could then be readily converted into a 2-cyclohexen-1-one by aldol-cyclodehydration.[8,9]

Unfortunately, our initial efforts to react the pyrrolidine enamines **5** with methyl vinyl ketone gave unsatisfactory results. We investigated, therefore, the reaction of ketones **4** with diethyl lithiomorpholinomethylphosphonate[10] (**7**) and obtained the expected morpholine enamines of the homologous aldehydes **8**, which were isolated by flash distillation. Treatment of the crude enamines **8** with methyl vinyl ketone (MVK) followed by acid-catalyzed hydrolysis of the intermediate adduct afforded the δ-keto aldehydes **9** which spontaneously underwent cycloaldolization and dehydration to give the 4,4-disubstituted 2-cyclohexen-1-ones **10** (eq 2).

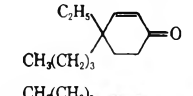
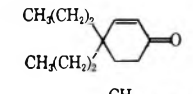
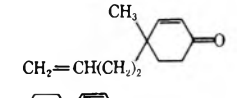
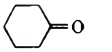
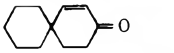
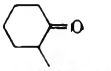
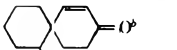
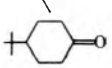
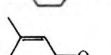
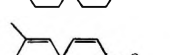
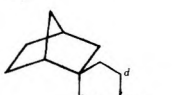
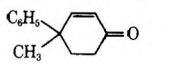


(2)

7 **8** **9** **10**

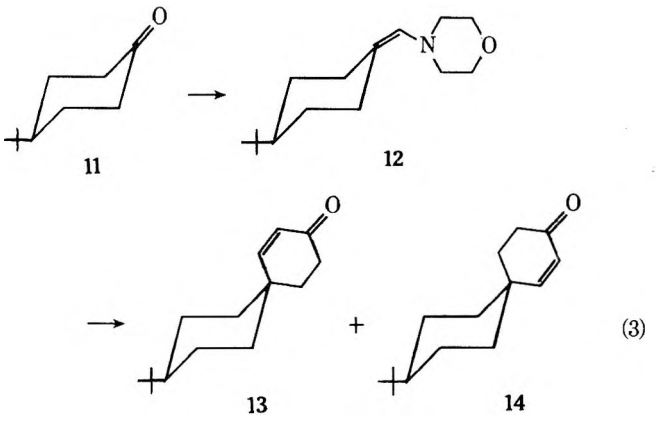
This spiroannelation procedure, which may be executed without the purification of any intermediates, is generally applicable to a wide variety of acyclic, cyclic, aromatic, and α,β-unsaturated ketones, and the product 4,4-disubstituted 2-cyclohexenones may be isolated in fair to moderate *overall* yields (see Table I).[11] Preliminary results have also indicated

Table I. Spiroannelation of Ketones

Ketone **4**	Cyclohexenone **10**	% yield[a]
$C_2H_5CO(CH_2)_3CH_3$		35
$CH_3(CH_2)_2CO(CH_2)_2CH_3$		36
$CH_3CO(CH_2)_2CH{=}CH_2$		33
		41
		36
		41
		30
		41
$C_6H_5COCH_3$		34

[a] Isolated yield based upon ketone but not optimized. [b] Obtained as an ~9/1 mixture of diastereomers. [c] Obtained as an ~9/1 mixture of diastereomers. [d] As judged by NMR, is >95% one diastereomer.

that this synthetic sequence proceeds with a considerable degree of stereoselectivity. For example, 4-*tert*-butylcyclohexanone (**11**) was smoothly converted to a diastereomeric mixture of the spiro[5.5]undecenones **13** and **14** in a ratio of 9:1 (eq 3).[12] This result is in accord with the expectation that



(3)

the initial reaction of methyl vinyl ketone with the enamine **12** will occur from the less hindered, equatorial face of **12.**

The application of this new spiroannelation procedure to the synthesis of spiro sesquiterpene natural products as well as alkaloid natural products containing spirocyclic rings and quaternary carbon atoms is presently under investigation.

Acknowledgment. We wish to thank the Research Corporation and the University Research Institute of the University of Texas at Austin for their generous financial support of this program.

Supplementary Material Available. Characterization of all new compounds, together with representative experimental details (5 pages). Ordering information is given on any current masthead page.

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(1) For a recent synthesis of acorone and related sesquiterpenes, see J. N. Marx and L. R. Norman, *J. Org. Chem.*, **40**, 1602 (1975), and references therein.
(2) For a recent synthesis of β-vetivone and related vetispiranes, see W. G. Dauben and D. J. Hart, *J. Am. Chem. Soc.*, **97**, 1622 (1975), and references therein.
(3) For a synthesis of α-chamigrene, see J. D. White, S. Torii, and J. Nogami, *Tetrahedron Lett.*, 2879 (1974).
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(10) E. K. Fields, *J. Am. Chem. Soc.*, **74**, 1528 (1952).
(11) All compounds were adequately characterized by spectral methods (ir, NMR, MS), and all new compounds gave satisfactory high resolution mass spectral and/or combustion analytical data.
(12) Although the two isomers **13** (major) and **14** (minor) were inseparable by preparative chromatographic techniques, their presence is easily detected by analytical GLC and ^{1}H and ^{13}C NMR spectra: **13**, ^{1}H NMR ($CDCl_3$, TMS) δ 7.17 (d, J = 10 Hz, -CH=CHCO-) and ^{13}C NMR ($CDCl_3$, TMS) δ 155.4 (-CH=CHCO-); **14**, ^{1}H NMR ($CDCl_3$, TMS) δ 6.52 (d, J = 10 Hz, -CH=CHCO-) and ^{13}C NMR ($CDCl_3$, TMS) δ 160.7 (-CH=CHCO-). The stereochemical assignment with respect to the newly created chiral center may be made on the basis of the ^{1}H and ^{13}C NMR spectra. The β-vinyl proton of the major isomer **13** is *deshielded* relative to the β-vinyl proton of **14**, owing to steric crowding. As expected the β-vinyl carbon of **13** is *shielded* relative to the β-vinyl carbon of **14** owing to steric compression.

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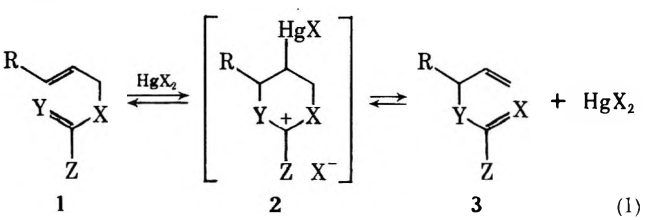
Mercury(II)-Catalyzed 3,3-Sigmatropic Rearrangements of Allylic *N,N*-Dimethylcarbamates. A Mild Method for Allylic Equilibrations and Contrathermodynamic Allylic Isomer Enrichments

Summary: Allylic *N,N*-dimethylcarbamates undergo allylic equilibration in high yield when treated at 25 °C in THF with catalytic amounts of mercuric trifluoroacetate. In certain cases the use of excess mercuric trifluoroacetate allows the less stable allylic isomer to be trapped.

Sir: The 1,3-isomerization of allylic alcohols and allylic alcohol derivatives has been investigated mechanistically for years,[1-3] and plays a key role in several synthetic[4] and commercial processes.[5] Popular methods for affecting this transformation include Lewis acid, protic acid, and transition metal catalyzed isomerization of allylic alcohols, or the corresponding acetates. Overall yields vary from 25 to 85%, and isomer conversions often only approach the equilibrium values.[1-5] Although methodology is well established[6] for the contrathermodynamic isomerization of alkenes, to our knowledge, no method exists for achieving contrathermodynamic *allylic* isomerizations.

The first examples of mercuric ion catalyzed [3,3]-sigmatropic rearrangements were recently reported from our laboratory.[7] This study revealed that trichloroacetimidic esters of 2-alken-1-ols **1** (X = O, Y = NH, Z = CCl_3) underwent rapid isomerization to the corresponding allylic trichloroacetamides **3** (X = O, Y = NH, Z = CCl_3) when treated in an aprotic solvent, at room temperature, with a catalytic amount of mercuric trifluoroacetate. The intramolecular iminomercuration–deoxymercuration mechanism of eq 1 (X = O, Y = NH, Z = CCl_3) was suggested for this catalyzed transformation.[7-9]



(1)

We anticipated that mercury(II) salts would catalyze the allylic isomerization (**1** → **3**) of other functional groups, and subsequent work in this laboratory has confirmed this expectation. In this communication we wish to report that mercuric trifluoroacetate is an effective catalyst at room temperature for the allylic equilibrium of *N,N*-dimethylcarbamic esters of allylic alcohols. Moreover, we wish to report that in certain cases a modification of this process results in the first approach to achieving contrathermodynamic allylic isomerizations.

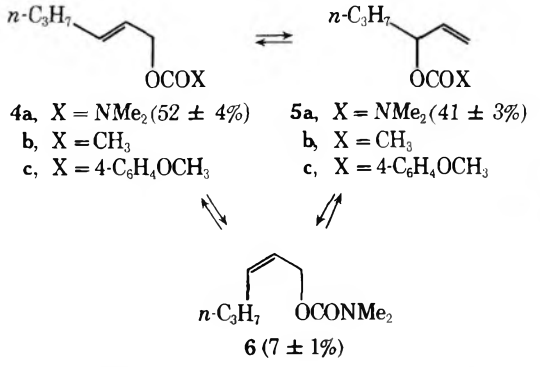
Treatment of the allylic carbamate isomers **4a** and **5a** at room temperature for 4–11 h with 0.4 equiv of *anhydrous* mercuric trifluoroacetate in dry tetrahydorfuran (THF) re-

Table I. Anhydrous Mercuric Trifluoroacetate Catalyzed Allylic Isomerization of 2-Alken-1-yl *N,N*-Dimethylcarbamates ($R_1R_2C{=}CHCH_2OCONMe_2$)[a]

Starting internal alkene isomer			Equiv[b] of HgX_2	Solvent[c]	Reaction time, hr	% yield[d]	Quenched product composition[e]	
R_1	R_2	No.					% terminal alkene	% internal alkene
n-C_3H_7	H	**4a**	0.3	THF	9	(97)	34	66[f]
n-C_3H_7	H	**4a**	1.1	THF	9	(80)	58	42[f]
n-C_3H_7	H	**4a**	1.1	THF	16	(98)	65	35[f]
n-C_3H_7	H	**4a**	3.0	THF	8	87	81	19[f]
n-C_3H_7	H	**4a**	1.1	C_6H_6	8	89	83	17[f]
$C_6H_5CH_2$	H	**10**	1.1	THF	9	(88)	57	43[f]
$C_6H_5CH_2$	H	**10**	1.1	C_6H_6	8	86	71	29[f]
CH_3	CH_3	**8**	1.2	THF	8–17	(66)	2	98

[a] Carbamate, 0.1 M. Reactions were quenched by adding 3.6 equiv of Ph_3P, dissolved in a small volume of the solvent, per equivalent of catalyst. Bis(triphenylphosphine)bis(trifluoroacetato)mercury(II) precipitates within minutes when induced by scratching and cooling. Chromatography is necessary to remove the last traces of this complex. [b] Prepared by the procedure of Brown,[20] mp 166–167 °C, and stored in a desiccator over KOH. [c] THF was distilled from sodium and benzophenone immediately before use. Benzene was distilled from CaH_2 and stored over molecular sieves. If water is not rigorously excluded considerable carbamate hydrolysis occurs. [d] Isolated yields, after chromatography, of the isomer mixture. Yields in parentheses refer to percent recoveries based on GLC or ^1H NMR analysis. [e] Internal/terminal isomer ratios were determined by both ^1H NMR and GLC analysis. In all cases the two methods agreed within 3%. [f] An *E/Z* isomer mixture.

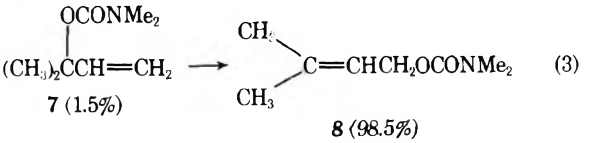
sulted in the formation, in >90% yield, of the apparent equilibrium mixture[10] of isomers shown in eq 2. Similar treatment



(2)

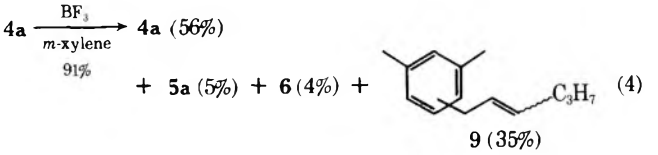
6 (7 ± 1%)

of acetate **4b** or anisate **4c** with up to 1.2 equiv of $Hg(OCOCF_3)_2$ afforded <10% of the corresponding terminal isomers **5b** or **5c**. A comparison of the initial rate of the catalyzed isomerization of **4a** in THF with the thermal, gas phase isomerization of several 2-butenyl derivatives,[12] allows one to make a rough estimate[13] for the rate enhancement of the catalyzed process (1 M catalyst) of 10^{13}. Under similar conditions (0.3 equiv of $Hg(OCOCF_3)_2$, 30 min, 25 °C) the tertiary allylic carbamate **7** is converted in 95% yield into a mixture of carbamate isomers containing 98.5% of the more stable[2b,4c] trisubstituted alkene isomer **8**.



(3)

Permissive evidence that the mercuric catalyzed equilibrations are occuring by the two-step mechanism of eq 1 (X = Y = O, Z = NMe_2), comes from our inability to trap allylic carbonium ions in the mercuric catalyzed reaction. For example, treatment (8 h, 25 °C) of carbamate **4a** in *m*-xylene as solvent with 0.4 equiv of $Hg(OCOCF_3)_2$ resulted in production (93% recovery) of the equilibrium mixture of carbamate isomers shown in eq 2. No trace of the allyl cation–Friedel-Crafts product, **9**, could be found. In contrast, treatment of carbamate **4a** in *m*-xylene with 2.5 equiv of boron trifluoride etherate (25 °C, 8 h) yielded the product mixture shown in eq 4.[14]



(4)

Equilibrium constants for formation of covalent alkene–mercuric trifluoroacetate adducts have been measured in THF[15] and benzene,[16] and are considerably higher for monothan for disubstituted alkenes. The addition of mercuriophilic reagents [for example norbornene,[15] pyridine,[15] or triphenylphosphine (Ph_3P)[7]] to these covalent adducts has also been shown to result in quantitative liberation of the alkene. Thus, treatment of an internal allylic carbamate such as **4a** with an excess of $Hg(OCOCF_3)_2$, followed by the addition of a mercuriophile, should yield an isomer mixture rich in the contrathermodynamic terminal isomer **5a**. That is, the excess catalyst is expected to preferentially trap the terminal alkene isomer as a covalent adduct,[17] thus selectively removing it from the equilibrating isomer pool. That this expectation has indeed been realized is apparent from the data in Table I. Thus, treatment of carbamate **4a** with 1.1 equiv of $Hg(OCOCF_3)_2$ in benzene for 8 h at room temperature, followed by quenching with Ph_3P and chromatographic workup, afforded, in 89% yield, an isomer mixture containing 83% terminal isomer, **5a**. Two trends are apparent. The contrathermodynamic isomer preference in THF increases with increasing catalyst concentration, and, for the same catalyst concentration, this preference is higher in benzene than THF. Both trends would be expected if this isomerization occurred as we have suggested since a larger fraction of the alkene isomers should, at comparable catalyst concentrations, be bound as covalent adducts in benzene[15,16] and also at higher catalyst concentrations. The mildness of this method is well demonstrated by the allylic isomerization of carbamate **10** to the corresponding terminal alkene isomer without the formation of even a trace of the more stable styrene isomer. This method fails, however, if the starting 2-alken-1-yl carbamate is disubstituted at C-3. Thus carbamate **8** yields only a trace of the tertiary allylic isomer **7** (i.e., the reverse of eq 3) when treated with 1.2 equiv of $Hg(OCOCF_3)_2$ in THF.[18]

The mercuric trifluoroacetate promoted[19] allylic carbamate equilibrium is notable for the mildness of the reaction conditions and the high isolated yields. Unwanted skeletal isomerizations would appear precluded since allylic carbonium ions are not intermediates. The method reported here for contrathermodynamic allylic isomer enrichment is limited to the conversion of carbamic esters of 2-alken-1-ols, which contain a disubstituted double bond, to the correspondinng 1-alken-3-ol derivatives. Although this method represents a general approach for achieving contrathermodynamic allylic isomerizations, the reaction conditions we have thus far investigated do not specifically afford only the contrathermodynamic isomer. One can imagine, however, that similar catalysts, which have even higher selectivities for binding specifically the terminal alkene isomer, may overcome this limitation.

Acknowledgment. We thank the National Science Foundation for support of this work under Grant No. GP-38634X.

Supplementary Material Available. Experimental procedure (2 pages). Ordering information is given on any current masthead page.

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(2) Cf. (a) E. A. Braude and P. H. Gores, *Nature*, **173**, 1091 (1954); (b) W. G. Young and I. D. Webb, *J. Am. Chem. Soc.*, **73**, 780 (1951); (c) H. L. Goering and M. M. Pombo, *ibid.*, **82**, 2515 (1960).

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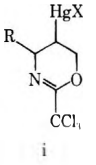
(8) Since in this case Y contains a protic hydrogen, the ion pair 2 would be in equilibrium with HX and the neutral adduct i.



i

(9) A mechanism similar to that shown in eq 1 has been suggested for the palladium(II)-catalyzed isomerization of allylic esters: P. M. Henry, *J. Am. Chem. Soc.*, **94**, 5200 (1972).

(10) Equilibration of the butenyl acetates in acetic acid by treatment with *p*-toluenesulfonic acid (0.3 M, 60 °C, 9–16 days)[2b] or perchloric acid (8.3 mM, 75 °C, 3–5 h)[11b] has been reported.[11] Recoveries varied from 30 to 84% and the equilibrium composition[11b] was 38.2% α-methylallyl acetate, 51.4% *trans*-crotyl acetate, and 10.4% *cis*-crotyl acetate.

(11) (a) Z. Rappoport, S. Winstein, and W. G. Young, *J. Am. Chem. Soc.*, **94**, 2320 (1972); (b) H. E. Green, Ph.D. Thesis, University of California, Los Angeles, Calif., 1965.

(12) E. S. Lewis, J. T. Hill, and E. R. Newman, *J. Am. Chem. Soc.*, **90**, 662 (1968).

(13) At 25 °C in THF the rate constant for the catalyzed conversion of **4a** to **5a** was measured by the initial rate method: $k_{cat} = 4 \pm 3 \times 10^{-3}$ mol l.$^{-1}$ s^{-1} (five determinations). The extent of reaction ranged from 3 to 30% and the equivalent of catalyst varied from 0.05 to 1.0.[14] The corresponding rate constant for the thermal, gas phase, isomerization was estimated by extrapolating rate constants[12] for the conversion of $CH_3CH{=}CHCH_2O(C{=}O)Z$ to $CH_3CHO(C{=}O)ZCH{=}CH_2$ (Z = CF_3, CH_3, and OCH_3) from 325 to 25 °C, plotting the logarithm of these extrapolated rate constants vs. σ_m (correlation coefficient, 1.00), and estimating $K_{thermal}$ for the conversion of **4a** to **5a** from this plot using the σ_m constant for the $N(CH_3)_2$ group; $k_{thermal} = 3 \times 10^{-17}$ s^{-1}.

(14) Details will be reported in the subsequent full paper and the Ph.D. thesis of C. B. Campbell.

(15) H. C. Brown and M.-H. Rei, *J. Chem. Soc., Chem. Commun.*, 1296 (1969).

(16) H. C. Brown, M.-H. Rei, and K.-T. Liu, *J. Am. Chem. Soc.*, **92**, 1760 (1970).

(17) A variety of structures would appear possible for these postulated covalent adducts. This aspect is under investigation.

(18) This result is not unexpected. The equilibrium constant for the formation of the mercuric trifluoroacetate complex of 3,3-dimethyl-1-butene is nine times less than that of 1-hexene.[15] A competing oxidation reaction also becomes important here at long reaction times.

(19) Winstein and coworkers[11a] have reported that the crotyl and α-methyl allyl acetates may be equilibrated by treatment at 75 °C for 23 h with 1.1–1.3 equiv of mercuric acetate in acetic acid. Less than 48% of the allylic esters were recovered from this treatment. An intermolecular acetoxymercuration–deactoxymercuration mechanism was suggested for this process.

(20) H. C. Brown and M.-H. Rei, *J. Am. Chem. Soc.*, **91**, 5646 (1969).

(21) A. P. Sloan Foundation Fellow, 1975–1977.

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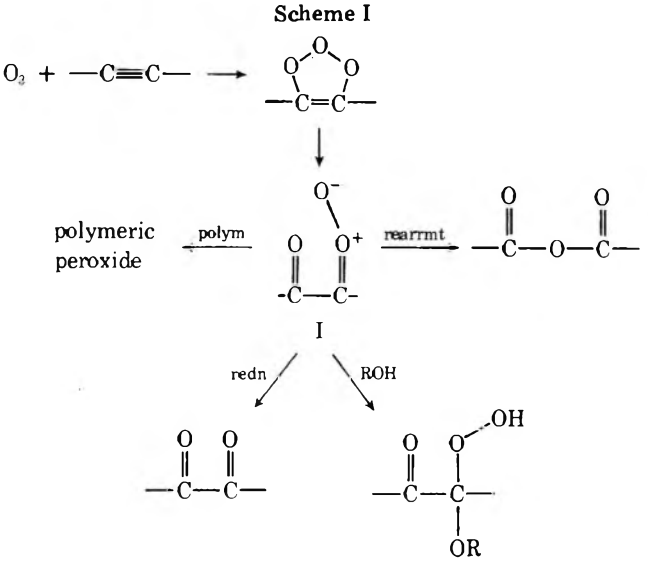
Reductive Trapping in the Ozonolysis of Diphenylacetylene

Summary: Evidence is presented that establishes the existence of a relatively stable (half-life ~35 min, −42 °C) reducible intermediate in the ozonolysis of diphenylacetylene.

Sir: The reaction of ozone with alkenes has been the subject of extensive study.[1] By comparison the number of mechanistic studies of the ozonolysis of alkynes has been relatively small, although recently there has been renewed interest.[2-10] The mechanism suggested by Criegee and Lederer is analogous to that for alkenes and a slightly modified version is depicted in Scheme I.[5]

Scheme I



The intermediacy of I, an α-carbonyl carbonyl oxide, is supported by solvent trapping,[5,6] reductive trapping,[8,9] and spectroscopic work.[7] The stability of I, whether it is a long-lived intermediate, and its mode of rearrangement to the anhydride products are open questions. In this work the reaction of diphenylacetylene and ozone has been studied in an effort to answer some of those questions.

Previous work has shown the products of the reaction of diphenylacetylene and ozone to be benzil, benzoic anhydride,

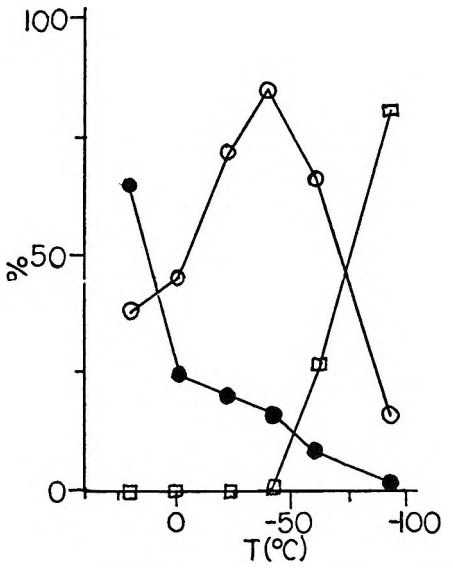


Figure 1. Plot of product mixture composition vs. temperature for O_3 + DPA with subsequent addition of Ph_2S: DPA (□), $(PhCO)_2O$ + $PhCO_2H$ (●), and (Ph–CO)$_2$ (○).

and benzoic acid.[2-4,8] In addition Yang and Libman have shown that ozonolysis of diphenylacetylene in the presence of TCNE at low temperature (−78 °C) in ethyl acetate gives rise to TCNE epoxide and benzil.[8] Our results confirm the earlier work with yields of benzoic anhydride/benzoic acid in the range of 70–80%. Solvents used include diethyl ether, acetone, and methycyclohexane. The ozonolyses, whether carried out at ambient temperatures or performed at low temperatures (−93, −42 °C) and then warmed, yield approximately the same product mixtures (see Table I).

Table I. Product Compositions of O_3 + Diphenylacetylene Reaction in Acetone

Expt	T, °C	Benzil, %	Benzoic anhydride, %[a]
1	20	26	45
2	−42	18	43
3	−93	27	35

[a] Benzoic acid present but not determined quantitatively.

In the low temperature reduction experiments using either Ph_3P or Ph_2S as reductant (both of which are known to efficiently reduce peroxides), varying amounts of benzoic anhydride, benzil, and diphenylacetylene were recovered, depending on either the temperature of the reaction or the time before addition of the reducing agent.[11,12] The product mixtures were independent of the amount of reducing agent added in excess of molar ratios of 1:1.

Figure 1 is a plot of the product mixture content vs. temperature in those experiments in which reducing agent (Ph_2S) was added after a fixed period of time (2 min) after ozone addition (~30 min). The plot indicates the production of benzil reached a maximum (~85%) at −42 °C. At lower temperatures increasing amounts of diphenylacetylene were recovered, indicating insufficient time for the completion of reaction of ozone with the acetylene, and at higher temperatures increasing amounts of benzoic anhydride are isolated. The reactions of ozone with alkynes are known to be significantly slower than ozone's reactions with alkenes.[10] The lack of reaction at the lowest temperature is therefore not surprising. The increasing benzil/benzoic anhydride ratios with decreasing temperature (see Table II) can only be explained by the trapping (by reduction) of some thermally unstable species. Reasonably stable at −42 °C, it is, on warming or carrying out the reaction at higher temperatures, converted to benzoic anhydride.

Table II. Ratio of Benzil to Benzoic Anhydride Acid on Addition of Ph_2S 2 Min after Ozonolysis

T, °C	Benzil/ benzoic anhydride acid	T, °C	Benzil/ benzoic anhydride acid
+20	0.59	−42	5.7
0	1.8	−62	8.1
−23	3.8	−93	16.

Product trapping by reduction as a function of time at a fixed temperature was performed. Addition of ozone to a solution of diphenylacetylene in acetone kept at −42 ± 2°C, with subsequent periodic withdrawals of aliquots of solution, was carried out. The aliquots were added to individual solutions of diphenyl sulfide in acetone at −42 °C. Workup and analysis of the quenched (by reduction) aliquots showed decreasing amounts of benzil and increasing amounts of benzoic anhydride as shown in Table III. If it is assumed that at −42 °C the ozone and diphenylacetylene reacted rapidly to give a thermally unstable species, and that the yield of benzil produced by reduction represents the concentration of that thermally unstable species, then the rate constant for disappearance of the unstable precursor can be obtained from a plot of the log of the benzil yield vs. time. Such a plot is linear (see supplementary material) and the slope gives a rate constant of 3.3 ± 0.8 × 10^{-4} s^{-1} and a half-life of ~35 ± 10 min at −42 °C.

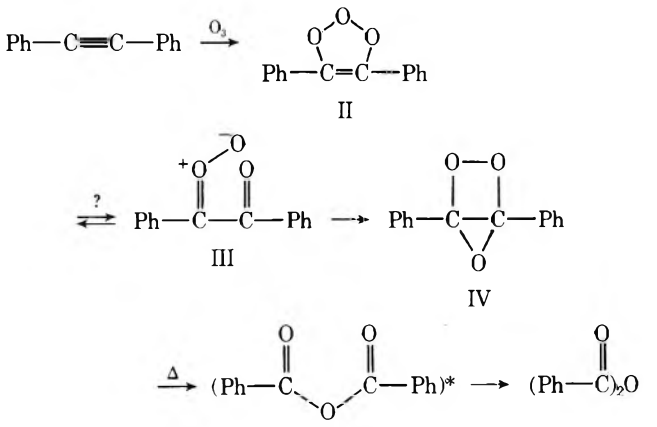
Table III. Percent Yield of Benzil on Addition of Ph_2S after Varying Periods of Time after Ozonolysis

Time, min	% yield of benzil (−42 °C)
0	79
15	59
30	55
45	31
60	25

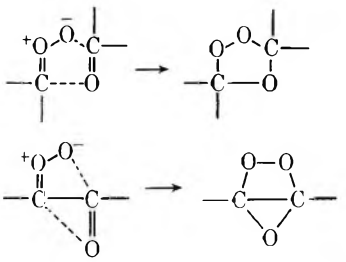
The nature of the transformation of this precursor species to benzoic anhydride has been further probed using energy acceptors capable of fluorescence. A solution of the precursor was prepared in acetone at −42 °C; excess or unreacted ozone was swept out by passing a stream of dry cooled nitrogen through the solution. To these solutions was added 9,10-diphenylanthracene, a known singlet energy acceptor.[13] On warming, the solutions were observed to chemiluminesce with the characteristic yellow-green color of the 9,10-diphenylanthracene fluorescence. Control experiments indicated the necessary presence of the benzoic anhydride precursor and the fluorescer to observe chemiluminescence.

Scheme II summarizes the suggested mechanism for the reaction. It is constructed in analogy with the well-studied reactions of alkenes, as well as solvent trapping and product study work done by others (already mentioned) on alkyne–ozone reactions. Species II, a 1,2,3-trioxolene, is just the 1,3-dipolar cycloaddition product of ozone and the alkyne and is analogous to the 1,2,3-trioxolane product from the addition of ozone to an alkene. Species III is an α-carbonyl carbonyl oxide. It is not clear whether II and III are in fact in equilibrium as suggested by Keay and Hamilton, and are the precursor to the benzoic anhydride.[9]

Scheme II



It is also possible species IV is the relatively stable benzoic anhydride precursor. Its formation is analogous to the addition of the carbonyl oxide to ketones and aldehydes in alkene ozonolyses to produce 1,2,4-trioxolanes (secondary ozonides) as shown below. Also the rate constant for transformation of



a species like IV to products would be relatively insensitive to polar substituent and solvent effects, a characteristic found for simple alkynes.[10] The exceptional stability (considering their strain and peroxidic nature) of dioxetanes (for cis-diethoxydioxetane $t_{1/2}$ = 10 min at 50 °C) also lends support for the possible existence of IV.[13] In addition, the observation of chemiluminescence on decomposition of the precursor in the presence of fluorescers serves as a direct indication of the presence of IV, even if only as a fleeting species.

It should be noted that the scheme presented in speculative. Other possibilities also present themselves. As noted by a referee species III may be a direct precursor to the chemiluminescence and the benzoic anhydride, although there is little precedent for the reaction. Also homolytic cleavage of species II to give a diradical is a possibility. This type of cleavage is suggested in gas phase ozone reactions.[14]

In conclusion the evidence presented lends supports for the existence of the relatively stable precursor $t_{1/2}$ = 35 min, −42 °C) to the isolable products from the ozonolysis of diphenylacetylene.

Acknowlegment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Supplementary Material Available. Plot of the log of the benzil yield vs. time to addition of Ph_2S and experimental precedures (3 pages). Ordering information is given on any current masthead.

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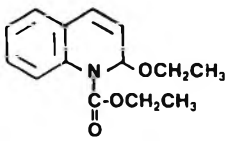

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iii)	Bz-Gly + Gly-OEt	Bz-Gly-Gly-OEt	99
iv)	Bz-Gly + Aniline	Bz-Gly-anilide	90
v)	CBZ-L-Ala + L-Ala-OEt	CBZ-L-Ala-L-Ala-OEt	98
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